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This bibliography is a rich and informative resource. It represents a comprehensive search of the medical literature on “familial Mediterranean fever” and the “autoinflammatory diseases” from 1947-2018. More than 6,000 references (taking 5,000 pages) are listed here including titles, authors, journal information, and abstracts (when available). This is a resource for finding research publications on a specific topic. Use the “word search” feature to find the articles that contain terms you specify. To activate word search, press “Control + F”. The search field will appear. Enter your search term in the search field and press “enter” and the arrow will take you to every reference in which that term appears. You can search on a topic such as “pregnancy” or on a specific mutation such as “M694V” or on an author’s name, or on a specific autoinflammatory disease. Only one search term can be entered at a time. You can cut and paste the references of interest into a text file in a separate document. In some instances, the abstracts may be enough to answer your questions. If you need more information there are some references (but not all) for which you can obtain the whole article on the internet. To obtain a copy of the complete article, go to this link:

<https://scholar.google.com> Paste the article’s title into the search field. When the reference is found, you will see on the right side of the screen if there is a pdf available for download. Some articles can only be obtained from the publisher for a fee.

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## BIBLIOGRAPHY WITH ABSTRACTS OF PUBLICATIONS ON FAMILIAL MEDITERRANEAN FEVER OR AUTOINFLAMMATORY DISEASE THROUGH 2018

1. J Dtsch Dermatol Ges. 2019 Jan;17(1):43-64. doi: 10.1111/ddg.13742.

Skin inflammation associated with arthritis, synovitis and enthesitis. Part 1: psoriatic arthritis, SAPHO syndrome, Still's disease, Behçet's disease.

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The coincidence of skin and joint inflammation poses a challenge for both dermatologists and rheumatologists. Adequate management of such disorders requires that physicians of both specialties have sound knowledge of the other discipline. In case of suspected joint involvement, familiarity with the diagnostic options available to rheumatologists enables dermatologists to selectively refer their patients for a rheumatology consult. The objective of the present review is to familiarize the reader with the stepwise diagnostic workup performed by rheumatologists today, including laboratory tests, musculoskeletal ultrasound, X-ray studies, and magnetic resonance imaging. Subsequently, we will discuss a number of disorders characterized by the concurrence of skin and joint inflammation, highlighting aspects of epidemiology, etiology and pathogenesis, clinical presentation, diagnosis and treatment. These disorders include psoriatic arthritis as well as autoinflammatory disorders such as SAPHO syndrome, Still's disease and Behçet's disease.

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DOI: 10.1111/ddg.13742

PMID: 30615277

2. Immunogenetics. 2019 Jan 5. doi: 10.1007/s00251-018-01101-w. [Epub ahead of print]

A Chinese DADA2 patient: report of two novel mutations and successful HSCT.

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Deficiency of adenosine deaminase 2 (DADA2) is an autoinflammatory disease caused by autosomal recessive mutations in Cat Eye Syndrome Chromosome Region 1 (CECR1) gene. In this report, we aimed to describe the clinical manifestations, immunological features, genotype, and treatments of one Chinese patient with novel CECR1 gene mutations. This patient initially presented with recurrent fever and rashes from the age of 3 months, but no pathogen was found. She then developed dry gangrene of the fingers at 5 months of age. Laboratory examinations revealed elevated levels of C-reactive protein and thrombocytes. The expression of interleukin-6 (IL-6) and IL-8 were both elevated. Sequencing results revealed that she had compound heterozygous mutations in CECR1 gene (c.1211T>C, p.Phe404Ser and c.1114 G>A, p.Val372Met). Subsequently, treatment with anti-IL-6 (tocilizumab) was started. However, she developed blurred vision in the right eye with occlusion of the central retinal artery, accompanied by unsteady gait. Magnetic resonance imaging (MRI) showed infarction of the right thalamus. Finally, she underwent hematopoietic stem cell transplantation (HSCT) and is currently in remission. Our findings suggest that HSCT could cure this disease.

DOI: 10.1007/s00251-018-01101-w

PMID: 30610243

3. J Allergy Clin Immunol. 2018 Dec 31. pii: S0091-6749(18)31641-5. doi: 10.1016/j.jaci.2018.11.009. [Epub ahead of print]

Early-onset generalized pustular psoriasis is representative of autoinflammatory keratinization diseases.

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DOI: 10.1016/j.jaci.2018.11.009

PMID: 30606494

4. Acta Neurol Belg. 2019 Jan 2. doi: 10.1007/s13760-018-01070-7. [Epub ahead of print]

Colchicine-induced myoneuropathy with myotonia in a patient with familial Mediterranean fever.

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DOI: 10.1007/s13760-018-01070-7

PMID: 30604339

5. Rheumatol Int. 2019 Jan 3. doi: 10.1007/s00296-018-04236-x. [Epub ahead of print]

Pediatric rheumatology in Turkey.

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Pediatric Rheumatology is an emerging specialty in Turkey with increasing number of available centers and specialists all over the country. In this paper, we sought to provide an overview on pediatric rheumatology service in our country, as well as to assess the principle published literature from Turkey in this field. A systematic literature search has been performed to achieve the significance and the impact of this manuscript. The most relevant used databases (PubMed/MEDLINE, Web of Science, SCOPUS) for peer-reviewed studies and reviews in English language published during the last 5 years were screened. In the first part of the manuscript, we tried to give more details on the history of pediatric rheumatology in Turkey. In further text, we put an accent over the most common rheumatologic conditions among children in Turkey, including Familial Mediterranean fever, juvenile idiopathic arthritis, juvenile spondyloarthropathies, and childhood vasculitides. Despite the considerable literature from Turkey on pediatric rheumatic diseases, a need for unique strategies that would guide the management of rheumatic diseases in childhood remains open. The cultural and historical inheritance together with geographical position make the Turkey a suitable ground for investigations in filed of auto-inflammation and all other inflammatory conditions. Prospective, multicentric studies especially among rheumatologic conditions common in this part of the world would give us more relevant data and open new horizons in diseases' management. International collaborations and databases should be highly encouraged and supported, to make the care of pediatric rheumatic disease uniform.

DOI: 10.1007/s00296-018-04236-x

PMID: 30604206

6. Rheumatol Int. 2019 Jan 2. doi: 10.1007/s00296-018-04237-w. [Epub ahead of print]

Efficacy and safety of long-term treatment with intravenous colchicine for familial Mediterranean fever (FMF) refractory to oral colchicine.

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Colchicine is the mainstay of treatment for familial Mediterranean fever (FMF). Intravenous (IV) colchicine, administered over several months, has been shown to be effective for FMF patients unresponsive to oral colchicine. The objective of this study was to evaluate the efficacy and safety of long-term IV colchicine treatment in oral colchicine-resistant FMF. We analyzed data of 15 patients with frequent FMF attacks, despite a maximal tolerated dose of oral colchicine (2-3 mg/day), who were treated with weekly IV injections of 1 mg of colchicine for at least 12 months. Treatment efficacy was determined by changes in frequency, duration and severity of FMF attacks. Safety was assessed according to adverse events. The mean duration of IV colchicine treatment was  $5.16 \pm 2.85$  years. Decreases were observed from pre-treatment period in the monthly mean rates of abdominal attacks (from  $5.6 \pm 3.7$  to  $1.9 \pm 3.3$ ,  $p = 0.0009$ ), joint attacks (from  $6.5 \pm 5.1$  to  $1.6 \pm 1.6$ ,  $p = 0.01$ ) and overall attacks (from  $22.3 \pm 16.2$  to  $7.4 \pm 5.7$ ,  $p = 0.002$ ) as well as in the mean duration (from  $3.8 \pm 1.5$  to  $2.4 \pm 1.1$  days per attack,  $p = 0.008$ ) and severity of attacks (from  $9.9 \pm 0.3$  to  $5.7 \pm 2.6$ , on a scale of 0-10,  $p < 0.05$ ). The rate of adverse events was low, and they were mainly gastrointestinal. No severe or serious adverse events were recorded. Long-term treatment with IV colchicine in

patients unresponsive to oral colchicine therapy is effective and safe.

DOI: 10.1007/s00296-018-04237-w

PMID: 30604205

7. Dtsch Med Wochenschr. 2019 Jan;144(1):35-38. doi: 10.1055/a-0794-8391. Epub 2019 Jan 2.

[Prenatal care in patients with renal disease].

[Article in German; Abstract available in German from the publisher]

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**HISTORY AND CLINICAL FINDINGS:** We report of three pregnancies, two with renal insufficiency and one with a history of renal transplantation. Pat.1 is a 32y at 20 weeks of gestation with acute renal failure, nephrotic syndrome and history of familial Mediterranean fever. Case 2 is a 23y with cirrhotic kidneys, stage 5 of chronic kidney disease and dialysis treatment 3 × a week. The pregnancy was an incidental finding. Pat. 3 is a 29y I/O with history of renal transplantation years ago.

**DIAGNOSIS, TREATMENT AND COURSE:** In pat. 1a renal biopsy confirmed the suspected diagnosis of AA amyloidosis. Due to deterioration of the kidney function, she required dialysis up to 6 × a week. In Case 2 the dialysis increased to 6 × a week as well. In both patients, we indicated delivery at 35 weeks of gestational age. Pat. 3 delivered at term without complications.

**CONCLUSION:** A close interdisciplinary cooperation improves neonatal outcome in pregnant women with CKD. Counseling and risk assessment of these patients should be initiated before pregnancy. The care of these high-risk pregnancies needs to be performed at a tertiary care center with the above-mentioned specialists.

**Publisher:** Wir berichten über drei Schwangere: zwei in verschiedenen Stadien der Niereninsuffizienz und eine Nierentransplantierte. Pat. 1 ist eine 32-Jährige I/O in der 20. SSW mit akutem Nierenversagen, nephrotischem Syndrom und familiärem

Mittelmeerfieber in der Anamnese. Pat. 2 ist eine 23-Jährige mit Schrumpfnieren bds. und Niereninsuffizienz Stad. V unter Dialyse 3 × wöchentlich, die Schwangerschaft war eine Zufallsdiagnose. Pat. 3 ist eine 29-Jährige im Z. n. Nierentransplantation vor mehreren Jahren. Bei Pat. 1 wurde die Verdachtsdiagnose einer AA-Amyloidose durch Nierenbiopsie bestätigt. Im Verlauf wurde sie zunehmend dialysepflichtig. Bei Pat. 2 musste die Dialyse ebenfalls eskaliert werden. Beide Schwangerschaften wurden vorzeitig beendet. Die transplantierte Pat. 3 wurde am Termin ohne Komplikationen im Verlauf entbunden. Die Verbesserung des fetalen Outcomes ist v. a. auf die interdisziplinäre Zusammenarbeit zurückzuführen. Ziel sollte sein, junge nierenkranke Frauen bereits vor einer Schwangerschaft umfassend über Risiken und Erfolgsaussichten zu beraten und zu betreuen.  
© Georg Thieme Verlag KG Stuttgart · New York.

DOI: 10.1055/a-0794-8391

PMID: 30602185

Conflict of interest statement: Disclosure The authors report no conflicts of interest in this work.

8. J Clin Rheumatol. 2018 Dec 28. doi: 10.1097/RHU.0000000000000963. [Epub ahead of print]

Coincidence of NOD2-Associated Autoinflammatory Disease (Yao Syndrome) and HCV Infection With Fatal Consequences: Interaction Between Genes and Environment.

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DOI: 10.1097/RHU.0000000000000963

PMID: 30601168

9. Cardiol J. 2018;25(6):753-755. doi: 10.5603/CJ.2018.0154.

Intermittent right bundle branch block in a child with familial mediterranean fever.

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DOI: 10.5603/CJ.2018.0154

PMID: 30600838

10. Trials. 2018 Dec 29;19(1):715. doi: 10.1186/s13063-018-3105-6.

Comparison of the efficacy and safety of tocilizumab for colchicine-resistant or colchicine-intolerant familial Mediterranean fever: study protocol for an investigator-initiated, multicenter, randomized, double-blind, placebo-controlled trial.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is an inherited disorder caused by a number of mutations of the Mediterranean fever (MEFV) gene, coding a protein named pyrin that acts as a major regulatory component of the inflammasome. The first-line drug for FMF treatment is colchicine, but 10% of patients with FMF do not respond well to colchicine. Although the efficacy of tocilizumab (TCZ), which is a recombinant, humanized, antihuman interleukin 6 (IL-6) receptor monoclonal antibody, has been reported to prevent FMF attacks, the effects of TCZ on individuals with colchicine-resistant or colchicine-intolerant FMF have not been evaluated in a randomized clinical trial.

**METHODS/DESIGN:** In this phase III, investigator-initiated, multicenter, double-blind, randomized, parallel-group trial, the efficacy and safety of TCZ will be compared with placebo in patients with colchicine-resistant or colchicine-intolerant FMF. The study will be conducted in nine centers in Japan. Participants (n = 24) will be randomly assigned to receive 162 mg of TCZ (n = 12) or placebo (n = 12) administered subcutaneously once weekly for 24 weeks. Rescue treatment will be allowed if rescue criteria are met. A primary endpoint is the number of fever attacks until 24 weeks. Secondary endpoints include the number of occurrences of accompanying symptoms during attacks; the time until a fever attack occurs; the duration of fever attacks; serum C-reactive protein and serum amyloid A; 36-item Short Form Health Survey; general evaluation by a physician (100-mm visual analogue scale); body temperature; the percentage of subjects who achieve FMF 50 at 12 weeks and 24 weeks; and pharmacodynamic assessment, including the measurement of serum TCZ level and soluble IL-6 receptor.

**DISCUSSION:** The study is expected to produce evidence regarding the efficacy of a potential new therapeutic agent, TCZ, in improving the clinical course and outcome for patients with colchicine-resistant or colchicine-intolerant FMF.

**TRIAL REGISTRATION:** University Hospital Medical Information Network Clinical Trials Registry, UMIN000028010 . Registered on 7 July 2017.

DOI: 10.1186/s13063-018-3105-6

PMCID: PMC6311086

PMID: 30594222

11. J Med Biochem. 2018 Dec 1;37(4):507-509. doi: 10.1515/jomb-2017-0066. eCollection 2018 Dec.

High Prevalence of Autoantibodies Against Monomeric C Reactive Protein (CRP) in Children with PFAPA Syndrome.

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PFAPA (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis) syndrome is an autoinflammatory disorder of unknown etiology. The aim of our study was to evaluate whether the presence of anti-mCRP autoantibodies (anti-mCRP) might possibly contribute to systemic inflammation during PFAPA flares. We carried out anti-mCRP testing (in-house ELISA) in a single-center, prospective cohort of 30 PFAPA patients (12 girls). We found a high prevalence (43.3%) of anti-mCRP antibodies in PFAPA patients during their febrile episodes, which implies the possible involvement of anti-mCRP antibodies in PFAPA pathogenesis.

Publisher: PFAPA (periodične groznice, aftozni stomatitis, faringitis, cervikalni adenitis) sindrom je autoinflamatorno oboljenje sa nepoznatom etiologijom. Cilj ove studije bio je da se utvrdi da li prisustvo anti-mCRP autoantitela (anti-mCRP) možda doprinosi sistemskoj inflamaciji tokom napada PFAPA. Sproveli smo anti-mCRP testiranje (interno sa ELISA) u jednocentričnoj prospektivnoj kohorti od 30 pacijenata sa PFAPA sindromom (12 devojčica). Otkrili smo visoku prevalencu (43,3%) anti-mCRP antitela kod obolelih od PFAPA tokom febrilnih epizoda, što ukazuje na potencijalno učešće antimCRP antitela u patogenezi PFAPA. DOI: 10.1515/jomb-2017-0066

PMCID: PMC6298472

PMID: 30584411

12. Clin Exp Rheumatol. 2018 Nov-Dec;36 Suppl 115(6):116-124. Epub 2018 Dec 12.

Potential role of pyrin, the protein mutated in familial Mediterranean fever, during inflammatory cell migration.

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Familial Mediterranean fever (FMF), the most common of the systemic autoinflammatory disorders, is caused by mutations in the MEFV (Mediterranean Fever) gene, which encodes the protein pyrin. Neutrophils, one of the major components during inflammation, are the main cell type that expresses pyrin. In response to an inflammatory stimulus, neutrophils migrate to their main active site. To date, several pyrin-interacting proteins have been demonstrated to co-localise with the cytoskeletal protein actin, which is important in the process of neutrophil migration and raises the question of whether pyrin plays a role in the actin cytoskeletal network during inflammatory cell migration. In this study, we examined the possible role of pyrin during inflammatory cell migration in neutrophils. We generated a cell migration assay with neutrophils and primary neutrophils from patients. We also knocked down pyrin expression using siRNA and then performed cell migration assay. We showed co-localisation of pyrin and F-actin at the leading edge during inflammatory cell migration. In pyrin knocked down cells, we identified a significant decrease in neutrophil migration. In addition, we demonstrated a dramatic increase in migration in the neutrophils of FMF patients compared with a healthy control group. These data together provide new insight into the cellular function of pyrin and demonstrate an important link between pyrin and polymerising actin in the process of inflammatory cell migration.



PMID: 30582517

13. Clin Exp Rheumatol. 2018 Nov-Dec;36 Suppl 115(6):110-115. Epub 2018 Dec 12.

Serum immunoglobulin D levels in patients with Behçet's disease according to different clinical manifestations.

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**OBJECTIVES:** Behçet's disease (BD) is an autoinflammatory disorders mainly characterised by recurrent oral aphthosis, genital ulcers, and uveitis. The involvement of immunoglobulin D (IgD) in BD physiopathology is still unclear. The aim of our study was to assess the role of IgD in BD by comparing circulating levels of IgD in a cohort of BD patients and healthy controls (HC), as well as by correlating IgD levels with BD activity and different clinical presentations.

**METHODS:** Serum IgD and SAA levels were analysed by ELISA assay in ninety-nine serum samples collected from 72 BD patients and in 29 HC subjects.

**RESULTS:** Serum concentration of IgD were higher in BD patients compared with HC

( $p=0.029$ ), in patients with high serum amyloid A (SAA) levels compared with patients with normal SAA levels ( $p=0.035$ ), and among subjects with active mucocutaneous involvement compared with other patients ( $p=0.036$ ). No correlations were identified between IgD serum levels and disease activity assessed by the BD current activity form (BDCAF) ( $p=0.640$ ). No differences were observed in the IgD serum levels between patients with and without specific disease manifestations. Increased SAA levels (Odds Ratio = 3.978, CI: 1.356 -11.676) and active mucocutaneous BD manifestations (Odds Ratio = 4.286, CI: 1.192 - 15.407) were associated with a high risk for increased IgD serum levels.

**CONCLUSIONS:** Serum IgD levels are significantly increased in BD patients, especially among patients with active mucocutaneous manifestations, suggesting a possible role of IgD in BD pathogenesis and in the onset of mucosal and skin lesions.

PMID: 30582507

14. Clin Exp Rheumatol. 2018 Nov-Dec;36 Suppl 115(6):150. Epub 2018 Nov 28.

Chronic non-bacterial osteomyelitis coexistent with familial Mediterranean fever.

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PMID: 30582506

15. Clin Exp Rheumatol. 2018 Nov-Dec;36 Suppl 115(6):151. Epub 2018 Dec 14.

Concurrent chronic recurrent multifocal osteomyelitis and familial Mediterranean fever. A case report.

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PMID: 30582505

16. Clin Exp Rheumatol. 2018 Nov-Dec;36 Suppl 115(6):68-73. Epub 2018 Dec 12.

Epidemiological profile of non-infectious uveitis from the rheumatologist's perspective: a survey from two tertiary referral centres in Italy.

Lopalco G(1), Venerito V(1), Sota J(2), Rigante D(3), Guerriero S(4), Orlando I(2), Franceschini R(5), Favale R(4), Lapadula G(1), Castelli B(3), Frediani B(2), Galeazzi M(2), La Torre F(6), Iannone F(1), Tosi GM(5), Fabiani C(7), Cantarini L(8).

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**OBJECTIVES:** To describe the epidemiology of non-infectious uveitis (NIU) in two tertiary referral rheumatology units in Central and Southern Italy.

**METHODS:** Two hundred and seventy-eight consecutive NIU patients (417 eyes) evaluated between January 2016 and January 2017 were enrolled. Collected data were analysed in accordance with the primary anatomic site of inflammation, clinical course, and laterality.

**RESULTS:** The mean age at NIU onset was  $36.92 \pm 18.30$  years with a female-to-male ratio of 1.34:1. Anterior uveitis (AU) was identified in 151 (54.32%), posterior uveitis (PU) in 67 (24.10%), intermediate uveitis (IU) in 5.40% and panuveitis (PanU) in 16.19% patients. Bilateral involvement was identified in 50% of our cohort. Uveitis was acute in 33.81% of patients, while 24.46% and 41.73% had a chronic and recurrent course, respectively. Gender and laterality did not influence the anatomical pattern, while disease course was significantly more acute or chronic in AU ( $p < 0.05$ ) and chronic in IU ( $p < 0.05$ ). An associated systemic disease was identified in 116 patients (41.73%). Twenty-seven patients (9.7%) had a specific isolated eye disease, 135 patients (48.56%) had idiopathic NIU. Uveitis associated with a systemic disease was significantly bilateral ( $p = 0.01$ ) and acute or chronic ( $p < 0.0001$ ), while the isolated form showed an association with chronic course ( $p < 0.0001$ ) and unilaterality ( $p = 0.01$ ).

**CONCLUSIONS:** The most common anatomic pattern of NIU has been AU, followed by PU, PanU and IU. A systemic disease (mainly Behçet's disease, ankylosing spondylitis and juvenile idiopathic arthritis) has been recognised in a fair proportion of the entire cohort. The rheumatologist should remain a central professional figure in the multidisciplinary team dealing with intraocular inflammation on a daily basis.

17. Indian J Ophthalmol. 2019 Jan;67(1):165-167. doi: 10.4103/ijo.IJO\_671\_18.

Familial Blau syndrome: First molecularly confirmed report from India.

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Blau syndrome (BS) is a rare autoinflammatory disorder characterized by the clinical triad of arthritis, uveitis, and dermatitis due to heterozygous gain-of-function mutations in the NOD2 gene. BS can mimic juvenile idiopathic arthritis (JIA)-associated uveitis, rheumatoid arthritis, and ocular tuberculosis. We report a family comprising a mother and her two children, all presenting with uveitis and arthritis. A NOD2 mutation was confirmed in all the three patients - the first such molecularly proven case report of familial BS from India.

DOI: 10.4103/ijo.IJO\_671\_18

PMID: 30574935

Conflict of interest statement: None

18. J Clin Immunol. 2018 Dec 20. doi: 10.1007/s10875-018-0572-1. [Epub ahead of print]

DDX58 and Classic Singleton-Merten Syndrome.

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**PURPOSE:** Singleton-Merten syndrome manifests as dental dysplasia, glaucoma, psoriasis, aortic calcification, and skeletal abnormalities including tendon rupture and arthropathy. Pathogenic variants in *IFIH1* have previously been associated with the classic Singleton-Merten syndrome, while variants in *DDX58* has been described in association with a milder phenotype, which is suggested to have a better prognosis. We studied a family with severe, "classic" Singleton-Merten syndrome.

**METHODS:** We undertook clinical phenotyping, next-generation sequencing, and functional studies of type I interferon production in patient whole blood and assessed the type I interferon promoter activity in HEK293 cells transfected with wild-type or mutant *DDX58* stimulated with Poly I:C.

RESULTS: We demonstrate a DDX58 autosomal dominant gain-of-function mutation, with constitutive upregulation of type I interferon.

CONCLUSIONS: DDX58 mutations may be associated with the classic features of Singleton-Merten syndrome including dental dysplasia, tendon rupture, and severe cardiac sequela.

DOI: 10.1007/s10875-018-0572-1

PMID: 30574673

19. *Pediatr Rheumatol Online J*. 2018 Dec 20;16(1):81. doi: 10.1186/s12969-018-0300-7.

Living with autoinflammatory diseases: identifying unmet needs of children, adolescents and adults.

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BACKGROUND: Autoinflammatory diseases (AIDs) illnesses of the innate immunity resulting in clinical signs and symptoms of systemic inflammation and loss of organ functions. While pathophysiological mechanisms are heavily studied and increasingly well understood, psychosocial needs are much less explored. The disease impact on the everyday life of patients including school and work is poorly studied. The purpose of the study was to identify the spectrum of unmet needs of children, adolescents and adults living with autoinflammatory disease and their families, to define key unmet needs and strategies and to develop and

evaluate a pilot intervention addressing the unmet need "school".

**METHODS:** A single-center, mixed-method study of AID patients and their families was conducted. Consecutive patients ages  $\geq 4$  years and their families were included. Expert consulting, focus groups and questionnaires explored the patient perspective of "unmet needs in AID". Quantitative and qualitative content analyses were performed and informed the development of a framework of unmet needs. A targeted pilot multimodular intervention for the unmet need "school" was developed and tested. Health-related Quality of Life (HRQoL) was evaluated using DISABKIDS-questionnaires and psychosocial impact evaluations.

**RESULTS:** The study included 83 patients and their families. These were 14 children, 9 adolescents and 25 adults with AID and 35 family members; patients' median age was 19 years (5-78). Expert consultations: 110 AID patients with 320 visits/year; 99 (90%) were children and adolescents. 78 patients and family members (94%) participated in 10 groups. Qualitative content analysis delineated 9 domains of unmet needs, the most relevant being school, health care system and public institutions. The pilot intervention "school" included 18 participants; median age was 9 years (7-16). HRQoL improved with the intervention including "understanding" by 53%, however improvement was not sustained over time.

**CONCLUSION:** Unmet needs of AID patients and families affect all areas of life. Accessible networks increasing knowledge and empowering patients, strategies supporting academic and workplace environments to ensure successful participation and integrated concepts addressing psychosocial needs are urgently needed.

DOI: 10.1186/s12969-018-0300-7

PMCID: PMC6302479

PMID: 30572912

20. Medicine (Baltimore). 2018 Dec;97(51):e13805. doi: 10.1097/MD.00000000000013805.

Antineutrophil cytoplasmic antibody-positive familial Mediterranean fever and hyperthyroidism: A case report.

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**RATIONALE:** Familial Mediterranean fever (FMF) is a genetic autoinflammatory disorder characterized by serositis and recurrent fever. Previous reports identified patients with antineutrophil cytoplasmic antibody (ANCA)-positive FMF, but vasculitis symptoms were not reported.

**PATIENT CONCERNS:** We report the case of a 44-year-old man with numbness. He had a history of 3 episodes of pleurisy and was being treated with propylthiouracil for hyperthyroidism. Because he was ANCA-positive, we suspected drug-induced ANCA-associated vasculitis and propylthiouracil was discontinued. However, his numbness was not ameliorated, and he again developed high fever with pleurisy.

**DIAGNOSIS:** Diagnosis of FMF was finally made, and genetic analysis revealed compound heterozygous mutations in exon 2 of the familial Mediterranean fever gene (L110P/E148Q).

**INTERVENTIONS:** The patient was treated with 0.5 mg/day of colchicine.

**OUTCOMES:** His numbness improved, and fever has not recurred.

**LESSONS:** Appearance of ANCA and development of vasculitis should be considered in a clinical course of FMF with hyperthyroidism.

DOI: 10.1097/MD.00000000000013805

PMID: 30572542 [Indexed for MEDLINE]

21. Intern Med. 2018 Dec 18. doi: 10.2169/internalmedicine.1401-18. [Epub ahead of print]

A Rare Case of Cryopyrin-associated Periodic Syndrome in an Elderly Woman with NLRP3 and MEFV Mutations.

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We herein report a case of a 75-year-old woman who presented with a low -grade fever, repeated cold-induced urticaria, and painful leg edemas with neutrocytosis. Because her mother also had cold-induced urticaria and her skin lesions histologically showed neutrophilic dermatitis, we suspected that she had familial cold autoinflammatory syndrome, a subtype of cryopyrin-associated periodic syndromes. Sequencing of the NLRP3 and MEFV genes revealed that she carried both the p.A439V missense mutation and p.E148Q homozygous mutation, which is commonly detected in familial Mediterranean fever patients. The administration of colchicine reduced the frequency and severity of her skin rash and leg edema.

DOI: 10.2169/internalmedicine.1401-18

PMID: 30568124

22. Cell Rep. 2018 Dec 18;25(12):3405-3421.e7. doi: 10.1016/j.celrep.2018.11.097.

The Cyclopeptide Astin C Specifically Inhibits the Innate Immune CDN Sensor STING.

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cGAS-STING signaling is essential for innate immunity. Its misregulation promotes cancer or autoimmune and autoinflammatory diseases, and it is imperative to identify effective lead compounds that specifically downregulate the pathway. We

report here that astin C, a cyclopeptide isolated from the medicinal plant *Aster tataricus*, inhibits cGAS-STING signaling and the innate inflammatory responses triggered by cytosolic DNAs. Moreover, mice treated with astin C are more susceptible to HSV-1 infection. Consistently, astin C markedly attenuates the autoinflammatory responses in *Trex1*<sup>-/-</sup> BMDM cells and in *Trex1*<sup>-/-</sup> mouse autoimmune disease model. Mechanistically, astin C specifically blocks the recruitment of IRF3 onto the STING signalosome. Collectively, this study characterizes a STING-specific small-molecular inhibitor that may be applied for potentially manipulating the STING-mediated clinical diseases.

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DOI: 10.1016/j.celrep.2018.11.097

PMID: 30566866

23. J Dermatol. 2018 Dec 18. doi: 10.1111/1346-8138.14722. [Epub ahead of print]

Hidradenitis suppurativa of the nape: Description of an atypical phenotype related to severe early-onset disease in men.

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Some patients with hidradenitis suppurativa (HS) develop severe inflammatory lesions of the nape. Through a single-center, cross-sectional study with a total of 377 patients, we sought to compare patients with and without nape involvement, to determine whether disease severity is greater in these patients and to describe their clinical characteristics. Thirty patients (90% male) were identified as having nape involvement. Patients with versus without nape involvement had greater disease severity, earlier disease onset, a family history of HS, lower body mass, and higher Dermatological Life Quality Index and pain scores. Amongst them, involvement of the trunk and gluteal regions predominated. A significant univariate relationship existed between patients with nape involvement and male sex, early disease onset, family history, scalp and gluteal involvement, Canoui-Poitaine phenotypes II and III, and Dowling-Degos disease. A

significant multivariate relationship existed with early disease onset, Dowling-Degos disease, and phenotypes II and III.

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DOI: 10.1111/1346-8138.14722

PMID: 30561771

24. Front Pediatr. 2018 Dec 3;6:377. doi: 10.3389/fped.2018.00377. eCollection 2018.

Vasculitis in Systemic Autoinflammatory Diseases.

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Autoinflammatory diseases (AID) are diseases of the innate immune system, characterized by recurrent episodes of localized or systemic inflammation. Vasculitis may accompany AID. The causes of the association of vasculitis with monogenic AID are still debated. Among the monogenic AID, Familial Mediterranean Fever (FMF) is the most common. IgA-related vasculitis (IgAV) and Polyarteritis Nodosa (PAN) involving small and/or medium-sized vessels have an increased frequency among FMF patients. There are also case reports revealing vasculitic features in Cryopyrin-Associated Periodic Fever Syndrome (CAPS), Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS), Mevalonate Kinase Deficiency (MKD), also known as Hyper IgD syndrome (HIDS), Deficiency of IL-1 Receptor Antagonist (DIRA) and Pyogenic Arthritis, Pyoderma gangrenosum, and Acne (PAPA) patients. Central nervous system vasculitis and vasculopathy have been reported in DIRA and PAPA patients whereas small vessel involvement affecting skin has been reported in CAPS, TRAPS, and MKD patients. Alternatively, vasculitis can also be a leading feature especially in the recently defined monogenic AID (Otolipenia, Deficiency of Adenosine Deaminase 2-DADA2, Haploinsufficiency of A20) and interferonopathies (STING-associated vasculopathy with onset in infancy-SAVI). DADA2 often presents as a PAN-like disease. In

otulipenia, patients have painful subcutaneous nodules caused by septal panniculitis with small and medium vessel vasculitis. Haploinsufficiency of A20 (also called Familial Behcet-like Autoinflammatory Syndrome) results in a phenotype very similar to the variable vessel vasculitis of Behcet's disease with recurrent oral-genital ulcers, in addition to, skin rash, uveitis, and polyarthritis. SAVI is an autoinflammatory vasculopathy with increased Interferon (IFN) signature, causing severe skin lesions resulting in ulceration, necrosis, and in some cases, amputation. Behcet's Disease (BD) is a multifactorial polygenic AID characterized by recurrent attacks of oral-genital ulcers, skin lesions, uveitis and a unique vasculitis affecting both arteries and veins of all sizes. Many clinical features overlap with other autoinflammatory diseases and overexpression of proinflammatory cytokines is an important feature of the disease.

DOI: 10.3389/fped.2018.00377

PMCID: PMC6287042

PMID: 30560109

25. Clin Exp Rheumatol. 2018 Nov 16. [Epub ahead of print]

Radiologist-rheumatologist multidisciplinary approach in the management of axial spondyloarthritis: a Delphi consensus statement.

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**OBJECTIVES:** The aim of this study was to develop a Delphi consensus statement between rheumatologists and radiologists for the diagnosis and monitoring of axial spondyloarthritis (axial-SpA).

**METHODS:** Following an extensive literature search to identify unmet needs and potential goals for a multidisciplinary approach, a scientific board comprising 28 Italian hospital-based rheumatologists (n=19) and radiologists (n=9) identified 8 "starting points", resulting in the development of 23 consensus statements covering issues from current practice guidelines to specific MRI protocols for the assessment of axial-SpA. Each participant anonymously expressed a level of agreement for each statement using a 5-point Likert scale (1="strongly disagree"; 5="strongly agree") via an online Delphi method. Total cumulative agreement (TCA) was defined as the sum of the percentage of response to items 4 ("agree") and 5 ("absolutely agree"). Consensus was defined as  $\geq 80\%$  total cumulative agreement for each statement.

**RESULTS:** After the first round of voting (28 participants), positive consensus was reached for 28/31 (90.3%) statements. Statements without consensus (n=3) were discussed in a face-to-face plenary session prior to the second vote (28 participants). After the second round voting, positive consensus was attained for all 31 statements, with mean final TCA of 95.5% (range 82.1-100%).

**CONCLUSIONS:** This Delphi consensus statement provides an aid to rheumatologists and radiologists for the diagnosis and monitoring of axial-SpA.

PMID: 30557127

26. Ocul Immunol Inflamm. 2018 Dec 17:1-9. doi: 10.1080/09273948.2018.1552305. [Epub ahead of print]

Ocular Involvement in Muckle-Wells Syndrome.

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**PURPOSE:** To present the ocular findings of the members of a family that has the diagnosis of Muckle Wells syndrome, a form of cryopyrin associated periodic syndrome (CAPS).

**MATERIALS AND METHODS:** Nine patients with MWS were included in this study. Each study participant underwent a systemic evaluation, comprehensive ophthalmic examination, and auxillary testings.

**RESULTS:** In this study, conjunctivitis was the most prominent ocular finding. Other relatively common ocular findings included band keratopathy, clinical signs of past uveitis, and corneal topography abnormalities. Nystagmus, corneal leukoma, and optic nerve pallor with epiretinal membrane were also detected. Rare ocular manifestations were posterior stromal corneal opacification with edema, anterior iris synechia, and mild cataract.

**CONCLUSION:** MWS is a rare systemic autoinflammatory disorder that presents with a variety of ocular findings. Exacerbation of systemic and ocular findings with cold is a hallmark of the disease.

DOI: 10.1080/09273948.2018.1552305

PMID: 30556770

27. Mod Rheumatol. 2018 Dec 17:1-13. doi: 10.1080/14397595.2018.1559488. [Epub ahead of print]

Long-Term Effectiveness and Safety of Canakinumab in Pediatric Familial Mediterranean fever patients.

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**BACKGROUND:** Little is known about the long-term efficacy and safety of canakinumab in paediatric FMF patients.

**AIM:** To present the single centre experience of colchicine-resistant paediatric-onset FMF patients who were treated with canakinumab by off-label use since 2012.

**METHODS:** The hospital files of 15 children who used canakinumab were retrospectively evaluated. Clinical and laboratory data of each visit were recorded. Drug-related adverse events were recorded. Complete remission was described as no attacks and normal acute phase reactants; partial remission was defined as decrease in severity and rate of attacks and/or elevated acute phase reactants with anti-IL-1 treatment.

**RESULTS:** The average duration of canakinumab use was 23.9 months (min:12 max:58 months). Twelve patients were M694V homozygotes. Eleven patients achieved complete remission after the first dose at 2 months and 12 patients at 6 months. Canakinumab interval was shortened in 2 patients from 150 mg/8 weeks to 150 mg/4 weeks. Except one, 14 patients achieved complete remission by 12 months. Two patients had mild urinary tract infections. One patient had bronchopneumonia requiring hospitalization. Two patients had teeth abscess. There were no serious adverse events such as opportunistic infections, malignancies, or deaths. Besides, no significant laboratory abnormalities occurred in complete blood count parameters, liver and kidney function tests.

**CONCLUSION:** To the best of our knowledge, this is the longest outcome study about canakinumab use in paediatric FMF patients. This study suggested that canakinumab is safe and effective in children with FMF in the long-term.

DOI: 10.1080/14397595.2018.1559488

PMID: 30556769

28. Fish Shellfish Immunol. 2018 Dec 13;86:764-771. doi: 10.1016/j.fsi.2018.12.025.  
[Epub ahead of print]

Effects of high-soy diet on S100 gene expression in liver and intestine of rainbow trout (*Oncorhynchus mykiss*).

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The current study examines expression of S100 genes, a group of calcium-sensing proteins poorly characterized in fishes. In mammals, these proteins are known to play roles beyond calcium-signaling, including mediation of inflammatory processes. Some S100 proteins also serve as biomarkers for a variety of autoinflammatory conditions. It is well known that salmonids exhibit varying degrees of intestinal enteritis when exposed to alternative feed ingredients containing antinutritional factors, with soybean meal (SBM) being one of the best characterized. The etiology of soy-caused distal enteritis isn't entirely understood but displays similar histopathological alterations to the gut observed in human mucosal inflammatory bowel diseases. We sought to determine if teleost S100 genes show a concomitant response like that observed in mammals, utilizing rainbow trout fed high-soy diets as a model for intestinal inflammation. We examined expression of fourteen known salmonid S100 genes in the liver, first segment of the mid-intestine (proximal intestine), and second segment of the mid-intestine (distal intestine). After 12 weeks on a high-soy diet containing 40% SBM, we observed upregulation of several S100 genes in the distal intestine (S100I2, A10a, V1, V2, and W), no changes in the proximal intestine, and downregulation of S100V2 in the liver. Overall, our results provide further knowledge of the expression of S100 genes and provide targets for future research regarding inflammatory processes in the rainbow trout gut.

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DOI: 10.1016/j.fsi.2018.12.025

PMID: 30553891

29. *Pediatr Nephrol*. 2018 Dec 14. doi: 10.1007/s00467-018-4155-4. [Epub ahead of print]

What's new in autoinflammation?

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The pathogenesis of autoinflammatory diseases has shed light on the concept of inflammation in general and on our understanding of the role of the innate immune system. The autoinflammatory diseases have a large spectrum with varying features of inflammation. The most common autoinflammatory diseases are those associated with periodic fevers. The delay in diagnosis of these four common diseases (familial Mediterranean fever, cryopyrin-associated periodic fever syndrome, mevalonate kinase deficiency, and TNF receptor-associated periodic fever syndrome) results in secondary amyloidosis of the kidney. The new work towards classification criteria for these diseases is presented. Recently a group of autoinflammatory diseases that are associated with vasculitis have also been identified. These are stimulators of interferon genes (STING)-associated vasculopathy of infancy (SAVI), which is a monogenic defect associated with excessive activity in interferon alpha and deficiency of adenosine deaminase 2, which is characterized by a polyarteritis nodosa-like picture. These monogenic diseases are now in our differential diagnosis of vasculitides. Secondary amyloidosis is a complication of autoinflammatory diseases. Understanding the inflammatory mechanisms in these diseases has led to the use of targeted biologics for this complication. It is hoped that enlightening the mechanisms underlying these monogenic autoinflammatory diseases will also teach us about the pathways in common diseases.

DOI: 10.1007/s00467-018-4155-4  
PMID: 30552566

30. *Pediatr Rheumatol Online J.* 2018 Dec 14;16(1):79. doi: 10.1186/s12969-018-0296-z.

Off-label use of tocilizumab to treat non-juvenile idiopathic arthritis in pediatric rheumatic patients: a literature review.

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Tocilizumab, an anti-interleukin-6 (IL-6) agent, is indicated as a treatment for several autoimmune or inflammatory diseases, including rheumatoid arthritis and juvenile idiopathic arthritis (JIA). IL-6 plays roles in both immune system dysregulation and inflammation, and thus efforts to extend the utility of tocilizumab in patients with autoinflammatory conditions are ongoing. Here, we survey the literature on the off-label use of tocilizumab in patients with juvenile-onset rheumatic diseases including juvenile systemic lupus erythematosus (SLE), juvenile dermatomyositis (DM), vasculitis, juvenile scleroderma, and other autoinflammatory diseases. There is no real evidence that tocilizumab is useful for patients with SLE and juvenile DM, but several cases of childhood Takayasu arteritis have experienced promising outcomes. In juvenile-onset scleroderma, for which no therapy that can halt disease progression is available, tocilizumab may stop progression and the associated functional impairment. Tocilizumab prevents systemic inflammation in patients with Kawasaki's disease, but may develop coronary aneurysms. Tocilizumab has been used to treat several pediatric autoinflammatory diseases, including JIA-associated uveitis and Castleman's disease. Further work in larger populations is necessary to confirm the effects of tocilizumab in patients with pediatric rheumatic diseases.

DOI: 10.1186/s12969-018-0296-z

PMCID: PMC6295005

PMID: 30547812

31. *Pediatr Rheumatol Online J*. 2018 Dec 14;16(1):78. doi: 10.1186/s12969-018-0294-1.

Disease burden and social impact of pediatric chronic nonbacterial osteomyelitis from the patient and family perspective.

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**BACKGROUND:** Chronic nonbacterial osteomyelitis (CNO) is an autoinflammatory bone disorder that if left untreated can result in bone destruction and severe continuing pain due to persistent inflammation. The impact this chronic disease has on the daily lives of affected children and their families is not well known.

The purpose of this study is to understand the disease burden and socioeconomic and psychological impact of CNO from the patients' and families' perspectives and identify areas of improvement for patient care and reduced disease burden based on patients' and families' responses.

**METHODS:** Participants were invited through a social media platform group and at clinic visits at Stanford Children's Health. An online survey was administered to patients with a diagnosis of CNO made at < 22 years of age and/or the parent/guardian of a patient with CNO diagnosis made at < 22 years of age.

**RESULTS:** There was a total of 284 survey participants. The median age at CNO diagnosis was 10 years (range 2-22+). Median time from first CNO symptom to diagnosis was 2 years. Antibiotics were used in 35% of patients prior to CNO diagnosis; of these, 24% received antibiotics for greater than 6 months. Between 25 and 61% reported a negative effect of CNO on relationships, school/work performance, or finances; and 19-50% reported effects on psychosocial well-being. The majority agreed patients' performance with daily tasks and hobbies was challenged by pain, fatigue and physical limitation related to CNO.

**CONCLUSIONS:** Patients with CNO experienced on average a 2-year delay in diagnosis and receiving effective treatments. At least 25% reported problems with relationships, school, work, finances and well-being due to CNO. Recognition of these challenges emphasizes the need to increase awareness of this disease and address the socioeconomic stressors and mental health issues in order to provide optimal care of children with CNO.

DOI: 10.1186/s12969-018-0294-1

PMCID: PMC6295016

PMID: 30547806

Sep 24.

Atypical type of familial Mediterranean fever: An underdiagnosed cause of chronic aseptic meningitis.

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We report an atypical case of familial Mediterranean fever (FMF) concomitant with chronic aseptic meningitis. The patient experienced fever, abdominal and back pain because of serositis, and headache because of aseptic meningitis for 4 weeks. Blood examinations revealed increased white blood cells and serum amyloid A level. Medications, including steroids, did not improve his symptoms. However, the patient experienced immediate relief after the administration of colchicine. We diagnosed him as having atypical FMF based on the symptoms, especially positive response to colchicine, and heterozygous mutations on exon2 and 5 (E148Q/S503C) in MEFV gene. Unlike typical FMF, a cause of recurrent aseptic meningitis, atypical FMF might be an underdiagnosed cause of chronic aseptic meningitis.

DOI: 10.1111/ncn3.12232

PMCID: PMC6282518

PMID: 30546872

33. Hum Mol Genet. 2018 Dec 12. doi: 10.1093/hmg/ddy425. [Epub ahead of print]

A robust pipeline with high replication rate for detection of somatic variants in the adaptive immune system as a source of common genetic variation in autoimmune disease.

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The role of somatic variants in diseases beyond cancer is increasingly being recognized, with potential roles in autoinflammatory and autoimmune diseases. However, as mutation rates and allele fractions are lower, studies in these diseases are substantially less tolerant of false positives and bio-informatics algorithms require high replication rates. We developed a pipeline combining two variant callers, MuTect2 and VarScan2, with technical filtering and prioritization. Our pipeline detects somatic variants with allele fractions as low as 0.5% and achieves a replication rate >55%. Validation in an independent dataset demonstrates excellent performance (sensitivity >57%, specificity >98%, replication rate >80%). We applied this pipeline to the autoimmune disease multiple sclerosis (MS) as a proof-of-principle. We demonstrate that 60% of MS patients carry 2-10 exonic somatic variants in their peripheral blood T and B cells, with the vast majority (80%) occurring in T cells and variants persisting over time. Synonymous variants significantly co-occur with nonsynonymous variants. Systematic characterization indicates somatic variants are enriched for being novel or very rare in public databases of germline variants and trend towards being more damaging and conserved, as reflected by higher CADD and GERP scores. Our pipeline and proof-of-principle now warrant further investigation of common somatic genetic variation on top of inherited genetic variation in the context of autoimmune disease, where it may offer subtle survival advantages to immune cells and contribute to the capacity of these cells to participate in the autoimmune reaction.



PMID: 30541027

34. Klin Padiatr. 2018 Dec 11. doi: 10.1055/a-0802-8950. [Epub ahead of print]

Case Report: Unexpected Benefit of Echocardiography in Childhood Polyarteritis Nodosa.

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DOI: 10.1055/a-0802-8950

PMID: 30537767

Conflict of interest statement: Disclosure The authors report no conflicts of interest in this work.

35. Exp Suppl. 2018;108:321-341. doi: 10.1007/978-3-319-89390-7\_14.

Genetics of Inflammasomes.

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Mutations in inflammasome genes are responsible for rare monogenic and polygenic autoinflammatory diseases. On the other side, genetic polymorphisms in the same molecules contribute to the development of common multifactorial diseases (i.e., autoimmune diseases, cardiovascular pathologies, cancer). In this chapter we depicted the current knowledge about inflammasome genetics.

DOI: 10.1007/978-3-319-89390-7\_14

PMID: 30536178

36. Clin Rheumatol. 2018 Dec 10. doi: 10.1007/s10067-018-4384-8. [Epub ahead of print]

Effect of interleukin-1 antagonists on the quality of life in familial Mediterranean fever patients.

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BACKGROUND: Familial Mediterranean fever (FMF) patients suffer from chronic

complications of disease such as AA amyloidosis, chronic arthritis, and spondylitis. Reduced quality of life (QoL) is a feature of chronic diseases but it is also impaired in patients with FMF. Despite the regular use of colchicine at a maximal dose, about 10% of patients do not respond well or resistant to colchicine (crFMF). IL-1 inhibitors have been shown to be effective in controlling attacks in crFMF patients. Herein, we aimed to investigate QoL changes of crFMF patients with IL-1 inhibitors.

**METHODS:** All patients were prospectively monitored for the frequency, duration, severity of attacks, patient global assessments (Visual Analog Scale; VAS), and laboratory features. Either anakinra or canakinumab was used as IL-1 antagonist treatments. Demographic information, MEFV gene mutations, attack characteristics, and previous treatments were registered. Short form-36 (SF-36) quality of life scale was implemented by the interviewer for evaluating the QoL before and 3 months after the treatment.

**RESULTS:** A total of 44 patients were included in this study. Striking improvements were detected in frequency, duration, and VAS severity of attacks ( $p < 0.001$ ). In the comparison of pre- and post-treatment, SF-36 sub-components significant improvements were observed on physical function, role limitation due to physical difficulty, role limitation due to emotional problem, energy, emotional well-being, social function, pain, general health, and health change.

**CONCLUSIONS:** In conclusion, IL-1 antagonists prevent attacks and improve QoL of crFMF.

DOI: 10.1007/s10067-018-4384-8

PMID: 30535829

37. Rheumatology (Oxford). 2018 Dec 7. doi: 10.1093/rheumatology/key384. [Epub ahead of print]

Tofacitinib for familial Mediterranean fever: a new alternative therapy?

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DOI: 10.1093/rheumatology/key384

PMID: 30535114

38. Reumatol Clin. 2018 Dec 4. pii: S1699-258X(18)30196-7. doi: 10.1016/j.reuma.2018.09.001. [Epub ahead of print]

AA amyloidosis associated with morbid obesity (clinical case).

[Article in English, Spanish]

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We present the case of a 45-year-old woman who was hospitalized due to severe macrocytic anemia and renal failure. The patient presented a morbid obesity. The immunological study showed anti-ENA anti-SSA (Ro52) positive, with negative antinuclear antibodies. Also in the proteinogram (serum immunofixation) the presence of monoclonal bands IgG lambda and IgG kappa, monoclonal component 7.2% (4.68g/L), with elevation of free light chains (kappa 95.94mg/L (3.3-19.4), evidenced, lambda 145.17mg/L (5.71-26.3)). The bone marrow study showed an infiltration of 5% of plasma cells and positive for AA amyloid. Finally, a percutaneous renal biopsy was performed, which again showed amyloid infiltration. In the genetic study, 2 mutations of the family Mediterranean fever gene (MEFV) have been identified. Secondary AA amyloidosis has been described associated with obesity, in addition to a percentage of cases of unknown etiology.

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DOI: 10.1016/j.reuma.2018.09.001  
PMID: 30527964

39. Best Pract Res Clin Rheumatol. 2018 Apr;32(2):261-270. doi:  
10.1016/j.berh.2018.08.010. Epub 2018 Sep 21.

Update on the epidemiology, risk factors and disease outcomes of Behçet's disease.

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Behçet's disease (BD) may be regarded as a polygenic autoinflammatory disease although adaptive immune system has also been implicated in pathogenesis. Different classification criteria sets exist for BD, including the new "International Criteria for BD." The pooled prevalence of BD was calculated as 10.3 per 100,000 population globally. BD is common along the Silk Road, including Turkey. Male sex and early onset are associated with a more severe disease course. For the follow-up of BD, there are five disease activity scales, one disease severity scale, and one QOL scale.

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DOI: 10.1016/j.berh.2018.08.010  
PMID: 30527431

40. Best Pract Res Clin Rheumatol. 2018 Apr;32(2):254-260. doi:  
10.1016/j.berh.2018.09.003. Epub 2018 Sep 29.

Update on the epidemiology and disease outcome of Familial Mediterranean fever.

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Autoinflammatory diseases (AIDs) are diseases of the innate immune system, with clinical and laboratory evidence of attacks of inflammation. The more common AIDs are those associated with periodic fevers: Familial Mediterranean fever (FMF); Mevalonate Kinase Deficiency (MKD)/Hyperimmunoglobulin D Syndrome (HIDS); Cryopyrin-associated Autoinflammatory Syndrome (CAPS); and Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS). Classification criteria have been developed for all these types. FMF is the most common AID worldwide with a particularly high prevalence in the Eastern Mediterranean region. Environmental factors are thought to affect the course of the disease. Outcome measures are being developed for AIDs.

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DOI: 10.1016/j.berh.2018.09.003

PMID: 30527430

41. Arthritis Res Ther. 2018 Dec 10;20(1):274. doi: 10.1186/s13075-018-1766-x.

Juvenile onset autoinflammatory disease due to a novel mutation in TNFAIP3 (A20).

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DOI: 10.1186/s13075-018-1766-x

PMCID: PMC6288856

PMID: 30526650

42. *Pediatr Rheumatol Online J.* 2018 Dec 7;16(1):77. doi: 10.1186/s12969-018-0289-y.

Educational initiatives and training for paediatric rheumatology in Europe.

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The Paediatric Rheumatology European Society (PReS) has over many years, developed a portfolio of educational activities to address increasing educational needs of workforce and support young clinicians to acquire skills to develop new knowledge and deliver clinical care in the future. These educational activities aim to facilitate growth of paediatric rheumatology and ultimately improve the clinical care for children and families. This article describes the current portfolio of PReS educational activities and their relevance to the international paediatric rheumatology community.

DOI: 10.1186/s12969-018-0289-y

PMCID: PMC6286498

PMID: 30526605

43. Asian Pac J Allergy Immunol. 2018 Dec 9. doi: 10.12932/AP-150818-0394. [Epub ahead of print]

Schnitzler's syndrome: A female elderly case presenting intractable non-pruritic febrile urticarial rash.

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Schnitzler's syndrome is an acquired autoinflammatory disease characterized by chronic urticarial rash and monoclonal gammopathy (predominantly IgM type). A 75-year-old Japanese woman complained of high fever and non-pruritic urticarial rash appearing almost every day for 3 years. Her abnormal laboratory data



included leukocytosis and neutrophilia with elevated erythrocyte sedimentation rate and C-reactive protein level. Hyperglobulinemia of IgA and IgM was also noted. Histological analysis revealed perivascular and interstitial neutrophilic infiltration without any signs of vasculitis. Immunofixation analysis confirmed IgM-kappa-type monoclonal gammopathy. Oral prednisolone initially improved her symptoms, but recurrence was observed upon its tapering. The addition of colchicine successfully controlled her symptoms and allowed a reduction in the dose of systemic steroid.

DOI: 10.12932/AP-150818-0394

PMID: 30525744

44. Intern Emerg Med. 2018 Dec 5. doi: 10.1007/s11739-018-1997-5. [Epub ahead of print]

A possible still role for colchicine in children with idiopathic recurrent acute pericarditis?

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DOI: 10.1007/s11739-018-1997-5

PMID: 30519917

45. Iran J Allergy Asthma Immunol. 2018 Oct 20;17(5):464-474.

Evaluation of ERAP1 Gene Single Nucleotide Polymorphism in Impressing the Inflammatory Cytokine Profile of Ankylosing Spondylitis Patients.

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Ankylosing spondylitis (AS), an autoinflammatory disease, has been associated with impaired Endoplasmic reticulum aminopeptidase (ERAP) 1 activity, which is involved in priming antigenic peptides. The purpose of this study was to evaluate if the genetic variant of ERAP1 gene could impress the inflammation status of the AS patients. For genotyping, 140 AS cases and 140 healthy controls were enrolled. After isolation of peripheral blood mononuclear cells (PBMCs) and DNA extraction, all the subjects were genotyped for rs27044 polymorphism using SSP-PCR assay. Total RNA of PBMCs was isolated, cDNA was synthesized, and quantitative analyses of mRNA expression of cytokines were performed via Real-time PCR using the SYBR Green Gene Expression MasterMix. To measure the concentration of cytokines in serum of subjects, Enzyme-linked immunosorbent assay (ELISA) was used. It was observed that the G allele of rs27044 polymorphism was significantly prevalent in AS patients. Moreover, the GG genotype and the GG+GC dominant model had significantly different distribution between study groups. There was a significant overexpression of mRNAs of IL-17A, IL-6, IL-33, TNF- $\alpha$ , and IFN- $\gamma$ , while IL-10 was significantly downregulated in AS patients. The ELISA results were in line with that of the gene expression analysis. No significant differences in mRNA expression and concentration of cytokine were identified among AS patients with three genotypes for rs27044 SNP. This study replicated the association of polymorphisms in ERAP1 gene with the risk of AS in a population from Iranian. However, it did not directly determine the inflammatory profile of the AS patients.

PMID: 30518188

46. Rheumatol Int. 2018 Dec 1. doi: 10.1007/s00296-018-4211-1. [Epub ahead of print]

Advances in rheumatology practice in Brazil.

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Despite resilient inequities, Brazil has seen progressive improvement in health care in the last 25 years. Infectious diseases rendered place to chronic non-communicable diseases as a major cause of death. Existence of traditional schools of medicine and training services in rheumatology helped form a reasonable number of specialists, though irregular distribution due to the economic issues favoring their clustering in major cities. The Brazilian Society of Rheumatology provides continued medical education, helps training rheumatologists, family physicians and other health professionals and has worked to publish national recommendations for the diagnosis and treatment of major rheumatic diseases. Access to medications and health care facilities is provided for most patients, free of direct charge, including biologics. Specialized services for autoimmune and rare diseases, including pediatric rheumatology and autoinflammatory diseases, have improved, particularly in developed centers of the southern best developed parts of the country. A major unmet need is the lack of access to non-pharmacological treatment modalities. In this article, we will summarize some of the strengths and points that need improvement to enhance access to the rheumatological health care in Brazil.

DOI: 10.1007/s00296-018-4211-1

PMID: 30506466

47. Eur J Rheumatol. 2018 Dec;5(4):230-234. doi: 10.5152/eurjrheum.2018.18036. Epub 2018 Oct 12.

IL1-blocking therapy in colchicine-resistant familial Mediterranean fever.

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**OBJECTIVE:** Approximately 10%-20% of patients with familial Mediterranean fever (FMF) show an inadequate response to colchicine. In our cohort study, patients with FMF with or without amyloidosis and with an inadequate response to colchicine were treated with anakinra or canakinumab.

**METHODS:** Clinical and laboratory parameters, Mediterranean fever (MEFV) mutations, and patient-reported outcomes were analyzed in 31 patients treated with anakinra or canakinumab.

**RESULTS:** In a cohort of 250 adult patients with FMF, 31 patients were treated with anakinra (n=29) or canakinumab (n=2). The median Pras FMF severity score was 8 (range, 5-14) and correlated with the presence of high-penetrance MEFV mutations (p.Met-694-Val or p.Met-680-Ile). The FMF severity score was 11 in patients with two high-penetrance MEFV mutations (68%), 9 in those with a single high-penetrance MEFV mutation (19%), and 7.5 in those without high-penetrance MEFV mutations (13%, p=0.2). FMF-related amyloid A amyloidosis was diagnosed in 12 (39%) patients. Anakinra was used daily in 20 patients, thrice a week in 7, and upon demand during attacks in 2. Two patients were treated with canakinumab. IL-1-blocking treatment showed a rapid (2±3 days) and persistent suppression of FMF symptoms and inflammatory parameters. The frequency of FMF attacks was significantly reduced (p<0.003). Both patient- and physician-reported FMF activity significantly improved (p<0.0001).

**CONCLUSION:** IL-1-blocking therapy was well tolerated over a median period of 2 years and reduced the frequency of FMF attacks in patients with colchicine-resistant FMF.

DOI: 10.5152/eurjrheum.2018.18036

PMCID: PMC6267760

PMID: 30501849

48. Turk Kardiyol Dern Ars. 2018 Dec;46(8):739-740.

Authors reply.

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Comment on

Turk Kardiyol Dern Ars. 2018 Dec;46(8):739.

Turk Kardiyol Dern Ars. 2018 Apr;46(3):184-190.

PMID: 30516539 [Indexed for MEDLINE]

49. Turk Kardiyol Dern Ars. 2018 Dec;46(8):739. doi: 10.5543/tkda.2018.44389.

Lipid disorders in Familial Mediterranean Fever patients: Is inflammation the only cause?

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Comment in

Turk Kardiyol Dern Ars. 2018 Dec;46(8):739-740.

Comment on

Turk Kardiyol Dern Ars. 2018 Apr;46(3):184-190.

PMID: 30516538 [Indexed for MEDLINE]

50. J Clin Med. 2018 Dec 1;7(12). pii: E504. doi: 10.3390/jcm7120504.

Sarcopenia in Patients with Rheumatic Diseases: Prevalence and Associated Risk

Factors.

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The prevalence of sarcopenia in rheumatic diseases has been evaluated in single diseases using various diagnostic approaches, generating conflicting data on the pathogenetic mechanism(s). Herein, we evaluated both muscle mass index (MMI) and muscle strength to assess sarcopenia and presarcopenia in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS). Moreover, we evaluated the possible impact of disease/patient-related characteristics, therapeutic regimens, and nutritional aspects on sarcopenia. The present study included 168 patients of both genders, aged 40–75 years. All patients underwent a nutritional evaluation, physical activity level assessment, rheumatologic evaluation, and an MMI and muscle strength assessment. The prevalence of sarcopenia was about 20% in all the three rheumatologic diseases,

whereas presarcopenia was significantly different in RA, PsA and AS ( $p = 0.006$ ). At multivariate analysis, only age  $\geq 60$  years and the presence of a disability were associated with a significantly increased risk of sarcopenia ( $p = 0.006$  and  $p = 0.01$ , respectively), while a higher C-reactive protein did not reach statistical significance. Sarcopenia is similar in RA, PsA and AS, whereas presarcopenia significantly differs in these three diseases. Disease activity/inflammation and nutritional aspects do not influence sarcopenia, while age  $\geq 60$  years and the presence of a disability significantly increase the risk of sarcopenia.

DOI: 10.3390/jcm7120504

PMCID: PMC6306844

PMID: 30513782

51. Turk J Pediatr. 2018;60(3):326-330. doi: 10.24953/turkjpmed.2018.03.016.

Polyarteritis nodosa in case of familial Mediterranean fever.

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Gökçe İ, Altuntaş Ü, Filinte D, Alpay H. Polyarteritis nodosa in case of familial Mediterranean fever. Turk J Pediatr 2018; 60: 326-330. Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent self-limited attacks of fever accompanied by peritonitis, pleuritis, and arthritis. Protracted febrile myalgia syndrome (PFMS) is a rare form of vasculitic disease which is an uncommon dramatic manifestation of FMF, characterized by severe crippling myalgia and high fever. Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis affecting medium or small arteries. It is rarely observed in children, but its incidence increases in the presence of FMF. In this article we described a 14-year-old child diagnosed with FMF associated with PAN. Physicians should be aware of this possible association.

DOI: 10.24953/turkjpmed.2018.03.016

PMID: 30511549

52. Nat Immunol. 2019 Jan;20(1):18-28. doi: 10.1038/s41590-018-0262-4. Epub 2018 Dec 3.

G3BP1 promotes DNA binding and activation of cGAS.

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Cyclic GMP-AMP synthase (cGAS) is a key sensor responsible for cytosolic DNA detection. Here we report that GTPase-activating protein SH3 domain-binding



protein 1 (G3BP1) is critical for DNA sensing and efficient activation of cGAS. G3BP1 enhanced DNA binding of cGAS by promoting the formation of large cGAS complexes. G3BP1 deficiency led to inefficient DNA binding by cGAS and inhibited cGAS-dependent interferon (IFN) production. The G3BP1 inhibitor epigallocatechin gallate (EGCG) disrupted existing G3BP1-cGAS complexes and inhibited DNA-triggered cGAS activation, thereby blocking DNA-induced IFN production both in vivo and in vitro. EGCG administration blunted self DNA-induced autoinflammatory responses in an Aicardi-Goutières syndrome (AGS) mouse model and reduced IFN-stimulated gene expression in cells from a patient with AGS. Thus, our study reveals that G3BP1 physically interacts with and primes cGAS for efficient activation. Furthermore, EGCG-mediated inhibition of G3BP1 provides a potential treatment for cGAS-related autoimmune diseases.

DOI: 10.1038/s41590-018-0262-4

PMID: 30510222

53. Eur J Rheumatol. 2018 Oct 12. doi: 10.5152/eurjrheum.2018.18115. [Epub ahead of print]

Exon 2: Is it the good police in familial mediterranean fever?

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**OBJECTIVE:** Familial Mediterranean fever (FMF) is the most common autoinflammatory disease. Most of the identified disease-causing mutations are located on exon 10. As the number of studies about the effect of the exonal location of the mutation and its phenotypic expression is limited, we aimed to investigate whether the exonic location of the Mediterranean fever (MEFV) mutation has an effect on the clinical manifestation in patients with FMF.

**METHODS:** Study population was derived from the main FMF registry that included 2246 patients from 15 different rheumatology clinics. We categorized the mutations according to their exon locations and retrieved the clinical and demographic information from the database.

**RESULTS:** Patients having the MEFV mutations on exon 2 or 10 (n:1526) were divided into three subgroups according to the location of the MEFV mutations: Group 1 (exon 2 mutations), Group 2 (exon 10 mutations), and Group 3 (both exon 2 and exon 10 mutations). Group 2 patients were of a significantly younger age at onset, and erysipiel-like erythema, arthritis, amyloidosis, and a family history

of FMF were more common in this group.

**CONCLUSION:** Patients with FMF and exon 10 mutations show more severe clinical symptoms and outcome. Exon 2 mutations tend to have a better outcome.

DOI: 10.5152/eurjrheum.2018.18115

PMID: 30489254

54. Br J Dermatol. 2018 Nov 29. doi: 10.1111/bjd.17466. [Epub ahead of print]

Association of Pyrin mutations and Autoinflammation with Complex Phenotype Hidradenitis Suppurativa: A Case Control Study.

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**BACKGROUND:** Hidradenitis suppurativa (HS) is a rare, debilitating neutrophilic dermatosis characterised by chronic inflammation of hair follicles. Many inflammatory conditions may accompany HS.

**AIM:** To investigate the association of variants of the MEFV gene with a complex HS phenotype.

**METHODS:** First, we identified the clinical characteristics of 119 HS patients with a complex phenotype (Hurley stage III disease and/or additional inflammatory symptoms). Then, we searched for MEFV variants among these patients. The odds ratios (OR) for pathogenic MEFV mutations were calculated using data from these HS patients and 191 healthy controls.

**RESULTS:** The male/female ratio was higher, and the mean age of onset was earlier,

in our complex HS group compared with HS patients in general. Five of the HS patients (4.2%) had a diagnosis of familial Mediterranean fever (FMF) with a standardized morbidity ratio of 45 (CI: 16.50-99.84,  $p<0.001$ ) when compared with the frequency of FMF in the general Turkish population. Of the patients with complex HS, 38% were positive for pathogenic variants of MEFV. The odds ratio for carrying a pathogenic MEFV allele was 2.80 (CI: 1.31-5.97,  $p<0.001$ ).

**CONCLUSION:** The frequency of MEFV mutations in a group of patients with complex HS was higher than that in healthy controls, suggesting that MEFV mutations may contribute to the pathogenesis of HS. Understanding the role of autoinflammation in HS is of fundamental importance for the development of novel therapies. This article is protected by copyright. All rights reserved.

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DOI: 10.1111/bjd.17466

PMID: 30488432

55. Clin Rheumatol. 2018 Nov 28. doi: 10.1007/s10067-018-4361-2. [Epub ahead of print]

Treatment options for periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome in children and adults: a narrative review.

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Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is the most frequent non-hereditary autoinflammatory disorder in childhood: Its onset is usually observed before 5 years, though reports regarding adulthood are increasing. The pathogenesis of the syndrome is not completely understood, but a multifactorial origin, probably based on a polygenic pattern of susceptibility, is the most probable rational pathogenetic hypothesis. Treatment of PFAPA syndrome relies on the administration of low-dose corticosteroids, which promptly abort flares but cannot prevent subsequent disease episodes over time. Tonsillectomy with or without adenoidectomy has proved to be successful in some pediatric patients, as proven by different studies. On the other hand, colchicine, cimetidine, nonsteroidal anti-inflammatory drugs, and interleukin-1 inhibitors have shown efficacy, which require further definite confirmations. This review is aimed at summarizing all the recent evidence about treatment options available for PFAPA syndrome both in pediatric and adult patients.

DOI: 10.1007/s10067-018-4361-2

PMID: 30488366

56. Curr Eye Res. 2018 Nov 27. doi: 10.1080/02713683.2018.1554150. [Epub ahead of print]

Increased Corneal Ectasia Risk in Patients with Familial Mediterranean Fever.

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**PURPOSE:** To evaluate the corneal tomographical parameters in patients with familial mediterranean fever and to compare data with those of healthy control

subjects.

**MATERIALS AND METHODS:** Forty eyes of 40 patients with familial mediterranean fever (familial mediterranean fever group) and 35 eyes of 35 healthy subjects (control group) were included to this prospective study. All participants underwent complete ophthalmological examination and tomographical analysis with Pentacam HR. Maximum keratometry, front and back astigmatism, thinnest pachymetry, maximum anterior and posterior elevation best-fit-sphere (BFS) at the 5.0 mm zone, front and back difference elevation, final D, average and maximum pachymetric progression index, maximum Ambrósio relational thickness parameters were noted.

**RESULTS:** Groups were similar in terms of age and gender ( $p = 0.77$  and  $p = 0.35$ ). Maximum keratometry, thinnest pachymetry, front and back astigmatism, maximum anterior elevation BFS at the 5.0 mm values were similar between groups ( $p = 0.22$ ,  $p = 0.52$ ,  $p = 0.49$ ,  $p = 0.29$ , and  $p = 0.31$ , respectively). Maximum posterior elevation BFS at the 5.0 mm and back difference elevation values were higher than control group in familial mediterranean fever group ( $p = 0.001$  and  $p = 0.04$ ). The mean values of final D, average and maximum pachymetric progression index were higher, and Ambrósio relational thickness was lower in familial mediterranean fever group compared to control group ( $p = 0.03$ ,  $p = 0.002$ ,  $p = 0.006$ , and  $p = 0.01$ , respectively).

**CONCLUSIONS:** Familial mediterranean fever patients carry increased corneal ectasia risk compared to healthy subjects. The corneal tomographical characteristics and the association of keratoconus with familial mediterranean fever may be important in a detailed refractive surgery work-up.

DOI: 10.1080/02713683.2018.1554150

PMID: 30482054

57. Ann Clin Transl Neurol. 2018 Oct 4;5(11):1428-1433. doi: 10.1002/acn3.656. eCollection 2018 Nov.

Cerebral autoinflammatory disease treated with anakinra.

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Interest in autoimmune encephalitis has been growing since the discovery of various autoimmune antibodies, such as N-methyl D-aspartate receptors antibody and leucine-rich glioma-inactivated 1 antibody. However, in contrast to autoimmune encephalitis associated with dysregulated adaptive immunity in the brain, the question of whether innate immunity-mediated autoinflammatory diseases exist in the brain has drawn much attention. Herein, we report a patient with microglia-dominant acute autoinflammatory encephalitis successfully treated with anakinra, an including interleukin-1 receptor blocker. In comparison to systemic autoinflammatory disease, we term this encephalitis cerebral autoinflammatory disease. Cerebral autoinflammatory disease could suggest new conceptual approaches to patients previously diagnosed with an unspecified encephalitis.

DOI: 10.1002/acn3.656

PMCID: PMC6243374

PMID: 30480037

58. Rheumatology (Oxford). 2018 Nov 23. doi: 10.1093/rheumatology/key328. [Epub ahead of print]

Familial Mediterranean fever: breaking all the (genetic) rules.

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Objective: FMF is an inherited autoinflammatory syndrome, characterized by attacks of painful periodic fever caused by diffuse serositis and risk of secondary amyloidosis due to IL-1 $\beta$ -mediated inflammation. The disease appears to be transmitted through autosomal recessive mutations in the MEFV gene encoding the pyrin protein Although more than 300 variants have been reported worldwide so

far, their association with symptom severity, the relative frequencies in different populations and the disease penetrance are far from being completely understood. We investigated genotype-phenotype correlations in two large nuclear families and verified whether commonly used web-based tools can usefully predict variant pathogenicity in FMF.

Methods: Peripheral blood samples were obtained from 15 patients of two families who had been diagnosed with FMF according to international criteria. The entire MEFV coding region was sequenced in all subjects, and 179 MEFV variants were surveyed with five different pathogenicity predictors.

Results: The inheritance of FMF could not be explained by traditional autosomal recessivity in both families. In silico tools demonstrated a significant association of variants' pathogenicity with their position along the coding sequence but not with variants' frequency.

Conclusion: By describing two large families with paradigmatic complexity of FMF genetics, we conclude that established concepts in assessing the causative role of variants identified in mutation screening cannot be easily translated into appropriate genetic counselling in FMF. Furthermore, we demonstrate that variants frequently associated with severe disease are not predicted to significantly impact protein function using in silico algorithms.

DOI: 10.1093/rheumatology/key328

PMID: 30476289

59. Joint Bone Spine. 2018 Nov 22. pii: S1297-319X(18)30426-3. doi: 10.1016/j.jbspin.2018.11.003. [Epub ahead of print]

New data in causes of autoinflammatory diseases.

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The spectrum of factors known to mediate autoinflammation has broadened recently to include not only interleukin-1 (IL-1) and interferon, but also abnormalities that impair NF- $\kappa$ B pathway negative regulation. The NF- $\kappa$ B pathway is activated upon contact of a ligand with tumor necrosis factor receptor 1 (TNFR1) and plays a pivotal role in triggering the inflammatory process by producing major cytokines such as IL-1, IL-6, and TNF. Negative regulation of the NF- $\kappa$ B pathway, which is essential to stop the inflammatory process, depends on the level of ubiquitination of the proteins associated with TNFR1 and of other intermediate compounds. A20 and otulin are proteins that influence the level of ubiquitination, and a deficiency in either can result in NF- $\kappa$ B activation with overproduction of pro-inflammatory cytokines. Similar to Behçet's disease, A20

haploinsufficiency manifests as oral and genital ulcers and, more rarely, as uveitis. However, transmission is dominant, symptom onset occurs at a younger age, and severe gastrointestinal involvement is at the forefront of the clinical picture. Clinical presentations are extremely diverse. Over their lifetime, affected patients simultaneously or sequentially experience autoinflammatory and autoimmune manifestations. Mild immune deficiency predominantly affecting humoral responses is less common. Otulin deficiency results in systemic inflammatory manifestations at a very young age, with panniculitis, lipodystrophy, and inflammatory bowel disease. The main differential diagnosis is proteasome-associated autoinflammatory syndrome. The treatment of A20 haploinsufficiency and otulin deficiency is challenging and remains unstandardized. The symptoms respond to high-dose glucocorticoid therapy. TNF antagonists and IL-1 antagonists have shown some measure of efficacy.

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DOI: 10.1016/j.jbspin.2018.11.003

PMID: 30471422

60. G Ital Dermatol Venereol. 2018 Jun;153(3 Suppl 2):8-17. doi: 10.23736/S0392-0488.17.05772-8.

Hidradenitis suppurativa and associated diseases.

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Hidradenitis suppurativa is a chronic, inflammatory, recurrent, debilitating skin disease characterized by recurrent abscesses, draining sinuses, and scarring, affecting principally areas of body friction. Although the disease pathogenesis is not fully understood, recent advances suggest that hidradenitis suppurativa should be viewed as a systemic inflammatory disease. Moreover, recent studies have defined hidradenitis suppurativa as a systemic disease linked to several

comorbidities. Metabolic disorders including obesity and metabolic syndrome are the most common associated conditions observed in patients with hidradenitis suppurativa. Autoimmune diseases, like inflammatory bowel diseases, autoinflammatory diseases, spondyloarthritis, some genetic keratin disorders and also the risk of skin tumor seems to occur more frequently in these patients. This disease can also have severe effects on self-esteem and quality of life and can be associated with psychiatric diseases. The link between hidradenitis suppurativa and systemic associations may be attributed to common genetic or environmental factors or shared inflammatory pathways. Due to these reasons it is mandatory that clinical intervention for hidradenitis suppurativa must include consideration and attention to these comorbidities and complications. In this article we have reviewed current available literature on diseases that can occur together with hidradenitis suppurativa.

DOI: 10.23736/S0392-0488.17.05772-8

PMID: 30468375

61. Immunol Allergy Clin North Am. 2019 Feb;39(1):13-29. doi: 10.1016/j.iac.2018.08.004. Epub 2018 Nov 1.

Hereditary Autoinflammatory Disorders: Recognition and Treatment.

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The autoinflammatory diseases encompass approximately 30 monogenic disorders in which inborn errors in the innate immune system lead to episodic systemic inflammation. Largely mediated by dysregulation of myeloid cells, interleukin (IL)-1 $\beta$ , type I interferon, and NF- $\kappa$ B, these disorders have rapidly expanded over the past several years, and increasing numbers of patients identified. Crossover disorders, bridging autoinflammation and immunodeficiency, have recently been described. This article focuses on the clinical presentation of IL-1 and interferon-driven autoinflammatory disorders, and discusses novel diseases with features of immunodeficiency. Approaches to the clinical diagnosis, genetic

testing, and treatment of these disorders are addressed.

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DOI: 10.1016/j.iac.2018.08.004

PMID: 30466770

62. *Acta Neuropathol.* 2018 Nov 21. doi: 10.1007/s00401-018-1933-9. [Epub ahead of print]

Inflammation in ALS/FTD pathogenesis.

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Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are neurodegenerative diseases that overlap in their clinical presentation, pathology and genetics, and likely represent a spectrum of one underlying disease. In ALS/FTD patients, neuroinflammation characterized by innate immune responses of tissue-resident glial cells is uniformly present on end-stage pathology, and human imaging studies and rodent models support that neuroinflammation begins early in disease pathogenesis. Additionally, changes in circulating immune cell populations and cytokines are found in ALS/FTD patients, and there is evidence for an autoinflammatory state. However, despite the prominent role of neuro- and systemic inflammation in ALS/FTD, and experimental evidence in rodents that altering microglial function can mitigate pathology, therapeutic approaches to decrease inflammation have thus far failed to alter disease course in humans. Here, we review the characteristics of inflammation in ALS/FTD in both the nervous and peripheral immune systems. We further discuss evidence for direct influence on immune cell function by mutations in ALS/FTD genes including C9orf72, TBK1 and OPTN, and how this could lead to the altered innate immune

system "tone" observed in these patients.

DOI: 10.1007/s00401-018-1933-9

PMID: 30465257

63. J Virol. 2018 Nov 21. pii: JVI.01806-18. doi: 10.1128/JVI.01806-18. [Epub ahead of print]

A human gain-of-function STING mutation causes immunodeficiency and gammaherpesvirus-induced pulmonary fibrosis in mice.

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We previously generated STING N153S knockin mice that have a human disease-associated gain-of-function mutation in STING. Patients with this mutation (STING N154S in human) develop STING-associated vasculopathy with onset in infancy (SAVI), a severe pediatric autoinflammatory disease characterized by pulmonary fibrosis. Since this mutation promotes up-regulation of antiviral type I interferon-stimulated genes (ISGs), we hypothesized that STING N153S knockin mice may develop more severe autoinflammatory disease in response to a virus challenge. To test this hypothesis, we infected heterozygous STING N153S mice with murine gammaherpesvirus 68 ( $\gamma$ HV68). STING N153S mice were highly vulnerable to infection and developed pulmonary fibrosis after infection. In addition to impairing CD8<sup>+</sup> T cell responses and humoral immunity, STING N153S also promoted replication of  $\gamma$ HV68 in cultured macrophages. In further support of a combined innate and adaptive immunodeficiency,  $\gamma$ HV68 infection was more severe in Rag1<sup>-/-</sup> STING N153S mice than in Rag1<sup>-/-</sup> littermate mice, which completely lack adaptive

immunity. Thus, a gain-of-function STING mutation creates a combined innate and adaptive immunodeficiency that leads to virus-induced pulmonary fibrosis. **IMPORTANCE** A variety of human rheumatologic disease-causing mutations have recently been identified. Some of these mutations are found in viral nucleic acid-sensing proteins, but whether viruses can influence the onset or progression of these human diseases is less well understood. One such autoinflammatory disease called STING-associated vasculopathy with onset in infancy (SAVI) affects children and leads to severe lung disease. We generated mice with a SAVI-associated STING mutation and infected them with  $\gamma$ HV68, a common DNA virus that is related to human Epstein-Barr virus. Mice with the human disease-causing STING mutation were more vulnerable to infection than wild-type littermate control animals. Furthermore, the STING mutant mice developed lung fibrosis similar to patients with SAVI. These findings reveal that a human STING mutation creates severe immunodeficiency, leading to virus-induced lung disease in mice.

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DOI: 10.1128/JVI.01806-18

PMID: 30463976

64. Front Pharmacol. 2018 Nov 6;9:1157. doi: 10.3389/fphar.2018.01157. eCollection 2018.

Anakinra Therapy for Non-cancer Inflammatory Diseases.

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Interleukin-1 (IL-1) is the prototypical inflammatory cytokine: two distinct ligands (IL-1 $\alpha$  and IL-1 $\beta$ ) bind the IL-1 type 1 receptor (IL-1R1) and induce a myriad of secondary inflammatory mediators, including prostaglandins, cytokines,

and chemokines. IL-1 $\alpha$  is constitutively present in endothelial and epithelial cells, whereas IL-1 $\beta$  is inducible in myeloid cells and released following cleavage by caspase-1. Over the past 30 years, IL-1-mediated inflammation has been established in a broad spectrum of diseases, ranging from rare autoinflammatory diseases to common conditions such as gout and rheumatoid arthritis (RA), type 2 diabetes, atherosclerosis, and acute myocardial infarction. Blocking IL-1 entered the clinical arena with anakinra, the recombinant form of the naturally occurring IL-1 receptor antagonist (IL-1Ra); IL-1Ra prevents the binding of IL-1 $\alpha$  as well as IL-1 $\beta$  to IL-1R1. Quenching IL-1-mediated inflammation prevents the detrimental consequences of tissue damage and organ dysfunction. Although anakinra is presently approved for the treatment of RA and cryopyrin-associated periodic syndromes, off-label use of anakinra far exceeds its approved indications. Dosing of 100 mg of anakinra subcutaneously provides clinically evident benefits within days and for some diseases, anakinra has been used daily for over 12 years. Compared to other biologics, anakinra has an unparalleled record of safety: opportunistic infections, particularly *Mycobacterium tuberculosis*, are rare even in populations at risk for reactivation of latent infections. Because of this excellent safety profile and relative short duration of action, anakinra can also be used as a diagnostic tool for undefined diseases mediated by IL-1. Although anakinra is presently in clinical trials to treat cancer, this review focuses on anakinra treatment of acute as well as chronic inflammatory diseases.

DOI: 10.3389/fphar.2018.01157

PMCID: PMC6232613

PMID: 30459597

65. Arthritis Res Ther. 2018 Nov 20;20(1):257. doi: 10.1186/s13075-018-1738-1.

Musculoskeletal manifestations occur predominantly in patients with later-onset familial Mediterranean fever: Data from a multicenter, prospective national cohort study in Japan.

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**BACKGROUND:** We showed previously that Japanese individuals with familial Mediterranean fever (FMF) have a more atypical phenotype compared to endemic areas. The clinical differences between young-onset FMF (YOFMF), adult-onset FMF (AOFMF), and late-onset FMF (LOFMF) in Japan are unclear.

**METHODS:** We enrolled 395 consecutive patients. We defined YOFMF, AOFMF, and LOFMF as the onset of FMF at < 20, 20-39, and  $\geq$  40 years of age, respectively. We compared clinical manifestations and MEFV mutations patterns among these groups.

**RESULTS:** Median ages at onset were YOFMF 12.5 years ( $n = 182$ ), AOFMF 28 years ( $n = 115$ ), and LOFMF 51 years ( $n = 90$ ). A family history, MEFV mutations in exon 10, and more than two MEFV mutations were significantly more frequent in the earlier-onset groups ( $p < 0.01$ ,  $p < 0.0001$ , and  $p < 0.001$ , respectively). In the accompanying manifestations, thoracic and abdominal pain were significantly more frequent in the earlier-onset groups ( $p < 0.01$  and  $p < 0.0001$ , respectively), whereas arthritis and myalgia were significantly more frequent in the later-onset groups ( $p < 0.0001$  and  $p < 0.01$ , respectively). The multiple logistic regression analysis revealed that the presence of MEFV exon 10 mutations and earlier onset were significantly associated with serositis, whereas the absence of MEFV exon 10 mutations, later onset, and the presence of erysipelas-like erythema were significantly associated with musculoskeletal manifestations. There was no significant between-group difference in the responsiveness to colchicine.

**CONCLUSIONS:** Our results indicate that the later-onset FMF patients had a lower percentage of MEFV mutations in exon 10 and predominantly presented arthritis and myalgia. It is important to distinguish their FMF from other inflammatory



diseases.

DOI: 10.1186/s13075-018-1738-1

PMCID: PMC6247522

PMID: 30458853

66. J Clin Invest. 2019 Jan 2;129(1):150-162. doi: 10.1172/JCI121372. Epub 2018 Nov 19.

TNF/TNFR axis promotes pyrin inflammasome activation and distinctly modulates pyrin inflammasomopathy.

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Pyrin is an inflammasome sensor that promotes caspase-1-mediated pyroptotic cell death and maturation of proinflammatory cytokines IL-1 $\beta$  and IL-18. Familial Mediterranean fever (FMF), an autoinflammatory disorder, is associated with mutations in the gene encoding pyrin (MEFV). FMF-knockin (FMF-KI) mice that express chimeric pyrin protein with FMF mutation (MefvV726A/V726A) exhibit an autoinflammatory disorder mediated by autoactivation of the pyrin inflammasome. Increase in the levels of TNF are observed in FMF-KI mice, and many features of FMF overlap with the autoinflammatory disorder associated with TNF receptor signaling. In this study, we assessed the contribution of TNF signaling to pyrin inflammasome activation and its consequent role in distinct FMF pathologies. TNF signaling promoted the expression of pyrin in response to multiple stimuli and was required for inflammasome activation in response to canonical pyrin stimuli and in myeloid cells from FMF-KI mice. TNF signaling promoted systemic wasting, anemia, and neutrophilia in the FMF-KI mice. Further, TNF-induced pathology was induced specifically through the TNFR1 receptor, while TNFR2-mediated signaling was distinctly protective in colitis and ankle joint inflammation. Overall, our data show that TNF is a critical modulator of pyrin expression, inflammasome activation, and pyrin-inflammasomopathy. Further, specific blockade of TNFR1 or activation of TNFR2 could provide substantial protection against FMF pathologies.

DOI: 10.1172/JCI121372

PMCID: PMC6307946 [Available on 2019-04-02]

PMID: 30457980

67. Calcif Tissue Int. 2018 Nov 19. doi: 10.1007/s00223-018-0495-0. [Epub ahead of print]

Chronic Non-bacterial Osteomyelitis: A Review.

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Chronic non-bacterial osteomyelitis (CNO) is a rare auto-inflammatory bone disorder, with a prevalence of around one in a million patients. In the more severe form, it is referred to as chronic recurrent multifocal osteomyelitis (CRMO). We present the current knowledge on epidemiology, pathophysiology as well as diagnostic options and treatment regimens. CNO/CRMO most commonly affects children and lesions are often seen in the metaphyseal plates of the long bones, but cases have been described affecting all age groups as well as lesions in almost every bone. It is, therefore, a disease that clinicians can encounter in many different settings. Diagnosis is mainly a matter of exclusion from differential diagnoses such as bacterial osteomyelitis and cancer. Magnetic resonance imaging is the best radiological method for diagnosis coupled with a low-grade inflammation and a history of recurring episodes. Treatment is based on case reports and consists of alleviating symptoms with non-steroidal anti-inflammatory drugs since the disease is often self-limiting. Recently, more active treatments using either bisphosphonates or biological treatment are becoming more common, to prevent long term bone damage. In general, due to its rarity, much remains unclear regarding CNO/CRMO. We review the known literature

on CNO/CRMO and propose areas of interest as well as possible ways to make current diagnostic criteria more detailed. We also find unifocal cases of the jaw to be a possible sub-type that may need its own set of criteria.

DOI: 10.1007/s00223-018-0495-0

PMID: 30456556

## 68. Cherubism.

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In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018.

2007 Feb 26.

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**CLINICAL CHARACTERISTICS:** Cherubism is a childhood-onset, autoinflammatory bone disease characterized by bilateral and symmetric proliferative fibroosseous lesions limited to the mandible and maxilla. The enlargement is usually symmetric in nature. The phenotype ranges from no clinical manifestations to severe mandibular and maxillary overgrowth with respiratory, vision, speech, and swallowing problems. In most affected persons, teeth are displaced, unerupted, unformed, or absent, or may appear to be floating in cystlike spaces; malocclusion, premature exfoliation of deciduous teeth, and root resorption have also been reported. The course and duration of the active process of bone destruction varies between affected individuals; the onset is usually in early childhood, and typically new lesions can occur until puberty. Regression of the lesions occurs as they become filled with bone and remodel during the second and third decade of life. By age 30 years, the facial abnormalities associated with cherubism are not usually recognizable and residual deformity of the jaws is rare. Typically, cherubism is an isolated benign condition; the affected person has normal intellectual skills and is without other physical anomalies.

**DIAGNOSIS/TESTING:** Diagnosis is established in a proband with typical clinical, radiographic, and histologic findings and/or a heterozygous pathogenic variant in SH3BP2 identified by molecular genetic testing.

**MANAGEMENT:** Treatment of manifestations: Given that cherubism is considered to be a self-limited condition that improves over time, treatment should be tailored to the individual's presentation and the evolution of the disease. Ongoing management by a craniofacial team in a major pediatric medical center is recommended; depending on the severity, surgery may be needed for functional and esthetic concerns. Surveillance: Long-term follow up with clinical, radiographic, dental, orthodontic, and ophthalmologic evaluations. Annual reviews are indicated while new cysts continue to form or established cysts enlarge; after the disorder becomes quiescent, follow up every two to five years. Testing of relatives at risk: When the pathogenic variant in the family is known, molecular testing can be used to identify mildly affected relatives who may benefit from early intervention; otherwise, clinical and radiographic evaluations can identify relatives at risk.

**GENETIC COUNSELING:** Cherubism is inherited in an autosomal dominant manner. The proportion of cases caused by de novo pathogenic variants is unknown because of variable expressivity and reduced penetrance. Each child of an individual with cherubism has a 50% chance of inheriting the pathogenic variant. Prenatal diagnosis for pregnancies at increased risk and preimplantation diagnosis are possible if the pathogenic variant has been identified in the family.

PMID: 20301316

69. Curr Opin Immunol. 2018 Dec;55:97-105. doi: 10.1016/j.coi.2018.09.014. Epub 2018 Nov 16.

Updates on autoinflammatory diseases.

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Autoinflammatory diseases are hyperinflammatory, immune dysregulatory diseases caused by innate immune cells dysregulation that present typically in the perinatal period with systemic and organ-targeted inflammation, but with improved genetic testing and the development of diagnostic criteria, milder and later-onset forms are being detected in adulthood. While the discovery of gain-of-function mutations in innate sensors linked to the production of proinflammatory cytokines provided the bases for anti-cytokine therapies that changed disease and patient outcomes, the field is expanding with the increasing discovery of disease-causing loss-of-function mutations in genes with cellular house-keeping functions that affect cell homeostasis and when dysregulated trigger innate inflammatory pathways. This review focuses on updates on molecular pathways and diseases that cause predominantly IL-1 $\beta$  and Type-I IFN-mediated autoinflammatory diseases.

Published by Elsevier Ltd.

DOI: 10.1016/j.coi.2018.09.014

PMID: 30453204

70. Joint Bone Spine. 2018 Nov 15. pii: S1297-319X(18)30300-2. doi: 10.1016/j.jbspin.2018.11.001. [Epub ahead of print]

The relapsing polychondritis damage index (RPDAM): Development of a disease-specific damage score for relapsing polychondritis.

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**OBJECTIVES:** Relapsing polychondritis is a rare, multi-systemic and inflammatory condition of unknown origin. We currently lack a core set of measures to assess and follow damage in patients suffering from this condition. Our primary aim was to derive a disease-specific damage measuring tool for relapsing polychondritis, the Relapsing Polychondritis Damage Index (RPDAM).

**METHODS:** We performed an international 4-round multicenter Delphi study during which experts were asked to rate the relevance of potential damage items for relapsing polychondritis (141 items were obtained from a literature review and 12 from expert suggestion), using a Likert Scale. The selection of items for each subsequent round was based on the median rating of each item.

**RESULTS:** Twenty-four experts from 11 nationalities participated in round 1 and 22 in rounds 2, 3 and 4. From the initial 153 potential damage items, 44 items were selected during round 1, 30 items during round 2 and 16 during round 3. During round 4, we refined the index to a total of 17 items referring to ear nose and throat, eye, respiratory, cardiovascular and hematological systems as well as to treatment-related specific damage items.

**CONCLUSION:** We have developed by international consensus a scoring system to assess damage in patients with relapsing polychondritis. Following its validation, the RPDAM may contribute to improve the care of patients suffering from this rare condition as well as to standardize data collection for future clinical trials.

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DOI: 10.1016/j.jbspin.2018.11.001

PMID: 30448476

71. Arch Biochem Biophys. 2018 Nov 16. pii: S0003-9861(18)30557-5. doi: 10.1016/j.abb.2018.11.013. [Epub ahead of print]

Development of covalent NLRP3 inflammasome inhibitors: Chemistry and biological activity.

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The NOD-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome is the best recognized and most widely implicated regulator of caspase-1 activation. It is a key regulator of innate immune response and is involved in many pathophysiological processes. Recent evidences for its inappropriate activation in autoinflammatory, autoimmune, as well as in neurodegenerative diseases attract a growing interest toward the development of small molecules NLRP3 inhibitors. Based on the knowledge of biochemical and structural aspects of NLRP3 activation, one successful strategy in the identification of NLRP3 inhibitors relies on the development of covalent irreversible inhibitors. Covalent inhibitors are reactive electrophilic molecules able to alkylate nucleophiles in the target protein. These inhibitors could ensure good efficacy and prolonged duration of action both in vitro and in vivo. In spite of these advantages, effects on other signalling pathways, prone to alkylation, may occur. In this review, we will illustrate the chemistry and the biological action of the most studied covalent NLRP3 inhibitors developed so far. A description of what we know about their mechanism of action will address the reader toward a critical understanding of NLRP3 inhibition by electrophilic compounds.

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DOI: 10.1016/j.abb.2018.11.013

PMID: 30448387

72. Clin Pharmacol Ther. 2018 Nov 17. doi: 10.1002/cpt.1302. [Epub ahead of print]

Dosage Considerations for Canakinumab in Children with Periodic Fever Syndromes.



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Periodic fever syndromes are a group of rare diseases with a highly variable onset, yet limited treatment options are available for children at an early age. Canakinumab has been approved to treat patients with cryopyrin-associated periodic syndrome (CAPS), a periodic fever syndrome, and systemic juvenile systemic arthritis (SJIA), with age cutoffs of 4 years and 2 years, respectively. In 2016, FDA approved canakinumab, without an age restriction, for the treatment of three conditions of periodic fever syndromes including familial Mediterranean fever (FMF), hyperimmunoglobulin D syndrome/mevalonate kinase deficiency (HIDS/MKD), and tumor necrosis factor (TNF) receptor associated periodic syndrome (TRAPS). This review discusses the PK, efficacy, safety, and exposure-response relationship of canakinumab, and provides the rationale for dosage recommendation in children younger than 2 years of age with the three conditions of periodic fever syndromes. The approval of canakinumab for these pediatric patients addresses a critical unmet medical need. This article is protected by copyright. All rights reserved.

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DOI: 10.1002/cpt.1302

PMID: 30447083

73. Curr Rheumatol Rep. 2018 Nov 17;20(12):87. doi: 10.1007/s11926-018-0788-3.

Autoinflammatory Disease-Associated Vasculitis/Vasculopathy.

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**PURPOSE OF REVIEW:** Autoinflammatory diseases (AIDs) constitute several disorders that share similar characteristics, clinical features, disease course, and prognosis. They are characterized by the presence of recurrent episodes of unprovoked inflammation due to dysregulated innate immune system in the absence of autoantibodies or infections. AIDs include periodic fever syndromes and other less commonly growing list of syndromes. In this review, vasculitis associated with different AIDs will be highlighted.

**RECENT FINDINGS:** Vasculitis is inflammation and necrosis of the blood vessels causing impaired blood flow, ischemia, and infarction of the dependent tissues. It is a very rare manifestation of AIDs and when it occurs, the skin is the most affected tissue than any other organs such as kidneys, lungs, or CNS. Although vasculitis and AIDs share similar manifestations such as fever, skin rashes, and neuropathy, vasculitis is not a characteristic feature of AIDs and still not clear if it represents a main clinical feature or a manifestation of other disease process.

DOI: 10.1007/s11926-018-0788-3

PMID: 30446874

74. Front Immunol. 2018 Nov 1;9:2524. doi: 10.3389/fimmu.2018.02524. eCollection 2018.

Cutaneous Vasculitis and Digital Ischaemia Caused by Heterozygous Gain-of-Function Mutation in C3.

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It is now increasingly recognized that some monogenic autoinflammatory diseases and immunodeficiencies cause vasculitis, although genetic causes of vasculitis are extremely rare. We describe a child of non-consanguineous parents who presented with cutaneous vasculitis, digital ischaemia and hypocomplementaemia. A heterozygous p.R1042G gain-of-function mutation (GOF) in the complement component C3 gene was identified as the cause, resulting in secondary C3 consumption and complete absence of alternative complement pathway activity, decreased classical complement activity, and low levels of serum C3 with normal C4 levels. The same heterozygous mutation and immunological defects were also identified in another symptomatic sibling and his father. C3 deficiency due GOF C3 mutations is thus now added to the growing list of monogenic causes of vasculitis and should always be considered in vasculitis patients found to have persistently low levels of C3 with normal C4.

DOI: 10.3389/fimmu.2018.02524

PMCID: PMC6221951

PMID: 30443255

75. Cas Lek Cesk. 2018 Summer;157(3):122-129.

Periodic fevers and other autoinflammatory diseases.

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Autoinflammatory diseases represent a relatively new and rapidly evolving group of rare disorders associated with mutations of genes encoding proteins with a key regulatory role in inflammatory response. Gradual discovery of mechanisms that link genetic disorder with its biochemical and immunological consequences leading to continuous or episodic inflammatory stimulation has enabled introduction of

directed immunotherapies. Periodic fever syndromes belong to the so far best-known entities: familial Mediterranean fever, mevalonate kinase deficiency, cryopyrinopathies and TNF-receptor associated periodic syndrome. These inherited disorders usually manifest in childhood with variably long febrile episodes accompanied with the spectrum of other skin and organ inflammatory features and elevation of laboratory markers of inflammation. Uncontrolled disease may lead to secondary amyloidosis. Directed anti-inflammatory therapy can prevent evolution of organ damage. In children benign syndrome of periodic fever with aphtae, pharyngitis and cervical adenitis is the most common self-limited disorder without clear genetic disposition. Following other autoinflammatory disease groups are described - pyogenic syndromes, disorders with skin and bone manifestations, granulomatous diseases, monogenic vasculopathies and diseases associated with proteasome disorder. Diagnosis of autoinflammatory diseases is often delayed due to their extreme rarity. Increasing efficacy and availability of molecular-genetic testing and centralization of diagnostics and clinical care in a specialized center for children as well as adults can in the future improve quality of care for patients with these rare conditions. Keywords: autoinflammatory diseases (AID), periodic fever syndromes, FMF, CAPS, MKD, TRAPS, PFAPA, NGS.

PMID: 30441946

76. Int J Dermatol. 2019 Jan;58(1):e16-e17. doi: 10.1111/ijd.14293. Epub 2018 Nov 14.

Successful therapy with secukinumab in a patient with generalized pustular psoriasis carrying homozygous IL36RN p.His32Arg mutation.

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DOI: 10.1111/ijd.14293

PMID: 30430544

77. J Int Med Res. 2018 Nov 14:300060518806105. doi: 10.1177/0300060518806105. [Epub ahead of print]

Failure of tocilizumab in treating two patients with refractory SAPHO syndrome: a case report.

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Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome is a rare autoinflammatory disease with no standard treatment. Interleukin (IL)-6 inhibitors represent a novel therapeutic option for rheumatoid arthritis and some autoinflammatory diseases. However, the clinical utility of IL-6 inhibitors in treating SAPHO syndrome has been poorly investigated. In the present report, we describe two patients with SAPHO syndrome that was unresponsive to conventional treatment. Tocilizumab, an anti-IL-6 receptor monoclonal antibody, was putatively administered according to positive IL-6 immunohistochemical staining in biopsied

bone tissues. However, the disease continued to progress, and new-onset or worsening skin lesions were noted with transient neutropenia. These cases demonstrate that tocilizumab may not be an ideal option for treating SAPHO syndrome.

DOI: 10.1177/0300060518806105

PMID: 30428761

78. J Dermatolog Treat. 2018 Nov 14:1-7. doi: 10.1080/09546634.2018.1543845. [Epub ahead of print]

Chronic Spontaneous Urticaria or Autoinflammatory Disease? The Therapeutic Effect of Omalizumab in a Pediatric Patient.

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Chronic spontaneous urticaria is a clinical condition characterized by spontaneous or inducible recurrent wheals. This condition may significantly affect quality of life of patients and of their families. Aetiology is not identified in 25-85% of cases that are indicated as "idiopathic", because all diagnostic tests are negative. Autoimmune processes may be present in 30-50% of patients, although a definite etiological diagnosis is seldom possible. Some patients, in fact, have autoantibodies against the high-affinity IgE receptor FcεR1 or IgE. These patients show an increased incidence of anti-thyroid autoantibodies and represent 30-50% of the patients designated as having chronic spontaneous urticaria. FCAS must be distinguished from acquired cold urticaria, which is characterized by a rash occurring within a few minutes after cold exposure, and is often described as "allergy to cold". Cold urticaria is rare in childhood and is not linked to inflammatory markers. The treatment is based on antihistamines. However, in non-responders a second line treatment with omalizumab can show efficacy. We describe the clinical case of a 9-year-old-female with recurrent monthly episodes of fever, arthralgia, abdominal

pain, and urticaria-angioedema who did not respond to steroids associated with antihistamines, however showed the complete resolution of the disease with omalizumab.

DOI: 10.1080/09546634.2018.1543845

PMID: 30426806

79. Clin Exp Rheumatol. 2018 Nov-Dec;36 Suppl 115(6):141-145. Epub 2018 Nov 5.

The frequency of juvenile spondyloarthropathies in childhood familial Mediterranean fever.

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**OBJECTIVES:** The aim of this study is to evaluate the frequency of juvenile spondyloarthropathies (JSpA) in childhood familial Mediterranean fever (FMF) patients from a single tertiary centre. Additionally, we aimed to investigate the main clinical characteristics of FMF patients with coexistence of JSpA clinical features.

**METHODS:** We evaluated 323 paediatric FMF patients who were followed at our clinic. All of the patients were evaluated by three different investigators (EO, DS, ET) for the presence of JSpA clinical signs, according to the recently proposed JSpA criteria. Patients preliminary diagnosed as FMF+JSpA were further evaluated by the experienced paediatric rheumatologist (OK) who made the final decision on the diagnosis of the patients.

**RESULTS:** The female/male ratio was 1.13 (n =172/151). Preliminarily, 33 (10.2%) out of 323 paediatric FMF patients had been classified as FMF+JSpA. An experienced paediatric rheumatologist re-evaluated the classified patients and all of them were diagnosed as definitive FMF+JSpA. The M694V mutation was the most common mutation, seen in (n=18/32) (56.3%) FMF+JSpA and in (n=152/251) (61.1%) FMF patients without JSpA/JIA.

CONCLUSIONS: Apart from acute monoarthritis of the lower extremities, the chronic arthritis should be kept on mind among FMF patients with articular involvement. The JSpA should be considered in FMF patients with oligoarthritis, inflammatory back pain and enthesopathy complaints with onset over 6 years. Newly proposed JSpA criteria can be used to spondyloarthropathies in childhood FMF.

PMID: 30418123

80. Clin Exp Rheumatol. 2018 Nov-Dec;36 Suppl 115(6):97-102. Epub 2018 Nov 12.

Which definition should be used to determine colchicine resistance among patients with familial Mediterranean fever?

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OBJECTIVES: Colchicine is the main therapy for familial Mediterranean fever (FMF); however, 5-10% of patients are colchicine-resistant. There is no standard and validated definition for colchicine resistance. We aimed to compare the existing definitions for colchicine resistance in both adult and paediatric FMF patients to find out the best definition to determine colchicine-resistant patients.

METHODS: 385 FMF patients were evaluated and patients receiving anti-interleukin-1 treatment were included. The anti-IL-1 therapy had been initiated by the experts in the past based on their experience. Eleven different definitions (found out after PubMed search for colchicine resistance in FMF) were



applied to all patients. Results were re-analysed after excluding the patients who had no clinical attacks but persistently high acute phase reactants (APRs) and/or amyloidosis.

**RESULTS:** Sixty patients (40 adults/20 children) who had been using anti-IL-1 therapy were included into this study as colchicine-resistant patients. The highest percentage of patients fulfilled definition 5 (93.3%). Definition 9 had the poorest performance (26%). Significantly, a higher percentage of adult patients met definitions 4 and 6 than paediatric patients (87.5% vs. 50%,  $p=0.002$ ; 75% vs. 40%,  $p=0.008$ , respectively). After excluding patients without clinical attacks, the highest percentage of patients fulfilled definition 2 (94.4%). We combined the attack frequency ( $>1$  typical episode/3 months) in definition 2 and presence of amyloidosis/APR increase (increase in  $\geq 2/3$  APRs) in definition 5 to create a new definition which was met by 59 (98.3%) colchicine-resistant FMF patients.

**CONCLUSIONS:** Definition of colchicine resistance is still controversial. Definitions with both clinical and laboratory criteria were met by a higher percentage of resistant patients than those without laboratory criteria. However, the proper definitions for the attack-free period and persistence of APRs are still lacking.

PMID: 30418112

81. Clin Exp Rheumatol. 2018 Nov-Dec;36 Suppl 115(6):86-89. Epub 2018 Nov 9.

Analysis of NLRP3, MVK and TNFRSF1A variants in adult Greek patients with autoinflammatory symptoms.

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**OBJECTIVES:** Autoinflammatory diseases are characterised by abnormal hyperactivity of the innate immune system, causing systemic inflammation. The cryopyrin associated periodic syndrome (CAPS), the hyper IgD syndrome (HIDS) and the TNF receptor-associated periodic syndrome (TRAPS), are autoinflammatory conditions associated with mutations in the NLRP3, MVK and TNFRSF1A genes, respectively. We present the experience of our Department with these rare syndromes analysing genetic and clinical data of adult patients encountered between January 2011 and September 2017.

**METHODS:** Eighty-eight adult patients with clinical suspicion of CAPS, HIDS and TRAPS were sequentially recruited and genetically tested for specific mutations in NLRP3, MVK and TNFRSF1A using Sanger sequencing. Clinical picture of mutation carriers was reviewed. Allele frequencies were compared to those described for the normal population by the 1000 Genomes project.

**RESULTS:** Seventy-two of the 88 adult patients were found to be positive for mutations or polymorphisms. One patient carried two pathogenic MVK mutations (pV377I/c.1129G>A and c.850delG) and another one carried a pathogenic heterozygous pA439V/c.1316C>T NLRP3 mutation. Seventeen patients carried variants of uncertain significance. The pS434S/c.1302C>T NLRP3 mutation is slightly increased in our patients compared to the reference population and seems to correlate with severe symptom presentation.

**CONCLUSIONS:** In rare cases, periodic fever and inflammatory symptoms in adults can be attributed to mutations in NLRP3, MVK and TNFRSF1A. Clinical assessment and genetic analysis are critical for proper diagnosis and treatment of autoinflammatory diseases.

PMID: 30418111

82. J Cell Physiol. 2018 Nov 11. doi: 10.1002/jcp.27436. [Epub ahead of print]

Inflammation and pericarditis: Are neutrophils actors behind the scenes?

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The morbidity of acute pericarditis is increasing over time impacting on patient quality of life. Recent clinical trials focused especially on clinical aspects, with a modest interest in pathophysiological mechanisms. This narrative review, based on papers in English language obtained via PubMed up to April 2018, aims at focusing on the role of the innate immunity in pericarditis and discussing future potential therapeutic strategies impacting on disease pathophysiology. In developed countries, most cases of pericarditis are referred to as idiopathic, although etiological causes have been described, with autoreactive/lymphocytic, malignant, and infectious ones as the most frequent causes. Apart the known impairment of the adaptive immunity, recently a large body evidence indicated the central role of the innate immune system in the pathogenesis of recurrent pericarditis, starting from similarities with autoinflammatory diseases. Accordingly, the "inflammasome" has been shown to behave as an important player in pericarditis development. Similarly, the beneficial effect of colchicine in recurrent pericarditis confirms that neutrophils are important effectors as colchicine, which can block neutrophil chemotaxis, interferes with neutrophil adhesion and recruitment to injured tissues and abrogate superoxide production. Anyway, the role of the adaptive immune system in pericarditis cannot be reduced to a black or white issue as mechanisms often overlap. Therefore, we believe that more efficient therapeutic strategies have to be investigated by targeting neutrophil-derived mediators (such as metalloproteinases) and disentangling the strict interplay between neutrophils and platelets. In this view, some progress has been done by using the recombinant human interleukin-1 receptor antagonist anakinra.

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DOI: 10.1002/jcp.27436

PMID: 30417336

83. *Mediterr J Hematol Infect Dis*. 2018 Nov 1;10(1):e2018067. doi: 10.4084/MJHID.2018.067. eCollection 2018.

# The Broad-Ranging Panorama of Systemic Autoinflammatory Disorders with Specific Focus on Acute Painful Symptoms and Hematologic Manifestations in Children.

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Systemic autoinflammatory disorders (SAIDs) are inherited defects of innate immunity characterized by recurrent sterile inflammatory attacks involving skin, joints, serosal membranes, gastrointestinal tube, and other tissues, which recur with variable rhythmicity and display reactive amyloidosis as a potential long-term complication. Dysregulated inflammasome activity leading to overproduction of many proinflammatory cytokines, such as interleukin-1 (IL-1), and delayed shutdown of inflammation are considered crucial pathogenic keys in the vast majority of SAIDs. Progress of cellular biology has partially clarified the mechanisms behind monogenic SAIDs, such as familial Mediterranean fever, tumor necrosis factor receptor-associated periodic syndrome, cryopyrin-associated periodic syndrome, mevalonate kinase deficiency, hereditary pyogenic diseases, idiopathic granulomatous diseases and defects of the ubiquitin-proteasome pathway. Whereas, little is clarified for the polygenic SAIDs, such as periodic fever, aphthous stomatitis, pharyngitis, and cervical adenopathy (PFAPA) syndrome. The puzzle of symptomatic febrile attacks recurring over time in children requires evaluating the mixture of clinical data, inflammatory parameters in different disease phases, the therapeutic efficacy of specific drugs such as colchicine, corticosteroids or IL-1 antagonists, and genotype analysis in selected cases. The long-term history of periodic fevers should also need to rule out chronic infections and malignancies. This review is conceived as a practical template for proper classification of children with recurring fevers and includes tips useful for the diagnostic approach to SAIDs, focusing on the specific acute painful symptoms and hematologic manifestations encountered in childhood.

DOI: 10.4084/MJHID.2018.067

PMCID: PMC6223578

PMID: 30416699

Conflict of interest statement: Competing interests: The author has declared that no competing interests exist.

84. Eur J Rheumatol. 2018 Nov 6:1-7. doi: 10.5152/eurjrheum.2018.18023. [Epub ahead of print]

Novel presentations of periodic fever syndromes: Discrepancies between genetic and clinical diagnoses.

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**OBJECTIVE:** The Periodic fever syndromes (PFS) are a group of disorders of the innate immune system. We investigated patients diagnosed with PFS at the Dartmouth Hitchcock Pediatric Rheumatology Clinic.

**METHODS:** Case acquisition was performed by reviewing ICD 9/10 coded records for familial Mediterranean fever (ICD 9 277.31), laboratory test records for PFS genetic screening, and clinic records between 1/1/2011 and 12/31/2017.

**RESULTS:** Twenty-seven cases had clinical evaluations including PFS genetic screening. Clinical diagnoses included familial Mediterranean fever (FMF) (10 cases), Muckle-Wells (2 cases), tumor necrosis factor receptor associated periodic syndrome (TRAPS) (4 cases), hyper IgD syndrome (HIDS) (1 case), Crohn's Disease (1 case), systemic onset juvenile idiopathic arthritis (SoJIA) (1 case), fever of unknown origin (FUO) (1 case), periodic fever adenitis pharyngitis aphthous ulcer (PFAPA) (6 cases), and cold-induced urticaria (1 case). Fifteen cases were associated with a genetic cause. Seven of the 10 FMF cases were confirmed genetically and were either heterozygous or compound heterozygotes. Both cases of Muckle-Wells had either a compound heterozygote for CIAS 1 or a NOD gene mutation. Both TRAPS cases presented atypically with patients developing systemic lupus erythematosus (SLE) or being asymptomatic. Two patients had novel syndromes. One FMF patient had a TRNT1 gene mutation who responded to intravenous immunoglobulin (IVIg) and colchicine after failing multiple treatments. The other had SoJIA with a LPIN 2 gene mutation but responded to colchicine. Only one of the 15 genetically proven cases had classical presentation and genetics (HIDS secondary to a mevalonate kinase (MVK) gene mutation).

**CONCLUSION:** PFS screening was helpful in over half of the cases to develop therapeutic treatment plans. Given the atypical clinical presentations seen with genetically determined PFS, extensive genetic testing is indicated for all patients presenting with a PFS, excluding classical PFAPA syndrome.

DOI: 10.5152/eurjrheum.2018.18023

PMID: 30407166

85. Clin Rheumatol. 2018 Nov 8. doi: 10.1007/s10067-018-4359-9. [Epub ahead of print]

S100A12 and vascular endothelial growth factor can differentiate Blau syndrome and familial Mediterranean fever from systemic juvenile idiopathic arthritis.

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**OBJECTIVES:** Systemic juvenile idiopathic arthritis (sJIA) has recently become regarded as one of the autoinflammatory syndromes (AIS). However, other AIS, such as familial Mediterranean fever (FMF) and Blau syndrome, have been initially misdiagnosed as sJIA because of the clinical similarities. Making the correct diagnosis in the early stage of these AIS is desirable. Therefore, we evaluated serum S100A12 and vascular endothelial growth factor (VEGF) levels to determine if they could be biomarkers for differentiating these AIS.

**METHOD:** Serum S100A12 and VEGF levels were examined in patients with Blau syndrome (n = 4), FMF (n = 4), and sJIA (n = 11) in the active and inactive phases.

**RESULTS:** In the active phase, S100A12 levels were significantly higher in patients with sJIA and FMF compared with those with Blau syndrome ( $p < 0.001$ ). VEGF levels of patients with sJIA were significantly higher than those of patients with others ( $p = 0.001$ ). In the inactive phase, there was no significant difference in VEGF levels. However, colchicine-resistant patients or patients without treatment with FMF showed high levels of S100A12 compared with others.

CONCLUSIONS: Measuring both serum S100A12 and VEGF levels may be useful for differentiating patients with Blau syndrome and FMF from those with sJIA at the early stage.

DOI: 10.1007/s10067-018-4359-9

PMID: 30406853

86. Int J Inflam. 2018 Oct 1;2018:1902791. doi: 10.1155/2018/1902791. eCollection 2018.

Familial Mediterranean Gene (MEFV) Mutation in Parents of Children with Familial Mediterranean Fever: What Are the Exceptions?

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Objectives: Familial Mediterranean Fever (FMF) is one of the most prevalent periodic fever syndromes; MEFV, the responsible gene for the disease, is in the short arm of chromosome16. In the considerable count of the FMF patients, only one mutation is found in the MEFV and parents, who were the obligatory carriers for that mutation, were asymptomatic. The aim of this study was to evaluate these asymptomatic parents in regard to mutation in MEFV gene and similarity between parents and offspring patients.

Methods: In this cross-sectional study, asymptomatic parents of FMF patients enrolled the study were referred to periodic fever clinic or pediatric rheumatology clinic of Tehran University of Medical Sciences. The patients should have at least one mutation in MEFV gene and none of them had any family history of autoinflammatory disease. Twelve mutations in MEFV gene were assessed in the

parents by Vienna Lab FMF Strip Assay kit by MAS PCR/Reverse hybridization. Results: Forty-three patients and their parents participated in the study. Sixty-three percent (27) of patients were male. Onset of disease symptoms in 31 patients (72%) was before 4 years of old. Nine (21%) of the patients had homozygote, 16 (37%) compound heterozygote, and 17(40%) heterozygote for MEFV mutation; there was a case of complex alleles mutations (2%). M694V/M694V in 4 patients (9%) was the most homozygote genotype, and M694V/R761H in 4 (9%) and E148Q in 7 (16%) were the most compound heterozygote and heterozygote genotype, respectively. M694V, M680I, and E148Q were the most mutation in the parents. Overall, 41 patients had mutations similar to their parents' mutation, except 2 whose parents had no mutation, but a patient did. Conclusion: It seems that occurrence of new mutations in offspring is not prevalent among FMF patients and there are other reasons for different clinical presentation in similar mutation carriers. On the other hand, in ethnicities with high prevalence of FMF, new mutation in descendant may occur, infrequently.

DOI: 10.1155/2018/1902791

PMCID: PMC6191955

PMID: 30402217

87. Clin Immunol. 2018 Oct 27. pii: S1521-6616(18)30432-7. doi: 10.1016/j.clim.2018.10.016. [Epub ahead of print]

Targeting cytokines to treat autoinflammatory diseases.

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Autoinflammatory diseases are rare group conditions manifested by recurrent fevers, systemic inflammation, and dysfunctions of the innate immune system. These conditions are characterized by overproduction or lack of inhibition of



various cytokines, and the advent of biologic drugs that block specific cytokines involved in these conditions have revolutionized their treatment. In this review, I will discuss the most common autoinflammatory conditions of adulthood including Familial Mediterranean Fever, cryopyrin-associated periodic syndrome, mevalonate kinase deficiency/hyperimmunoglobulinemia D Syndrome, TNF receptor-associated autoinflammatory syndrome, and systemic juvenile idiopathic arthritis/adult-onset Still's disease. I will discuss how IL-1, IL-6, IL-18, and TNF play pathogenic roles in these conditions and will review the evidence behind cytokine blockade for these diseases. Throughout the paper, I will reflect on gaps in knowledge of autoinflammatory diseases and will highlight the latest advances and newest drugs in development.

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DOI: 10.1016/j.clim.2018.10.016

PMID: 30394352

88. *Dermatol Ther (Heidelb)*. 2018 Dec;8(4):539-556. doi: 10.1007/s13555-018-0269-7. Epub 2018 Nov 3.

Scoping Review on Use of Drugs Targeting Interleukin 1 Pathway in DIRA and DITRA.

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**INTRODUCTION:** Deficiencies in interleukin (IL)-1 receptor (IL-R) antagonist (DIRA) and IL-36R antagonist (DITRA) are rare genetic autoinflammatory diseases related to alterations in antagonists of the IL-1 pathway. IL-1 antagonists may represent therapeutic alternatives. Here, we aim to provide a scoping review of knowledge on use of IL-1-targeting drugs in DIRA and DITRA.

**METHODS:** An a priori protocol was published, and the study was conducted using the methodology described in the Joanna Briggs Institute Reviewer's Manual and the recently published PRISMA Extension for Scoping Review statement. A three-step search using MEDLINE and EMBASE databases until March 2018 with additional hand searching was performed. Data charting was performed. The search, article selection, and data extraction were carried out by two researchers independently.

**RESULTS:** Twenty-four studies on use of anti-IL-1 drugs were included [15 studies including patients with diagnosis of DIRA (n = 19) and 9 studies including patients with diagnosis of DITRA (n = 9)]. Most studies followed a multicenter observational design. Among all patients who received treatment with anti-IL-1 drugs, nine and four mutations in IL1RN and IL36RN were found, respectively. Patients with DIRA were treated with anakinra (n = 17), canakinumab (n = 2), or rinolacept (n = 6). All patients with DITRA were treated with anakinra, and only one case was also treated with canakinumab. Time-to-response frequencies were evaluated as immediate, short, and medium-long term for DIRA (17/17, 15/17, and 9/10, respectively) and DITRA (7/9, 3/9, and 2/9, respectively). Most DITRA patients in whom anti-IL-1 treatment failed experienced good response to anti-tumor necrosis factor alpha or anti-IL-12/23 drugs. The safety profiles of treatments were similar in both diseases.

**CONCLUSIONS:** Evidence on use of anti-IL-1 drugs in DIRA and DITRA is scarce and based on observational studies. Larger studies with better methodological quality are needed to increase confidence in use of these drugs in patients with DIRA and DITRA.

DOI: 10.1007/s13555-018-0269-7

PMCID: PMC6261121

PMID: 30392030

## Chronic Recurrent Multifocal Osteomyelitis (CRMO) and Synovitis Acne Pustulosis Hyperostosis Osteitis (SAPHO) Syndrome - Two Presentations of the Same Disease?

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The two most common entities among generally rare but under-diagnosed autoinflammatory bone disorders are chronic recurrent multifocal osteomyelitis (CRMO) and synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome. Due to their similarities, many authors consider CRMO to be a subtype of SAPHO syndrome. The aim of this study was to compare clinical, laboratory, and imaging features and outcomes of patients with CRMO and SAPHO. The analysis of the data from 6 children with CRMO (four girls and two boys, age 3.5-14 years) and of 6 children (6 boys, age 13.5-17.5 years) with SAPHO syndrome was performed. The initiating symptoms in all patients with CRMO were bone pain with multifocal bone lesions. There were no skin manifestations. Five out of six patients achieved control with nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, while one patient required disease-modifying antirheumatic drugs (DMARDs). The initiating symptom in five patients with SAPHO syndrome were severe acne, while in one patient acne occurred two years after the disease onset. Two patients typically developed inflamed sternoclavicular joints and sternum, while the others showed changes affecting other skeletal regions. Three patients achieved control with NSAIDs and corticosteroids, the others required DMARDs and TNF $\alpha$  inhibitors. In comparison with patients with CRMO, patients with SAPHO suffered more frequent and longer lasting exacerbations. In conclusion, CRMO and SAPHO syndrome have an array of common characteristics, but also a number of differences. Nevertheless, further investigation into the etiopathogenesis is required to establish a definite relationship between CRMO and SAPHO.

90. Cell. 2018 Nov 1;175(4):901-902. doi: 10.1016/j.cell.2018.10.032.

Boosting Immunity by Targeting Post-translational Prenylation of Small GTPases.

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Diseases leading to immune activation and autoinflammatory phenotypes may provide a reservoir of potentially druggable pathways for optimizing immune adjuvants or boosting antitumor immune responses. Now, Xia et al. report that lipophilic statins or biphosphonates, targeting the mevalonate pathway, act as efficient vaccine adjuvants and synergize with anti-PD1 against cancer.

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DOI: 10.1016/j.cell.2018.10.032

PMID: 30388448

91. PLoS Biol. 2018 Nov 2;16(11):e3000047. doi: 10.1371/journal.pbio.3000047.  
eCollection 2018 Nov.

Gasdermin D mediates the pathogenesis of neonatal-onset multisystem inflammatory disease in mice.

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Mutated NLRP3 assembles a hyperactive inflammasome, which causes excessive secretion of interleukin (IL)-1 $\beta$  and IL-18 and, ultimately, a spectrum of autoinflammatory disorders known as cryopyrinopathies of which neonatal-onset multisystem inflammatory disease (NOMID) is the most severe phenotype. NOMID mice phenocopy several features of the human disease as they develop severe systemic inflammation driven by IL-1 $\beta$  and IL-18 overproduction associated with damage to multiple organs, including spleen, skin, liver, and skeleton. Secretion of IL-1 $\beta$  and IL-18 requires gasdermin D (GSDMD), which-upon activation by the inflammasomes-translocates to the plasma membrane where it forms pores through which these cytokines are released. However, excessive pore formation resulting from sustained activation of GSDMD compromises membrane integrity and ultimately causes a pro-inflammatory form of cell death, termed pyroptosis. In this study, we first established a strong correlation between NLRP3 inflammasome activation and GSDMD processing and pyroptosis in vitro. Next, we used NOMID mice to determine the extent to which GSDMD-driven pyroptosis influences the pathogenesis of this disorder. Remarkably, all NOMID-associated inflammatory symptoms are prevented upon ablation of GSDMD. Thus, GSDMD-dependent actions are required for the pathogenesis of NOMID in mice.

DOI: 10.1371/journal.pbio.3000047

PMCID: PMC6235378

PMID: 30388107

Conflict of interest statement: I have read the journal's policy and the authors of this manuscript have the following competing interests: GM is a consultant for Aclaris Therapeutics, Inc., and holds stocks of this company. RC receives research support from Amgen, and holds stock of Amgen, Eli- Lilly, and Merck & Co.

92. Arthritis Care Res (Hoboken). 2018 Nov 2. doi: 10.1002/acr.23804. [Epub ahead of print]

A Pilot Study of Infrared Thermal Imaging to Detect Active Bone Lesions in Children with Chronic Nonbacterial Osteomyelitis.

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**OBJECTIVE:** Chronic nonbacterial osteomyelitis (CNO) is an autoinflammatory bone disease. An inexpensive and rapid imaging tool, infrared thermal imaging, was evaluated for its utility to detect active bone lesions in extremities of children with CNO.

**METHODS:** Children with suspected active CNO and healthy controls were enrolled. All subjects underwent infrared thermal imaging of lower extremities. Patients in the CNO group also received an MRI examination. Hyperintensity within bone marrow on a fluid-sensitive T2-weighted MRI sequence was considered confirmatory for inflammation. Infrared thermal data were analyzed using custom software by dividing the leg below the knee into three equal segments longitudinally and adding the distal femur segment as an equal length above knee. Median and 95th percentile temperatures were recorded for each leg segment. Temperature differences between inflamed and uninflamed segments in all subjects (both inter- and intra-subject) were evaluated using a linear mixed-effects model.

**RESULTS:** Thirty children in the suspected/known CNO group and thirty-one healthy children were enrolled. Within healthy controls, males had significantly higher temperature in their lower extremities than females ( $p < 0.05$ ). There was no difference in temperature detected between inflamed leg segments of CNO patients versus uninflamed leg segments of healthy controls. However, within the CNO group, significantly higher temperatures were detected for inflamed vs.

uninflamed distal tibia/fibula segments ( $p < 0.01$ ).

**CONCLUSION:** Children with active CNO lesions in the distal tibia/fibula exhibited higher regional temperatures on average than healthy limbs. Larger studies are warranted to further evaluate the clinical utility of infrared thermal imaging for CNO detection. This article is protected by copyright. All rights reserved.

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DOI: 10.1002/acr.23804

PMID: 30387916

93. Front Immunol. 2018 Oct 17;9:2422. doi: 10.3389/fimmu.2018.02422. eCollection 2018.

Dynamics of Inflammatory Response in Autoinflammatory Disorders: Autonomous and Hyperinflammatory States.

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Autoinflammatory diseases were originally defined as a group of monogenic disorders associated with seemingly unprovoked inflammatory episodes mediated mainly by the innate immune system and without direct involvement of adaptive immunity. The renewed concept encompasses a larger group of disorders including multifactorial diseases, which share the same inflammatory and clinical features with the monogenic disorders. Coining of the "auto" prefix to these inflammatory diseases suggests a constitutively active and self-augmenting innate immune response, but only a subgroup of them including cryopyrin-associated periodic syndrome (CAPS), associated with dominantly inherited gain-of-function NLRP3 variants, fits well with the definition of the "autonomous" inflammatory conditions. However, the "autoinflammation" concept also includes another group of disorders characterized by episodes of exaggerated inflammatory response only when challenged by certain triggers. The dynamics of this latter group can be better defined as a "hyperinflammatory" state, which shares similar characteristics with the innate memory or trained immunity. Differentiation of

"autonomous" and "hyperinflammatory" states of autoinflammatory disorders can provide additional insights to understand their pathogenesis and develop better management strategies since both conditions may have different inflammatory dynamics affecting the severity and frequency of clinical findings and treatment responses.

DOI: 10.3389/fimmu.2018.02422

PMCID: PMC6200036

PMID: 30386349

94. Front Immunol. 2018 Oct 17;9:2334. doi: 10.3389/fimmu.2018.02334. eCollection 2018.

Exploring the Role of Autophagy-Related Gene 5 (ATG5) Yields Important Insights Into Autophagy in Autoimmune/Autoinflammatory Diseases.

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Autophagy is a highly conserved process that degrades certain intracellular contents in both physiological and pathological conditions. Autophagy-related proteins (ATG) are key players in this pathway, among which ATG5 is indispensable in both canonical and non-canonical autophagy. Recent studies demonstrate that ATG5 modulates the immune system and crosstalks with apoptosis. However, our knowledge of the pathogenesis and regulatory mechanisms of autophagy in various immune related diseases is lacking. Thus, a deeper understanding of ATG5's role in the autophagy mechanism may shed light on the link between autophagy and the immune response, and lead to the development of new therapies for autoimmune diseases and autoinflammatory diseases. In this focused review, we discuss the latest insights into the role of ATG5 in autoimmunity. Although these studies are at a relatively early stage, ATG5 may eventually come to be regarded as a "guardian of immune integrity." Notably, accumulating evidence indicates that other ATG genes may have similar functions.



DOI: 10.3389/fimmu.2018.02334

PMCID: PMC6199349

PMID: 30386331

95. J Rheumatol. 2018 Nov 1. pii: jrheum.180056. doi: 10.3899/jrheum.180056. [Epub ahead of print]

An International Delphi Survey for the Definition of New Classification Criteria for Familial Mediterranean Fever, Mevalonate Kinase Deficiency, TNF Receptor-associated Periodic Fever Syndromes, and Cryopyrin-associated Periodic Syndrome.

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Rheumatology, Nijmegen, the Netherlands; Unité Romande d'Immuno-rhumatologie Pédiatrique, Centre hospitalier universitaire vaudois (CHUV), University of Lausanne, Lausanne; Geneva University Hospitals, Geneva, Switzerland. This study is part of the International Study Group for Systemic Autoinflammatory Diseases project, funded by the E-Rare-3 program, grant number 9003037603. S. Federici, MD, PhD, Istituto Giannina Gaslini, Clinica Pediatrica e Reumatologia, PRINTO; F. Vanoni, MD, Ospedale Regionale di Bellinzona e Valli, Dipartimento di Pediatria, and Geneva University Hospitals; E. Ben-Chetrit, MD, Hadassah-Hebrew University Hospital, Rheumatology Unit; L. Cantarini, MD, PhD, University of Siena, Department of Medical Sciences, Surgery and Neurosciences, Rheumatology Unit; J. Frenkel, MD, PhD, Wilhelmina Kinderziekenhuis, Universitair Medisch Centrum Utrecht, Afdeling Kinderreumatologie; R. Goldbach-Mansky, MD, MHS, Rady Children's Specialists of San Diego; A. Gul, MD, İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi, Pediatrik Romatoloji; H. Hoffman, MD, Rady Children's Specialists of San Diego; I. Koné-Paut, MD, Department of Pediatric Rheumatology, National Referral Centre of Auto-Inflammatory Diseases CEREMAI, CHU de Bicêtre, AP-HP, University of Paris Sud, le Kremlin Bicêtre; J. Kuemmerle-Deschner, MD, Division of Rheumatology, Department of Pediatrics and Autoinflammation Reference Center Tübingen, University Hospital Tübingen; H.J. Lachmann, MD, Royal Free Campus, National Amyloidosis Centre; A. Martini, MD, Istituto Giannina Gaslini, Direzione Scientifica; L. Obici, MD, Fondazione IRCCS Policlinico San Matteo, Centro per lo Studio e la Cura delle Amiloidosi Sistemiche; S. Ozen, MD, Hacettepe University, Department of Pediatric Rheumatology; A. Simon, MD, PhD, Radboud UMC, Pediatric Rheumatology; M. Hofer, MD, Unité Romande d'Immuno-rhumatologie Pédiatrique, CHUV, University of Lausanne, and Geneva University Hospitals; N. Ruperto, MD, MPH, Istituto Giannina Gaslini, Clinica Pediatrica e Reumatologia, PRINTO; M. Gattorno, MD, Istituto Giannina Gaslini, Clinica Pediatrica e Reumatologia, PRINTO. These authors contributed equally to this article: S. Federici, F. Vanoni, N. Ruperto, and M. Gattorno. Address correspondence to Dr. S. Federici, Istituto Giannina Gaslini, Pediatric Division, Via Gaslini 5, Genoa 16147, Italy. E-mail: [silviafederici@gmail.com](mailto:silviafederici@gmail.com). Accepted for publication July 18, 2018.

**OBJECTIVE:** Provisional evidence-based classification criteria for hereditary periodic fever (HPF) have been recently developed. However, no consensus on how to combine clinical criteria, laboratory tests, and results of molecular analysis has been reached. The objective of this study is to understand which variables physicians consider important for the classification of patients with HPF.

**METHODS:** Two Delphi surveys were sent to health professionals in the field of autoinflammation. In the first open survey, 124 researchers could list all the

variables they consider useful for the diagnosis of each monogenic periodic fever. The variables could be of any type and each researcher could complete the survey for 1 or more diseases. In the second survey, 162 researchers were asked to select, from a list of items coming from the first survey, the 10 top variables and to rank them by assigning a score from 10 to 1.

**RESULTS:** The response rates to the Delphi surveys were 85% for the first session and 87% for the second. The variables selected for each disease (corresponding to the third quartile, considering the total score obtained by the variables after the second Delphi survey) were 21 for mevalonate kinase deficiency, 22 for cryopyrinopathies, 18 for familial Mediterranean fever, and 20 for tumor necrosis factor receptor-associated periodic fever syndrome. A positive genetic test reached the top rank in all the HPF.

**CONCLUSION:** Our process led to the identification of those features considered the most important as candidate variables to be included in a new set of evidence-based classification criteria for HPF.

DOI: 10.3899/jrheum.180056

PMID: 30385706

96. Immunol Lett. 2018 Sep;201:38-44. doi: 10.1016/j.imlet.2018.10.013. Epub 2018 Oct 29.

Critical regulation of Th17 cell differentiation by serum amyloid-A signalling in Behcet's disease.

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The current understandings on cellular and molecular biology suggest that Th17 axis plays a pivotal role in Behcet's disease (BD) pathogenesis. Recently the role of serum amyloid-A (SAA) as a potential marker of disease activity in BD patients has been explored, and it has been reported that the occurrence of specific clinical features are significantly associated with high serum levels of this inflammatory mediator. The aim of this study was to investigate the cytokine-like activity of SAA in inducing Th17 differentiation from CD4 + T naive cells in BD. Purified peripheral monocytes from BD and healthy control (HC) were stimulated with SAA "in vitro", and secreted IL-8, TNF- $\alpha$ , IL-18, IFN- $\alpha$ , IFN- $\gamma$ , IL-1 $\beta$  and IL-6 were measured using a Bio-Rad multiplex cytokine immunoassay. To assess Th17 differentiation, purified CD4 + T cells were challenged with anti-CD3/CD28 antibodies, while cultured with supernatant derived from SAA stimulated monocytes, and intracellular staining of IL-17A and IFN- $\gamma$  was evaluated by flow-cytometry. Furthermore, peripheral blood mononuclear cells (PBMCs) were stimulated with SAA and transcript levels of RAR-related orphan nuclear receptor (ROR)- $\gamma$ t and IL-17A were assessed by Real-time PCR. Upon stimulation with SAA, monocytes obtained from both HC and BD groups released large amounts of IL-8, IL-6, TNF- $\alpha$ , IL-1 $\beta$  and IFN- $\alpha$ . Monocytes-derived supernatants from BD patients, but not HC, were capable of promoting Th17 but not Th1 differentiation from CD4 + T cells. However, SAA did not induce up-regulation of Th17 specific mRNA transcript such as IL-17A and (ROR)- $\gamma$ t in PBMCs from both HC and BD. In BD patients SAA induced Th17 polarization rather than Th1 differentiation from CD4 + T cells. These data suggest that a critical regulation of Th17 may be the functional link between acute SAA increase and the induction of Th17 mediated inflammatory response in BD.

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DOI: 10.1016/j.imlet.2018.10.013

PMID: 30385329

97. Aging (Albany NY). 2018 Oct 31;10(10):2935-2943. doi: 10.18632/aging.101600.

The influence of the TNF $\alpha$  rs1800629 polymorphism on some inflammatory biomarkers in 45-60-year-old women with metabolic syndrome.

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**INTRODUCTION:** There are reports that the TNF $\alpha$  gene (rs1800629) can be involved in the pathogenesis of metabolic syndrome through an increased production of pro-inflammatory cytokines. Therefore, we have decided to search for the relationship between the TNF $\alpha$  gene polymorphisms and serum levels of proinflammatory cytokines (IL-1 $\alpha$ , IL-1 $\beta$ , IL-6, TNF $\alpha$ , IFN $\gamma$ ) and CRP in women with metabolic syndrome.

**MATERIAL AND METHODS:** The study sample consisted of 416 women aged 45-60 years, including 118 with metabolic syndrome. The participants were surveyed and subjected to anthropometric, biochemical and genetic analysis.

**RESULTS:** We noticed that in the group meeting the criteria for metabolic syndrome, the G/G genotype of the TNF $\alpha$  gene was related to higher IL-6 levels than in the remainder group. The carriers of the A/G genotype in the metabolic syndrome group had significantly higher levels of IFN $\gamma$  than those in the group without this syndrome. CRP was significantly higher in the group with metabolic syndrome, irrespective of the women's genotypes.

**CONCLUSIONS:** The upregulation of IFN $\gamma$  and IL-6 and CRP suggests that autoinflammatory process may play a significant role in the pathogenesis of metabolic syndrome. However, a direct relationship between the TNF $\alpha$  gene polymorphisms and inflammatory biomarkers analyzed in our study was not confirmed.

DOI: 10.18632/aging.101600

PMCID: PMC6224245

PMID: 30383538

## Renal Amyloidosis in Deficiency of Adenosine Deaminase 2: Successful Experience With Canakinumab.

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Deficiency of adenosine deaminase 2 (DADA2) is a rare autoinflammatory disease that was firstly described in patients with early-onset strokes, livedo reticularis, and periodic fever resembling polyarteritis nodosa. In reported case series, researchers described highly variable manifestations, including autoimmunity, immunodeficiency, hepatosplenomegaly, pancytopenia, ichthyosiform rash, and arthritis, in patients with DADA2. A thirteen-year-old female patient who was born to consanguineous parents was admitted to our hospital with generalized edema and leg pain. A physical examination revealed splenomegaly and left knee arthritis. Nephrotic-range proteinuria and hypoalbuminemia were present, and a renal biopsy revealed amyloidosis. Despite the absence of periodic fever and livedo reticularis, our patient had suggestive features of DADA2, including low serum immunoglobulin G and immunoglobulin M levels, hepatosplenomegaly, and renal amyloidosis. We found a heterozygote Met694Val mutation in the Mediterranean fever gene and a novel homozygote Thr317Argfs\*25 (c.950-950delCys) mutation in the cat eye chromosome region 1 gene. A functional analysis revealed absent plasma adenosine deaminase 2 activity. Canakinumab was administered because of unresponsive proteinuria despite 2 months of treatment with colchicine and methylprednisolone. Proteinuria improved after 7 doses of canakinumab. In conclusion, DADA2 should be considered in the differential diagnosis of renal amyloidosis, particularly in the absence of homozygote Mediterranean fever mutations. Although anti-tumor necrosis factor agents are widely offered in DADA2 treatment, we speculate that canakinumab may be an

appropriate treatment of renal amyloidosis in DADA2.

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DOI: 10.1542/peds.2018-0948

PMID: 30377239

Conflict of interest statement: POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

99. J Allergy Clin Immunol. 2018 Dec;142(6):1710-1718. doi: 10.1016/j.jaci.2018.10.015. Epub 2018 Oct 25.

Regulatory T-cell therapy for autoimmune and autoinflammatory diseases: The next frontier.

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Forkhead box P3-expressing regulatory T (Treg) cells are essential for self-tolerance, with an emerging role in tissue repair and regeneration. Their ability to traffic to tissue and perform complex therapeutic tasks in response to the tissue microenvironment make them an attractive candidate for drug development. Early experiences of Treg cell therapy in patients with graft-versus-host disease, type 1 diabetes, and organ transplantation have shown that it is feasible, safe, and potentially efficacious in some settings. Many ongoing trials in patients with a wide variety of diseases will further enhance our knowledge about the optimal approaches for Treg cell manufacturing and

dosing. We review the current preclinical rationale supporting Treg cell therapy in a variety of disease settings ranging from tissue transplantation, autoimmune diseases, and non-immune-mediated inflammatory settings. We point out challenges in development of Treg cell therapy and speculate how synthetic biology can be used to enhance the feasibility and efficacy of Treg cell therapy for autoimmune and autoinflammatory diseases.

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DOI: 10.1016/j.jaci.2018.10.015

PMID: 30367909

100. F1000Res. 2018 Oct 16;7. pii: F1000 Faculty Rev-1647. doi: 10.12688/f1000research.15500.1. eCollection 2018.

Cholesterol metabolism in innate and adaptive response.

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It has been long recognized that cholesterol is a critical molecule in mammalian cell biology, primarily for its contribution to the plasma membrane's composition and its role in assuring proper transmembrane receptor signaling as part of lipid rafts. Efforts have also been made to characterize the cholesterol biosynthetic pathway, cholesterol homeostasis, and cholesterol-derived metabolites in order to gain insights into their dysregulation during metabolic diseases. Despite the central role cholesterol metabolism plays in shaping human health, its regulation during immune activation, such as immune response to pathogens or autoimmune/autoinflammatory diseases, is poorly understood. The immune system is composed of several type of cells with distinct developmental origin, life span, molecular requirements, and gene expressions. It is unclear whether the same array of cholesterol metabolism regulators are equally employed by different



immune cells and whether distinct cholesterol metabolites have similar biological consequences in different immune cells. In this review, we will describe how cholesterol metabolism is controlled during the adaptive and the innate immune response and the role for intracellular and extracellular receptors for cholesterol and its derivatives.

DOI: 10.12688/f1000research.15500.1

PMCID: PMC6192436

PMID: 30364153

Conflict of interest statement: No competing interests were disclosed.No competing interests were disclosed.No competing interests were disclosed.

101. Intern Emerg Med. 2018 Oct 25. doi: 10.1007/s11739-018-1970-3. [Epub ahead of print]

Long-term effectiveness and safety of switching from originator to biosimilar infliximab in patients with Behçet's disease.

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DOI: 10.1007/s11739-018-1970-3

PMID: 30361849

102. J Pediatr. 2019 Jan;204:270-274. doi: 10.1016/j.jpeds.2018.08.080. Epub 2018 Oct 22.

Familial Mediterranean Fever Is Commonly Diagnosed in Children in Israel with Periodic Fever Aphthous Stomatitis, Pharyngitis, and Adenitis Syndrome.

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**OBJECTIVES:** To describe a cohort of pediatric patients diagnosed with periodic fever aphthous stomatitis, pharyngitis and adenitis (PFAPA) and familial Mediterranean fever (FMF) and compare them with children diagnosed solely with PFAPA (sPFAPA).

**STUDY DESIGN:** Clinical, laboratory, and genetic data of all pediatric patients diagnosed with sPFAPA or PFAPA/FMF were retrospectively collected from 2 primary Israeli medical referral centers and compared.

**RESULTS:** Of 270 patients with PFAPA, more than one-half were of Mediterranean ancestry. Among patients with PFAPA, 51 (18.9%) also were diagnosed with FMF (PFAPA/FMF). Genetic data on the 9 most common MEFV variants were available for 45 children (88%) in the PFAPA/FMF group. Two variants were found in 15 children (33.3 %), 1 variant was found 27 patients (60%), and 3 patients (6.6%) had no

variants. Abdominal pain, myalgia, and arthralgia each were more commonly reported in the PFAPA/FMF group compared with the sPFAPA group (90% vs 49% [ $P < .0001$ ]; 46% vs 23% [ $P = .02$ ]; and 30% vs 17% [ $P = .049$ ], respectively).

Colchicine was more commonly prescribed for the PFAPA/FMF group compared with the sPFAPA group (82% vs 29%;  $P < .0001$ ), but alleviation of PFAPA symptoms with colchicine was similar between groups (75% vs 63%;  $P = .23$ ).

**CONCLUSION:** We show a strong association between 2 common autoinflammatory syndromes, PFAPA and FMF, in patients from Mediterranean ancestry. Clinicians should be aware that presentation of 1 disease may clinically evolve into another. The association between PFAPA and FMF poses the question similar pathogenesis and genetic influence of the MEFV gene on PFAPA.

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DOI: 10.1016/j.jpeds.2018.08.080

PMID: 30361059

103. Cell Rep. 2018 Oct 23;25(4):921-933.e5. doi: 10.1016/j.celrep.2018.09.001.

IFN $\alpha$  Impairs Autophagic Degradation of mtDNA Promoting Autoreactivity of SLE Monocytes in a STING-Dependent Fashion.

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Interferon  $\alpha$  (IFN $\alpha$ ) is a prompt and efficient orchestrator of host defense against nucleic acids but upon chronicity becomes a potent mediator of autoimmunity. Sustained IFN $\alpha$  signaling is linked to pathogenesis of systemic lupus erythematosus (SLE), an incurable autoimmune disease characterized by aberrant self-DNA sensing that culminates in anti-DNA autoantibody-mediated pathology. IFN $\alpha$  instructs monocytes differentiation into autoinflammatory dendritic cells (DCs) than potentiates the survival and expansion of autoreactive lymphocytes, but the molecular mechanism bridging sterile IFN $\alpha$ -danger alarm with adaptive response against self-DNA remains elusive. Herein, we demonstrate IFN $\alpha$ -mediated deregulation of mitochondrial metabolism and impairment of autophagic degradation, leading to cytosolic accumulation of mtDNA that is sensed via stimulator of interferon genes (STING) to promote induction of autoinflammatory DCs. Identification of mtDNA as a cell-autonomous enhancer of IFN $\alpha$  signaling underlines the significance of efficient mitochondrial recycling in the maintenance of peripheral tolerance. Antioxidant treatment and metabolic rescue of autolysosomal degradation emerge as drug targets in SLE and other IFN $\alpha$ -related pathologies.

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DOI: 10.1016/j.celrep.2018.09.001

PMCID: PMC6218203

PMID: 30355498

104. Cell Death Dis. 2018 Oct 23;9(11):1088. doi: 10.1038/s41419-018-1121-9.

Progressive waves of IL-1 $\beta$  release by primary human monocytes via sequential activation of vesicular and gasdermin D-mediated secretory pathways.

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IL-1 $\beta$  is an essential cytokine, but its release needs to be strictly controlled to avoid severe inflammatory manifestations. Lacking a signal sequence, IL-1 $\beta$  does not follow the endoplasmic reticulum-Golgi route. Several pathways have been proposed to mediate its release. One involves the translocation of pro-IL-1 $\beta$  into intracellular vesicles of lysosomal origin that eventually fuse with the plasma membrane. Another exploits pores formed on the plasma membrane upon proteolytic cleavage of gasdermin D (GSDMD). Here we investigated how primary monocytes-the main source of IL-1 $\beta$  in humans-control IL-1 $\beta$  release in response to pro-inflammatory stimuli of increasing intensity and found that two different routes are induced depending on the strength of activation. Triggering of Toll-like receptor 4 (TLR4) by LPS induces slow IL-1 $\beta$  release through LAMP2A+ vesicles. In contrast, the simultaneous stimulation of TLR2, TLR4 and TLR7/8 drives high levels of ROS, GSDMD cleavage and faster IL-1 $\beta$  secretion. Drugs blocking ROS production prevent GSDMD cleavage supporting a role of oxidative stress in GSDMD-mediated secretion. Singly stimulated monocytes undergo apoptosis, whereas triple stimulation triggers pyroptosis, which might amplify inflammation. In both cases, however, IL-1 $\beta$  secretion precedes cell death. Inhibition of caspases 4/5 prevents GSDMD cleavage and pore-mediated secretion, but not vesicular release. The two pathways also display other distinct pharmacologic sensitivities that reflect the underlying mechanisms. Remarkably, single TLR4 stimulation is sufficient to activate massive, GSDMD-mediated IL-1 $\beta$  secretion in monocytes from patients affected by Cryopyrin Associated Periodic Syndrome (CAPS), an autoinflammatory disease linked to NLRP3 mutations. The exaggerated sensitivity to activation correlates with high basal ROS levels in CAPS monocytes. In conclusion, the vesicular pathway limits IL-1 $\beta$  release upon low pathogen load while stronger stimulation or concomitant cell stress induce instead uncontrolled secretion via GSDMD leading to detrimental inflammatory

manifestations.

DOI: 10.1038/s41419-018-1121-9

PMCID: PMC6199333

PMID: 30352992

105. Orv Hetil. 2018 Oct;159(43):1761-1766. doi: 10.1556/650.2018.31137.

[Chronic, nonbacterial, multicentric osteomyelitis in the mandible].

[Article in Hungarian; Abstract available in Hungarian from the publisher]

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Chronic nonbacterial osteomyelitis is a sterile inflammatory osteitis that most commonly develops in the long bones, but it can occur in any bone. Mandibular lesions are found in 1.5-3% of disease foci in patients and it is poorly characterized in the maxillofacial surgery literature due to the use of inconsistent terminology. The purpose of this study was to present the clinical experience of chronic nonbacterial multicentric osteomyelitis and a collection of research and information of the disease. This is a retrospective study of 2 cases with mandibular lesions radiographically consistent with osteomyelitis without infection. Medical records were reviewed for history, clinical features, imaging and pathology. The study included 2 patients (2 females, age of 17 and 43 years). Both reported mandibular pain and swelling, radiographic finding of multifocal intraosseal inflammatory lesions. Computed tomography scans typically showed expansion of the affected mandible with sclerosis of the medullary space, small foci of poorly defined lytic destruction with lamellated periosteal reaction. Both patients showed a long ineffective antibiotic therapy and recurrent flare-ups of inflammation. After the proper course of treatment (nonsteroid and steroid therapy), a long painless period was reached. Chronic multicentric

nonbacterial osteomyelitis has been reported to be uncommon in the mandible, but it may be more common with correct diagnosis, typified by recurrent pain and swelling with characteristic pathologic and radiologic features. The current treatment modalities include nonsteroidal anti-inflammatory drugs or steroids. Orv Hetil. 2018; 159(43): 1761-1766.

Publisher: Absztrakt: A krónikus, nem bakteriális multicentrikus osteomyelitis ritka steril gyulladásos csontelváltozás, amely a legtöbbször a hosszú csöves csontokat érinti, de létrejöhet más csontokban is. A mandibulában az esetek 1,5–3%-ában fordul elő. A maxillofacialis sebészeti irodalomban az elnevezéssel kapcsolatban nincs egységes álláspont, bizonyos fokú konfúzió észlelhető. A dolgozat célja bemutatni a betegséget és az ezzel kapcsolatos kutatásokat, információkat az arc-állcsont sebészetre koncentrálni. Két esetet retrospektíve tárgyalnak, mindkettőnek a mandibulájában többszörös elváltozás volt. Klinikailag, radiológiailag, hisztológiailag nem bakteriális eredetű idült, többgócú csontgyulladást lehetett megállapítani. A betegség mindkét esetben több évig tartott. A dolgozat egy 17 és egy 43 éves nő kapcsán tárgyalja a krónikus, nem bakteriális, multicentrikus recidiváló osteomyelitis diagnosztikus kritériumait: állcsontfájdalom és -duzzanat, radiológiailag többszöri gyulladásos elváltozás. A komputertomográfus vizsgálat az érintett mandibularész típusos expanzióját, a csontvelő sclerosisát, kis gócban rosszul meghatározható felritkulásokat és a periosteum lamelláris reakcióját mutatta. Mindkét beteg esetében hosszú eredménytelen antibiotikus kezelés történt, a gyulladás többszöri fellángolásával. A megfelelő kezelés után, amely nonszteroid gyulladáscsökkentőkből, majd szteroidból állt, hosszú fájdalom- és gyulladásmentes időszak következett be. A krónikus, többgócú, nem bakteriális eredetű osteomyelitis ritkán fordul elő az állcsontokban, de valószínű, hogy korrekt diagnózis esetén az irodalomban leírtaknál gyakoribb lehet. A tipikus ismétlődő fájdalom és duzzanat, a hosszadalmas lefolyás a radiológiai ismérvekkel együtt megadja a kórismét, és a kezelésben elkerülhető lehet az eredménytelen antibiotikus terápia és a többszöri biopszia. A megfelelő gyógymód: a nonszteroid gyulladáscsökkentők vagy szteroidok, minimáldózisú fenntartó kezeléssel. Orv Hetil. 2018; 159(43): 1761–1766.  
DOI: 10.1556/650.2018.31137  
PMID: 30346236

# Role of fecal calprotectin in the assessment of intestinal inflammation in children with familial Mediterranean fever.

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**AIM:** Familial Mediterranean fever (FMF) is the most common auto-inflammatory disease with recurrent fever and serositis episodes. In recent years, some cases with FMF were reported with gastrointestinal involvement without amyloidosis, vasculitis and inflammatory bowel disease (IBD). It is not yet known whether gastrointestinal involvement is a part of the disease or not. The aim of this study is to investigate the frequency of intestinal inflammation by using a noninvasive method, fecal calprotectin measurement, in pediatric FMF patients.

**METHOD:** Sixty-five FMF patients, 30 healthy controls and 11 patients with acute ulcerative colitis were included in the study. A standard survey inquiring gastrointestinal and other clinical symptoms was completed. The medications, MEFV mutations, whole blood count and C-reactive protein levels were recorded. Fecal calprotectin was studied with the enzyme-linked immunosorbent assay method from the feces samples of the all subjects.

**RESULTS:** None of the FMF patients had clinical signs of IBD. Fecal calprotectin levels of the FMF patients were found to be significantly higher than the healthy controls ( $174.8 \pm 150.8$  vs  $52.9 \pm 36.5$ ,  $p < 0.001$ ). Fecal calprotectin levels of the ulcerative colitis patients were significantly higher than the FMF patients ( $523.5 \pm 183$  vs  $174.8 \pm 150.8$ ,  $p = 0.001$ ). There was a correlation between fecal calprotectin levels and neutrophil/lymphocyte ratio ( $r = 0.324$ ,  $p = 0.009$ ).

**CONCLUSION:** Our results supported subclinical intestinal inflammation in pediatric FMF patients. Further studies are needed to clarify the reason for intestinal inflammation in FMF patients.



Australia, Ltd.

DOI: 10.1111/1756-185X.13396

PMID: 30345692

107. *Pediatr Gastroenterol Hepatol Nutr.* 2018 Oct;21(4):271-277. doi: 10.5223/pghn.2018.21.4.271. Epub 2018 Oct 10.

Endoscopic Findings of Children with Familial Mediterranean Fever.

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**Purpose:** Familial Mediterranean fever (FMF) is an auto inflammatory disease characterized by periodic fever, synovitis and serositis. Patients may be admitted to gastroenterology units due to gastrointestinal symptoms. In this study; we aimed to analyze endoscopic findings and diagnostic utility of endoscopic procedure in children with FMF.

**Methods:** Patient with FMF that was performed endoscopy for the gastrointestinal symptoms were included to the study (39 of 164 patients, 53 procedure). A control group was randomly designed as age and gender matched four endoscopic procedures per one endoscopic procedure of patients with FMF (n=212).

**Results:** No different was found between the patients and control group in esophagogastrosocopy findings. However, the diagnosis of gastrointestinal pathology was made by esophagogastrosocopy in 46.2% patients. Colonoscopic examination revealed that the frequency of inflammatory bowel disease (IBD) was higher in undiagnosed patients compared to both the control group (50.0% vs. 6.9%,  $p<0.05$ , odds ratio [OR]:13.4 and 95% confidence interval [95% CI]: 2.1-84.3) and the patients under colchicine treatment (50.0% vs. 8.3%,  $p<0.05$ , OR: 11 and 95% CI: 0.8-147.8). Colonoscopic procedure that was made after the diagnosis was found to provide contribution by 16.7% in determining the etiology of the

additional symptoms.

Conclusion: Patients with FMF may be admitted to pediatric gastroenterology outpatient clinic prior to diagnosis or during the follow-up period. The frequency of IBD is high in undiagnosed patients with FMF. Endoscopic procedures may be helpful in these patients for the diagnosis accompanying mucosal lesions.

DOI: 10.5223/pghn.2018.21.4.271

PMCID: PMC6182485

PMID: 30345240

108. Oncotarget. 2018 Sep 28;9(76):34357-34378. doi: 10.18632/oncotarget.26173. eCollection 2018 Sep 28.

Functional characterization of phospholipase C- $\gamma$ 2 mutant protein causing both somatic ibrutinib resistance and a germline monogenic autoinflammatory disorder.

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Depending on its occurrence in the germline or somatic context, a single point mutation, S707Y, of phospholipase C- $\gamma$ 2 (PLC $\gamma$ 2) gives rise to two distinct human disease states: acquired resistance of chronic lymphocytic leukemia cells (CLL) to inhibitors of Bruton's tyrosine kinase (Btk) and dominantly inherited autoinflammation and PLC $\gamma$ 2-associated antibody deficiency and immune dysregulation, APLAID, respectively. The functional relationships of the PLC $\gamma$ 2S707Y mutation to other PLCG2 mutations causing (i) Btk inhibitor resistance

of CLL cells and (ii) the APLAID-related human disease PLC $\gamma$ 2-associated antibody deficiency and immune dysregulation, PLAID, revealing different clinical characteristics including cold-induced urticaria, respectively, are currently incompletely understood. Here, we show that PLC $\gamma$ 2S707 point mutants displayed much higher activities at 37° C than the CLL Btk inhibitor resistance mutants R665W and L845F and the two PLAID mutants, PLC $\gamma$ 2 $\Delta$ 19 and PLC $\gamma$ 2 $\Delta$ 20-22. Combinations of CLL Btk inhibitor resistance mutations synergized to enhance PLC $\gamma$ 2 activity, with distinct functional consequences for different temporal orders of the individual mutations. Enhanced activity of PLC $\gamma$ 2S707Y was not observed in a cell-free system, suggesting that PLC $\gamma$ 2 activation in intact cells is dependent on regulatory rather than mutant-enzyme-inherent influences. Unlike the two PLAID mutants, PLC $\gamma$ 2S707Y was insensitive to activation by cooling and retained marked hyperresponsiveness to activated Rac upon cooling. In contrast to the PLAID mutants, which are insensitive to activation by endogenously expressed EGF receptors, the S707Y mutation markedly enhanced the stimulatory effect of EGF, explaining some of the pathophysiological discrepancies between immune cells of PLAID and APLAID patients in response to receptor-tyrosine-kinase activation.

DOI: 10.18632/oncotarget.26173

PMCID: PMC6188132

PMID: 30344948

Conflict of interest statement: CONFLICTS OF INTEREST The authors declare that they have no conflicts of interest.

109. ACS Med Chem Lett. 2018 Sep 19;9(10):965-966. doi: 10.1021/acsmchemlett.8b00416. eCollection 2018 Oct 11.

NLRP3 Modulators for the Treatment of Autoinflammatory Disorders.

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DOI: 10.1021/acsmchemlett.8b00416

PMCID: PMC6187397 [Available on 2019-10-11]

PMID: 30344900

Conflict of interest statement: The author declares no competing financial interest.

110. J Cell Physiol. 2018 Oct 20. doi: 10.1002/jcp.27576. [Epub ahead of print]

Behçet's disease: An immunogenetic perspective.

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Behçet's disease (BD) is a chronic and rare multisystemic disorder defined by autoimmunity and inflammatory characteristics, manifested by ocular lesions, recurrent genital and oral ulcers, skin symptoms and arthritis as well as neurological, intestinal, and vascular involvement. Despite the unknown cause of BD, there is some strong documentation for immunological, genetic, environmental, and infectious factors playing a role in the pathogenesis of BD. While the nature of the genetic variants remains unidentified, many genetic risk factors are considered to contribute to BD susceptibility. Along with human leukocyte antigen gene encoding B\*51 (HLA-B\*51) and areas including the major histocompatibility complex class I, genome-wide association studies have recognized numerous other

BD susceptibility genes including those encoding interleukin (IL)-10, IL-12 receptor  $\beta$  2 (IL-12RB2), IL-23 receptor (IL-23R), C-C chemokine receptor 1 gene, signal transducer and activator of transcription 4 (STAT4), endoplasmic reticulum aminopeptidase (ERAP1), and genes encoding killer cell lectin-like receptor family members (KLRC4-KLRK1). It is believed that BD could be considered as a disorder lying in between autoimmune and autoinflammatory syndromes. The positive responses to classical immunosuppressive agents like azathioprine and cyclosporine and involvement of autoantigens in the initiation of the disorder are the main BD features that reflect the autoimmune nature of the disorder. In this review, we address recent findings on the role of common cytokines, antibodies and immunogenetic factors in BD.

© 2018 Wiley Periodicals, Inc.

DOI: 10.1002/jcp.27576

PMID: 30341905

111. Oral Maxillofac Surg. 2018 Dec;22(4):365-368. doi: 10.1007/s10006-018-0727-5. Epub 2018 Oct 19.

A novel treatment of temporomandibular joint arthritis as a complication in familial Mediterranean fever-literature review and a case report.

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**OBJECTIVES:** Articular involvement in familial Mediterranean fever (FMF) ranges between 40 and 70% of the patients. Involvement of temporomandibular joint (TMJ) in FMF is very rare, and only a few cases have been reported in the literature. There are no specific guidelines for treatment. We hereby present a new treatment for TMJ inflammation in FMF.

**MATERIALS AND METHODS:** A literature search was performed using PubMed according to the following criteria: key terms included in the search were FMF arthritis, TMJ involvement in FMF patients, and arthroscopy in FMF patients. All keywords were included both as medical subject headings (MeSH) terms and text words. Selections were limited to the English language.

**RESULTS:** Literature search yielded four reported cases of TMJ involvement in FMF patients. The four cases were treated differently, with no clear guidelines for management of TMJ involvement. Our patient suffered from painful swelling and redness over the involved TMJ area and severe trismus. She was treated by arthroscopic lysis and lavage of her TMJ followed by aggressive physiotherapy resulting to improvement of her mouth opening.

**CONCLUSIONS:** The adverse effect of TMJ arthritis in FMF patients can be avascular necrosis and destruction of the mandibular condylar head. TMJ arthroscopy allows lysis and lavage of the joint with minimal operative and postoperative complication, resulting with satisfactory results. Thus, in case of TMJ arthritis in FMF, we recommend TMJ arthroscopy as soon as possible, following aggressive physiotherapy in order to gain normal mouth opening.

**CLINICAL RELEVANCE:** FMF rates have been described among the Mediterranean and Middle Eastern population ranging from 1:5 to 1:3; thus, TMJ involvement due to the disease is not so rare in this region, and a clear treatment protocol is needed.

DOI: 10.1007/s10006-018-0727-5

PMID: 30341473

112. Br J Dermatol. 2018 Oct 19. doi: 10.1111/bjd.17334. [Epub ahead of print]

Association of CCL2 with systemic inflammation in Schnitzler syndrome.

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**BACKGROUND:** Schnitzler syndrome (SchS) is a rare autoinflammatory disease characterized by urticarial exanthema, bone and joint alterations, fever and monoclonal gammopathy, which manifest mostly in the second half of life. It involves overactivation of the interleukin (IL)-1 system, but the exact pathophysiological pathways remain largely unknown.

**OBJECTIVES:** To identify and characterize the pathogenetic players in SchS.

**METHODS:** Blood parameters were quantified in patients with SchS compared with healthy controls and patients with psoriasis and hidradenitis suppurativa using enzyme-linked immunosorbent assay (ELISA). CCL2 expression in cultured primary cells was analysed by quantitative reverse-transcriptase polymerase chain reaction and ELISA.

**RESULTS:** CCL2, a chemoattractant for monocytic and further mononuclear immune cells, was found to be significantly elevated in patients with SchS. CCL2 levels showed a positive association with global disease activity, especially with bone pain, but not disease duration, gammopathy, neutrophilia or skin disease. In vitro stimulation assays demonstrated a strong CCL2 production capacity of mononuclear immune cells and fibroblasts, but not epithelial or endothelial cells. Among a range of inflammatory mediators, only IL-1 $\beta$  (immune cells, fibroblasts) and tumour necrosis factor (TNF)- $\alpha$  (fibroblasts) were important CCL2 inducers. TNF- $\alpha$ , but not IL-17, strengthened the CCL2-inducing effect of IL-1 $\beta$  in fibroblasts. Accordingly, CCL2 levels positively correlated with both TNF- $\alpha$  and IL-1 $\beta$  serum levels in patients with SchS. Therapeutic IL-1 $\beta$  blockade decreased CCL2 blood levels in these patients as early as 1 week after the initiation of treatment.

**CONCLUSIONS:** CCL2 may be an important component of the pathogenetic cascade leading to bone alterations, and a suitable marker of disease activity in patients with SchS.

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DOI: 10.1111/bjd.17334

PMID: 30339714

113. Cochrane Database Syst Rev. 2018 Oct 19;10:CD010893. doi: 10.1002/14651858.CD010893.pub3.

Interventions for reducing inflammation in familial Mediterranean fever.

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Update of

Cochrane Database Syst Rev. 2015 Mar 20;(3):CD010893.

**BACKGROUND:** Familial Mediterranean fever, a hereditary auto-inflammatory disease, mainly affects ethnic groups living in the Mediterranean region. Early studies reported colchicine as a potential drug for preventing attacks of familial Mediterranean fever. For those people who are colchicine-resistant or intolerant, drugs such as rilonacept, anakinra, canakinumab, etanercept, infliximab, thalidomide and interferon-alpha might be beneficial. This is an updated version of the review.

**OBJECTIVES:** To evaluate the efficacy and safety of interventions for reducing inflammation in people with familial Mediterranean fever.

**SEARCH METHODS:** We used detailed search strategies to search the following databases: CENTRAL; MEDLINE; Embase; Chinese Biomedical Literature Database (CBM); China National Knowledge Infrastructure Database (CNKI); Wan Fang; and VIP. In addition, we also searched the clinical trials registries including ClinicalTrials.gov, the International Standard Randomized Controlled Trial Number Register, the WHO International Clinical Trials Registry Platform and the Chinese Clinical Trial Registry, as well as references listed in relevant reports. Date of last search: 21 August 2018.

**SELECTION CRITERIA:** Randomized controlled studies (RCTs) of people diagnosed with familial Mediterranean fever, comparing active interventions (including colchicine, anakinra, rilonacept, canakinumab, etanercept, infliximab, thalidomide, interferon-alpha, ImmunoGuard™ (a herbal dietary supplement) and non-steroidal anti-inflammatory drugs) with placebo or no treatment, or comparing active drugs to each other.



**DATA COLLECTION AND ANALYSIS:** The authors independently selected studies, extracted data and assessed risk of bias. We pooled data to present the risk ratio or mean difference with their 95% confidence intervals. We assessed overall evidence quality according to the GRADE approach.

**MAIN RESULTS:** We included nine RCTs with a total of 249 participants (aged three to 53 years); five were of cross-over and four of parallel design. Six studies used oral colchicine, one used oral ImmunoGuard™ and the remaining two used rilonacept or anakinra as a subcutaneous injection. The duration of each study arm ranged from one to eight months. The three studies of ImmunoGuard™, rilonacept and anakinra were generally well-designed, except for an unclear risk of detection bias in one of these. However, some inadequacy existed in the four older studies on colchicine, which had an unclear risk of selection bias, detection bias and reporting bias, and also a high risk of attrition bias and other potential bias. Neither of the two studies comparing a single to a divided dose of colchicine were adequately blinded, furthermore one study had an unclear risk of selection bias and reporting bias, a high risk of attrition bias and other potential bias. We aimed to report on the number of participants experiencing an attack, the timing of attacks, the prevention of amyloid A amyloidosis, any adverse drug reactions and the response of a number of biochemical markers from the acute phase of an attack, but data were not available for all outcomes across all comparisons. One study (15 participants) reported a significant reduction in the number of people experiencing attacks at three months with 0.6 mg colchicine three times daily (14% versus 100%), risk ratio 0.21 (95% confidence interval 0.05 to 0.95) (low-quality evidence). A further study (22 participants) of 0.5 mg colchicine twice daily showed no significant reduction in the number of participants experiencing attacks at two months (low-quality evidence). A study of rilonacept in individuals who were colchicine-resistant or intolerant (14 participants) also showed no reduction at three months (moderate-quality evidence). Likewise, a study of anakinra given to colchicine-resistant people (25 participants) showed no reduction in the number of participants experiencing an attack at four months (moderate-quality evidence). Three studies reported no significant differences in duration of attacks: one comparing colchicine to placebo (15 participants) (very low-quality evidence); one comparing single-dose colchicine to divided-dose colchicine (90 participants) (moderate-quality evidence); and one comparing rilonacept to placebo (14 participants) (low-quality evidence). Three studies reported no significant differences in the number of days between attacks: two comparing colchicine to placebo (24 participants in total) (very low-quality evidence); and one comparing rilonacept to placebo (14 participants) (low-quality evidence). No

study reported on the prevention of amyloid A amyloidosis. One study of colchicine reported loose stools and frequent bowel movements (very low-quality evidence) and a second reported diarrhoea (very low-quality evidence). The riloncept study reported no significant differences in gastrointestinal symptoms, hypertension, headache, respiratory tract infections, injection site reactions and herpes, compared to placebo (low-quality evidence). The ImmunoGuard study observed no side effects (moderate-quality evidence). The anakinra study reported no significant differences between intervention and placebo, including injection site reaction, headache, presyncope, dyspnea and itching (moderate-quality evidence). When comparing single and divided doses of colchicine, one study reported no difference in adverse events (including anorexia, nausea, diarrhoea, abdominal pain, vomiting and elevated liver enzymes) between groups (moderate-quality evidence) and the second study reported no adverse effects were detected. The riloncept study reported no significant reduction in acute phase response indicators after three months (low-quality evidence). In the ImmunoGuard™ study, these indicators were not reduced after one month of treatment (moderate-quality evidence). The anakinra study, reported that C-reactive protein was significantly reduced after four months (moderate-quality evidence). One of the single dose versus divided dose colchicine studies reported no significant reduction in acute phase response indicators after eight months (low-quality evidence), while the second study reported no significant reduction in serum amyloid A concentration after six months (moderate-quality evidence).

**AUTHORS' CONCLUSIONS:** There were limited RCTs assessing interventions for people with familial Mediterranean fever. Based on the evidence, three times daily colchicine appears to reduce the number of people experiencing attacks, colchicine single dose and divided dose might not be different for children with familial Mediterranean fever and anakinra might reduce C-reactive protein in colchicine-resistant participants; however, only a few RCTs contributed data for analysis. Further RCTs examining active interventions, not only colchicine, are necessary before a comprehensive conclusion regarding the efficacy and safety of interventions for reducing inflammation in familial Mediterranean fever can be drawn.

DOI: 10.1002/14651858.CD010893.pub3

PMID: 30338514

## Early canakinumab therapy for the sensorineural deafness in a family with Muckle-Wells syndrome due to a novel mutation of NLRP3 gene.

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Cryopyrin-associated periodic syndrome (CAPS) is one of the autoinflammatory disorders caused by mutations in NLRP3 gene. The over-production of interleukin (IL)-1 $\beta$  induced by NLRP3 gene mutations plays an important role in the pathophysiology of CAPS. We diagnosed 3 patients with CAPS, who were lineal family members having a novel mutation of NLRP3 gene. The objective of this report is to compare the characteristics of symptoms and differences in the therapeutic responses of them, who had the same mutation. In addition, we aimed

to examine the usefulness of cytokine measurement for diagnosis or determination of treatment effect of CAPS. A 5-year-old Japanese boy (proband) came to our hospital because of short stature, reached the diagnosis of Muckle-Wells syndrome (MWS) due to a mutation in NLRP3 gene, which had not been reported so far (p.G328E, c.G983A). His mother and grandmother harbored the same mutation of NLRP3. We measured serum concentrations of cytokines in the proband assessed by flow-cytometric bead array. All of them had episodic skin eruptions with conjunctivitis, hearing loss, and arthralgia, but not periodic fever, cold-triggered episodes, and chronic aseptic meningitis. Only the proband had short stature. Canakinumab therapy led to a prompt relief of symptoms and normalized laboratory data in all patients. Audiograms demonstrated an improved hearing level in the proband, but not two others despite of the same mutation. All cytokines did not show any characteristic findings. Sensorineural hearing loss and itchy rash but not serum cytokine profile deserved attention to the diagnosis and treatment start of CAPS. The early intervention of IL-1 $\beta$  blockade may reduce the chance of complete deafness in patients with CAPS.

DOI: 10.1007/s10067-018-4331-8

PMID: 30338413

115. Clin Rheumatol. 2018 Oct 16. doi: 10.1007/s10067-018-4338-1. [Epub ahead of print]

Evaluation of hematological parameters in children with FMF.

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In this study, we aimed to investigate whether neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and mean platelet volume (MPV) might be helpful in the diagnosis of subclinical inflammation of familial Mediterranean fever (FMF). Clinical, laboratory, and genetic results of the patients who were

followed up with the diagnosis of FMF were obtained retrospectively from the hospital files and recorded to standardized form. Age- and sex-matched healthy subjects were included as the control group. Eighty-three of the 143 patients (58.0%) were male and 60 (42.0%) were female. The mean age of our patients was  $164.62 \pm 51.20$  months and the mean age of the control group was  $164.92 \pm 51.10$  months. The mean diagnosis age of our patients was  $98.10 \pm 49.11$  months. The mean follow-up time of the patients was  $66.03 \pm 36.37$  months. 91.60% of our patients had abdominal pain, 78.32% fever, and 28.67% joint pain. The mean NLR of the patients was significantly higher than the mean levels at attack-free period and the control group. However, no statistically significant difference was found between the mean levels at attack-free period and the control group. MPV levels were statistically significantly high during acute attack when compared with the control group. However, they showed no statistically significant difference between acute attack and attack-free period. NLR is a useful marker to predict inflammation in FMF patients. However, our results did not support the idea that MPV might reflect acute attack and attack-free period.

DOI: 10.1007/s10067-018-4338-1

PMID: 30328023

116. Oral Maxillofac Surg. 2018 Oct 16. doi: 10.1007/s10006-018-0731-9. [Epub ahead of print]

Total mandibular reconstruction following diffuse sclerosing osteomyelitis.

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**BACKGROUND:** Diffuse sclerosing osteomyelitis (DSO) is a non-purulent chronic recurrent inflammation and affects the mandible in many cases. Belonging to the group of autoinflammatory diseases, in children and in cases with various

additional symptoms including synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO syndrome), therapy usually consists of non-surgical treatment. Against this background, we present an unusual course of DSO in an adult female patient.

**CASE REPORT:** A 50-year-old female suffering from DSO without SAPHO syndrome was pretreated for years with conservative drug regimens and local surgery. Previous therapy was not successful, and subsequently, multiple surgical procedures were carried out focused on recurrent acute exacerbations of DSO. Surgery resulted in a total resection and alloplastic and autoplasmic reconstruction of the mandible including both temporomandibular joints. Prosthetic rehabilitation was possible after dental implant loading, and the final outcome was very satisfactory.

**CONCLUSION:** In the event that non-surgical options are not successful in DSO, an extended surgical therapy becomes necessary. Even if surgery results in complete resection of the mandible, a satisfactory rehabilitation can be achieved after complex reconstruction.

DOI: 10.1007/s10006-018-0731-9

PMID: 30327981

117. Turk J Pediatr. 2018;60(2):159-164. doi: 10.24953/turkjpeds.2018.02.007.

Evaluation of Restless Legs syndrome and growing pains in children with familial Mediterranean f.

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Altuğ-Gücenmez Ö, Makay B, Kaçar A, Ünsal E. Evaluation of restless legs syndrome and growing pains in children with familial Mediterranean fever. Turk J Pediatr 2018; 60: 159-164. Growing pains (GP) and restless leg syndrome (RLS) are one of the frequently seen pain syndromes of childhood. These two pain syndromes -GP and RLS- may be confused with exertional leg pain (ELP) of familial Mediterranean fever (FMF). The aim of this study was to evaluate the frequency of fulfilling the criterion for GP and RLS among children with FMF. Sixty FMF patients and 70 healthy controls were enrolled. Clinical and demographic data of patients were

recorded. A questionnaire including the symptoms of GP and RLS were applied to all participants and their parents. Twenty-seven patients (45%) had ELP. Ten FMF patients and 10 healthy children fulfilled GP criteria. There was not a significant difference between patients and controls regarding GP. Three FMF patients and 7 healthy controls fulfilled RLS criteria. There was not a significant difference between two groups regarding RLS. Two out of 27 FMF patients with ELP had RLS while one out of 33 FMF patients without ELP had RLS. Eight out of 27 FMF patients with ELP fulfilled GP criteria while two out of 33 FMF patients without ELP fulfilled GP criteria ( $p=0.01$ ). There was a significant inverse correlation with FMF severity score and GP ( $p=0.003$  and  $r=-0.376$ ). There was not a significant association with FMF severity score and RLS. This study suggested that GP and RLS are not more common in pediatric FMF patients than their healthy peers.

DOI: 10.24953/turkjpmed.2018.02.007

PMID: 30325122

118. Expert Rev Clin Immunol. 2018 Dec;14(12):979-992. doi: 10.1080/1744666X.2018.1536548. Epub 2018 Oct 22.

Anakinra for the treatment of adult-onset Still's disease.

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**INTRODUCTION:** Adult onset Still's disease (AOSD) is an uncommon systemic inflammatory disease on the clinical spectrum of autoinflammatory disorders. Its

presentation and clinical course may result in several well-differentiated phenotypes: from a systemic and highly symptomatic pattern to a chronic articular pattern. Overproduction of numerous pro-inflammatory cytokines is observed in AOSD. Anakinra (ANK), a human interleukin (IL)-1R antagonist, has recently been approved in the EU for the treatment of AOSD. Areas covered: In this review, we discuss the main studies on the efficacy and safety on ANK for the treatment of AOSD. The vast majority of them are retrospective studies and case series. Expert commentary: Overall, ANK is an effective biologic agent for the treatment of AOSD, especially for the systemic pattern and also for those patients who have life-threatening complications, which frequently occur over the course of the disease. The initial dose usually indicated of ANK in adults is 100 mg/day subcutaneously, although dose reduction can be performed in some cases once the disease is under control. The safety profile of ANK is favorable and similar to that described in other rheumatic diseases. In conclusion, ANK is an effective and safe agent for the treatment of AOSD.

DOI: 10.1080/1744666X.2018.1536548

PMID: 30324816

119. Curr Opin Pediatr. 2018 Dec;30(6):837-847. doi: 10.1097/MOP.0000000000000696.

New autoinflammatory diseases.

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**PURPOSE OF REVIEW:** Advances in sequencing techniques and systematic cohort-analysis of patients with autoinflammatory phenotypes have enabled a burst in the recognition of new autoinflammatory diseases and contributed to the description of the mechanisms involved in autoinflammation. This review focuses on new genetic and mechanistic discoveries that have broadened the definition of autoinflammatory diseases in the context of the established landscape, providing



new therapeutic opportunities and avenues for further discoveries.

RECENT FINDINGS: Mechanistic insights of inflammatory diseases open opportunities for new targeted therapies. Advances in high-throughput screening of small-molecule inhibitors accelerate the discovery of new and more specific therapeutic options. Recent evidence establishes IL-18 as a driver of macrophage activation, emerging as a new biomarker and therapeutic target. Finally, the identification of escape of nonsense-mediated decay as the genetic mechanism resulting in a monogenic immune-dysregulatory disease, unveils a possibility for future discoveries.

SUMMARY: Recent mechanistic findings in autoinflammatory diseases as well as the identification of specific biomarkers and discovery of new diseases, continue to pave the way for ever more specific targeted approaches. These therapies are not only applicable to monogenic autoinflammatory syndromes but also for other diseases in which the same pathways are dysregulated.

DOI: 10.1097/MOP.0000000000000696

PMID: 30320618

120. Biochim Biophys Acta Mol Basis Dis. 2018 Dec;1864(12):3726-3734. doi: 10.1016/j.bbadis.2018.09.016. Epub 2018 Sep 14.

FRA1 mediates the activation of keratinocytes: Implications for the development of psoriatic plaques.

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In this study we investigated the role of FRA1, a transcription factor from the AP-1 family, in the regulation of keratinocyte characteristics important for the development of psoriatic plaques. FRA1 is characterized by elevated expression in the skin of psoriasis patients, thus leading us to predict it to be one of the major regulators of keratinocyte phenotype during the development of psoriatic lesions. Pathway analysis of RNAseq data allowed us to identify FRA1-mediated signaling cascades leading to the manifestation of the most prominent skin characteristics of the disease: the development of inflammation, epithelial-mesenchymal transition, activation of metalloproteases, and keratinocyte proliferation and migration. We have confirmed that FRA1-overexpressing keratinocytes produce elevated amounts of proinflammatory cytokines and active matrix metalloproteases, leading to the induction of the autoinflammatory loop and paracrine activation in neighbor cells. Therefore, the elevated expression of FRA1 and its altered transcriptional regulation in the skin of patients with psoriasis is an important driving factor in the development of psoriatic plaques.

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DOI: 10.1016/j.bbadis.2018.09.016

PMID: 30318470

121. Rev Pneumol Clin. 2018 Oct;74(5):292-298. doi: 10.1016/j.pneumo.2018.09.011. Epub 2018 Oct 11.

[Bronchiectasis in adults: Etiological diagnosis].

[Article in French]

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Bronchiectasis is defined by a permanent and irreversible increase in airway caliber. Computed tomography (CT) scan is required for diagnosis and allows differentiating localized (affecting only one lobe) from diffuse (affecting two or more lobes) bronchiectasis. Localized bronchiectasis is usually related to a local cause (e.g., tumor, compression by lymph nodes, foreign body) whereas there are multiple causes of diffuse bronchiectasis. Main causes of diffuse bronchiectasis can be grouped into 5 categories: (1) immune deficiencies; (2) genetic disorders responsible for abnormal mucociliary clearance (e.g., cystic fibrosis and primary ciliary dyskinesia); (3) autoinflammatory and connective tissue diseases (e.g., rheumatoid arthritis, Sjogren syndrome); (4) chronic airway inflammatory disorders (e.g., allergic broncho-pulmonary aspergillosis) or chronic infections (e.g., by nontuberculous mycobacteria) and; (5) sequelae of pulmonary insults (e.g., infection, radiotherapy). In the absence of a specific cause, bronchiectasis are called idiopathic. Bronchoscopy is the cornerstone for etiological diagnosis in localized bronchiectasis. Investigation of diffuse bronchiectasis includes standardized biological tests, eventually completed by specialized explorations (e.g., analysis of epithelial ion transport and/or ciliary beating). After this systematic approach, an etiological diagnosis is obtained in approximately 60% of cases, often resulting in therapeutic consequences and in some cases in genetic counselling.

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DOI: 10.1016/j.pneumo.2018.09.011

PMID: 30318255

122. Autoimmun Rev. 2018 Dec;17(12):1259-1264. doi: 10.1016/j.autrev.2018.07.003. Epub 2018 Oct 12.

Autoinflammatory/autoimmunity syndrome induced by adjuvants (ASIA; Shoenfeld's syndrome): A new flame.

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In the present review, recent findings regarding autoimmune/inflammatory syndrome by adjuvants (ASIA) are described. Patients with ASIA present with complaints such as fatigue, cognitive impairment, arthralgias, myalgias, pyrexia, dry eyes and dry mouth. During the last few years, it has been postulated that these symptoms in patients with foreign body implants are due to a chronic inflammatory process and an adjuvant effect of the implanted biomaterial. Ultimately, these inflammatory reactions result in (an increase of) allergies, autoimmune diseases, immune deficiency and/or lymphomas. Pre-existent allergic disease has been found to be an important risk factor for the development of ASIA after foreign body implantation. Explantation of the foreign body results in the majority of patients in an amelioration of the symptoms. There is an urgent need to start adequately adjusted epidemiological studies to obtain better evidence which percentage of patients does develop symptoms and/or diseases such as ASIA, immune deficiency, and/or autoimmune diseases after implant surgery.

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DOI: 10.1016/j.autrev.2018.07.003

PMID: 30316995

123. Clin Exp Immunol. 2019 Jan;195(1):1-9. doi: 10.1111/cei.13224. Epub 2018 Nov 11.

IL4-10 fusion protein: a novel immunoregulatory drug combining activities of interleukin 4 and interleukin 10.

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The objective of this study was to test the capacity of a newly developed fusion protein of interleukin 4 (IL-4) and IL-10 [IL4-10 fusion protein (FP)] to shift multiple pro-inflammatory pathways towards immune regulation, and to inhibit pro-inflammatory activity in arthritis models. The effects of IL4-10 FP in comparison with IL-4, IL-10 and IL-4 plus IL-10 on pro- and anti-inflammatory mediators, T cells and immunoglobulin (Ig) receptors in favour of immunoregulatory activity were studied. In addition, the capacity of IL4-10 FP to inhibit pro-inflammatory activity in ex-vivo and in-vivo arthritis models was investigated. IL4-10 FP robustly inhibited pro-inflammatory cytokine [IL-1 $\beta$ , tumour necrosis factor (TNF)- $\alpha$ , IL-6 and IL-8] production in whole blood cultures, mediated by both the IL-10 and the IL-4 moiety. IL4-10 fusion protein induced IL-1 receptor antagonist (IL-1RA) production and preserved soluble TNF receptor (sTNFR) levels, strongly increasing IL-1RA/IL-1 $\beta$  and sTNFR/TNF- $\alpha$  ratios. In addition, IL4-10 FP strongly inhibited T helper (Th) type 1 and 17 cytokine secretion, while maintaining FoxP3 expression and up-regulating Th2 activity. In addition, while largely leaving expression of activating Fc gamma receptor (Fc $\gamma$ R)I, III and Fc epsilon receptor (Fc $\epsilon$ R) unaffected, it significantly shifted the Fc $\gamma$ RIIa/Fc $\gamma$ RIIb ratio in favour of the inhibitory Fc $\gamma$ RIIb. Moreover, IL4-10 FP robustly inhibited secretion of pro-inflammatory cytokines by rheumatoid arthritis synovial tissue and suppressed experimental arthritis in mice, without inducing B cell hyperactivity. IL4-10 fusion protein is a novel drug, signalling cells to induce immunoregulatory activity that overcomes limitations of IL-4 and IL-10 stand-alone therapy, and therefore has therapeutic potential for inflammatory diseases such as rheumatoid arthritis.

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DOI: 10.1111/cei.13224

PMCID: PMC6300648

PMID: 30307604

124. Pathologe. 2018 Dec;39(Suppl 2):278-284. doi: 10.1007/s00292-018-0497-8.

[Systematic analysis of pathological changes in inflammatory dermatoses : New dermatopathological criteria and algorithms].

[Article in German]

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Standardized analysis of histological findings in a routinely stained section without knowledge of the clinical picture ("blind fashion") allows an objective assessment of the pathological changes. In inflammatory dermatoses diagnostic algorithms and criteria have been proven. They follow defined main inflammatory patterns, the composition of the inflammatory infiltrate and additional criteria. Taking into account the stage of development and the possibility of collision phenomena, this approach will give a histological diagnosis, or at least a limited number of differential diagnoses. However, the final diagnosis always results from the synopsis of the clinical picture and additional parameters. The modern development of algorithms and new histological criteria are outlined in autoimmune dermatoses, autoinflammatory syndromes, drug reactions and genodermatoses.

DOI: 10.1007/s00292-018-0497-8

PMID: 30302562

125. Prz Gastroenterol. 2018;13(3):234-241. doi: 10.5114/pg.2018.76954. Epub 2018 Jul 5.

Endoscopic findings in patients with familial Mediterranean fever and dyspeptic symptoms.

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**Aim:** The aim of the study was to evaluate the clinical, endoscopic, histopathological, laboratory, and imaging findings of patients with familial Mediterranean fever (FMF) presenting with dyspeptic symptoms.

**Material and methods:** Endoscopy was performed in 28 patients with FMF undergoing colchicine therapy, who presented to our hospital between 2012 and 2014 with abdominal pain, diarrhoea, and dyspeptic complaints. Upper gastrointestinal system endoscopy was performed in all patients; 16 of these underwent colonoscopy. Demographic characteristics, clinical and laboratory data, genetic analysis, imaging data, and endoscopy and colonoscopy findings were evaluated in all patients.

**Results:** Histopathological analysis of biopsy specimens revealed gastrointestinal pathology in 21 (75%) patients. Upper endoscopy analysis revealed that 14 (50%) patients had antral gastritis (8 *Helicobacter pylori* (-) antral gastritis and 6 *H. pylori* (+) chronic active gastritis) and 2 (7%) cases had giardiasis. Four antral gastritis cases had concomitant esophagitis, and 2 patients had widespread ulcers in the terminal ileum. The rest had a normal colonic appearance; however, three patients with normal colonoscopic findings were found to have chronic active colitis on histopathological examination.

**Conclusions:** In this study, most patients with FMF presenting with dyspeptic complaints had gastrointestinal pathology. Furthermore, there was higher inflammatory bowel disease incidence in these patients.

DOI: 10.5114/pg.2018.76954

PMCID: PMC6173081

PMID: 30302169

126. Clin Exp Rheumatol. 2018 Nov-Dec;36 Suppl 115(6):80-85. Epub 2018 Sep 27.

Inflammation and cardiovascular disease in familial Mediterranean fever. An analysis of hospital admissions for acute cardiovascular event.

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**OBJECTIVES:** Patients, suffering from inflammatory disorders, are at an increased risk to develop cardiovascular disease (CVD). Here, we examine whether in familial Mediterranean fever (FMF), a model of inflammatory diseases, inflammation also increases the risk to develop cardiovascular (CV) disease.

**METHODS:** To explore the role of inflammation in the occurrence of CVD in FMF, we identified all FMF patients  $\leq 55$  years old with CVD, admitted to our center over a 15-year period. Correlates of inflammation, such as severity of FMF and dose of colchicine, as well as the presence of traditional CV risk factors were compared between the FMF patients with CVD (FMF- CVD) and control FMF patients with- out CVD.

**RESULTS:** Twenty-three FMF-CVD and 40 control patients were compared. The severity of FMF, and the dose of colchicine, were similar in the 2 study groups; therefore, not associated with CVD. Compared with FMF patients without CVD, the FMF-CVD group comprised a higher proportion of men (78 vs. 40%  $p=0.005$ ), and of patients with diabetes (31 vs. 7%,  $p=0.016$ ) and inflammatory comorbidities such as Behçet's disease (30 vs. 7%,  $p=0.005$ ). Multivariate analysis revealed that only diabetes mellitus and inflammatory comorbidities were independent factors associated with FMF-CVD.

**CONCLUSIONS:** In FMF patients treated with colchicine, CVD is not associated with FMF-related inflammation.

PMID: 30299242

127. Front Pharmacol. 2018 Sep 21;9:1074. doi: 10.3389/fphar.2018.01074. eCollection 2018.

Development and Role in Therapy of Canakinumab in Adult-Onset Still's Disease.

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Adult-onset Still's disease (AOSD) is a rare inflammatory disease of unknown etiology typically characterized by episodes of spiking fever, evanescent rash, arthralgia, leukocytosis, and hyperferritinemia. The pivotal role of interleukin (IL)-1 and other pro-inflammatory cytokines gives rise to the development of new targeted therapies. Currently, AOSD patients can benefit from efficient and well tolerated biologic agents, such as IL-1, IL-6, and tumour necrosis factor (TNF)- $\alpha$  antagonists. Canakinumab, a human monoclonal anti-IL-1 $\beta$  antibody, is indicated for the treatment of different autoinflammatory syndromes in adults, adolescents, and children and it has recently been approved for AOSD treatment. In this article, we summarize the structural and biochemical data describing the molecular interactions between Canakinumab and its target antigen. Some special considerations of the pharmacological properties of Canakinumab are included. We also review the safety, efficacy and tolerability of this drug for the treatment of AOSD.

DOI: 10.3389/fphar.2018.01074

PMCID: PMC6160871

PMID: 30298010

128. Expert Rev Clin Immunol. 2018 Nov;14(11):965-976. doi: 10.1080/1744666X.2018.1533403. Epub 2018 Oct 12.

Pathogenesis of adult onset still's disease: current understanding and new insights.

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**INTRODUCTION:** Adult-onset Still's disease (AOSD) is a rare inflammatory disorder typically characterized by fever, arthritis, and hyperferritinemia. Concerning

AOSD pathogenesis, it is categorized as a multigenic autoinflammatory disease, at the 'crossroads' of autoinflammatory and autoimmune diseases, because of the involvement of both arms of immune system. Areas covered: This work is conceived as narrative overview assessing the pathogenesis of AOSD. We performed a narrative synthesis of published information, summarizing the contents of previous studies and providing a possible rationale for future researches. MedLine database was searched for identification of suitable studies. In reporting the available evidence, we described the results according to distinct pathogenic steps associated with different clinical features of the disease. Expert commentary: AOSD is a systemic severe inflammatory disorder of unknown etiology affecting young adults. Although pathogenesis of the disease is not fully clarified, the role of the pro-inflammatory cytokines is well-recognized and biologic drugs, blocking these molecules, are routinely used in clinical practice. Finally, given that multiple recent lines of evidence have suggested new insights in AOSD pathogenesis, new therapeutic targets have been highlighted and the results of studies with new drugs could further improve the management of these patients.

DOI: 10.1080/1744666X.2018.1533403

PMID: 30295095

129. Taiwan J Ophthalmol. 2018 Jul-Sep;8(3):117-120. doi: 10.4103/tjo.tjo\_32\_18.

Recommendation of using systemic anti-tumor necrosis factor-alpha for the treatment of noninfectious uveitis in Taiwan.

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Noninfectious uveitis is a sight-threatening disease with an autoimmune or autoinflammatory basis. Systemic treatment is required if intraocular inflammation threatens a patient's vision or cannot be controlled locally and when it is associated with systemic rheumatic diseases. Corticosteroids and immunomodulatory chemotherapy are the conventional initial treatments. However, the various side effects of these therapies increase the burden on patients, not only physically but also mentally. Moreover, uncontrolled inflammation and poor visual outcomes have sometimes been recorded despite the combination of these medications or their high dosage. Antitumor necrosis factor-alpha (anti-TNF- $\alpha$ ) and other biologic agents have been widely used to treat rheumatic diseases for >15 years. Randomized controlled clinical trials have demonstrated that anti-TNF- $\alpha$  can reduce and delay episodes of intraocular inflammation not only in patients with active uveitis but also in corticosteroid-dependent patients with inactive uveitis. The Taiwan Food and Drug Administration approved the use of adalimumab, an anti-TNF- $\alpha$  agent, for treating nonanterior noninfectious uveitis (NANIU) in 2017. This report provides a recommendation and a proposed stepladder approach for using anti-TNF- $\alpha$  agents to treat NANIU in Taiwan.

DOI: 10.4103/tjo.tjo\_32\_18

PMCID: PMC6169331

PMID: 30294525

Conflict of interest statement: The authors declare that there are no conflicts of interests of this paper.

130. J Res Med Sci. 2018 Sep 24;23:78. doi: 10.4103/jrms.JRMS\_1001\_16. eCollection 2018.

Is there any relationship between human foamy virus infections and familial Mediterranean fever?

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Background: Familial Mediterranean fever (FMF) is generally defined as an autosomal recessive disease, characterized by the automatic activation of the innate immune system in the absence of a detectable pathogenic stimulant. We hypothesize that the pathogenic factors, besides the genetic causes, may affect the development of FMF symptoms. To test this hypothesis, we examined the effects of human foamy virus (HFV) positivity on the occurrence of the clinical symptoms of FMF.

Materials and Methods: Two hundred and twenty-two FMF patients with definitive diagnosis according to Tel Hashomer criteria (study group 1 [SG1]), 205 symptomatic FMF patients who had definitive diagnosis according to the same criteria but did not carry any of the 12 most commonly occurring MEFV gene mutations (study group 2 [SG2]), and 200 healthy individuals were included as control group (study group 3 [SG3]) in the study. The genetic analysis was applied in the Molecular Genetics Laboratory of the Department of Medical Biology, Faculty of Medicine, Ondokuz Mayıs University. This study was designed

as a case-control study. HFV positivity was tested by amplifying the HFV bel1 gene sequence with polymerase chain reaction technique. Statistical analyses were conducted using SPSS version 23.0 software.

Results: HFV positivity showed significant differences between the study groups ( $P = 0.002$ ). While 43 (19.02%) of the 222 SG1 patients were positive for the HFV bel1 gene sequence, 33 (16.09%) of the 205 SG2 patients were positive for the same sequence. Only 15 (7.5%) of the SG3 participants were positive for the presence of HFV bel1 gene sequence.

Conclusion: The results of our study suggested that HFV positivity can be a stimulant pathogenic factor of natural immune system which can cause the emergence of FMF symptoms.

DOI: 10.4103/jrms.JRMS\_1001\_16

PMCID: PMC6161489

PMID: 30294346

Conflict of interest statement: There are no conflicts of interest.

131. Rheumatol Int. 2018 Oct 6. doi: 10.1007/s00296-018-4163-5. [Epub ahead of print]

Protracted febrile myalgia as a challenging manifestation of familial Mediterranean fever: case-based review.

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Protracted febrile myalgia syndrome (PFMS) in familial Mediterranean fever (FMF) patients is a vasculitic condition characterized by severe myalgia, fever, abdominal pain, diarrhea, and arthralgia/arthritis episodes lasting 4-6 weeks. Symptoms typically resolve with corticosteroid treatment. However, in recent years, corticosteroid-resistant PFMS patients have been reported. We herein report five pediatric FMF patients complicated with PFMS. In addition, demographic findings, Mediterranean fever (MEFV) gene analysis, symptoms at

disease onset, time interval between the diagnoses of FMF and PFMS, co-existent diseases, and treatment responses were evaluated. Resolution of all PFMS symptoms was accepted as complete response, while decreased symptoms without full recovery as partial response. We searched PubMed using the keywords 'protracted febrile myalgia' and 'anakinra', and reviewed the literature. There were three male and two female patients. Median age at the diagnosis of FMF was 6 (3-10) years. The time from diagnosis of FMF to the development of PFMS was changed from 0 to 8 (median: 2) years. All of the patients, except one, had homozygous M694V mutation. All patients were treated with corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) first. Two out of five patients were exhibited partial response, while others exhibited complete response. Patients with partial response to the conventional therapies were treated with anakinra, and achieved a great response after the first dose. Anti-interleukin-1 (IL-1) therapy may be a beneficial and a reasonable treatment option, when there is insufficient response to NSAID and corticosteroid therapies in pediatric PFMS patients.

DOI: 10.1007/s00296-018-4163-5

PMID: 30293156

132. J Biol Chem. 2018 Dec 7;293(49):18864-18878. doi: 10.1074/jbc.RA118.004350. Epub 2018 Oct 5.

Human DPP9 represses NLRP1 inflammasome and protects against autoinflammatory diseases via both peptidase activity and FIIND domain binding.

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The inflammasome is a critical molecular complex that activates interleukin-1 driven inflammation in response to pathogen- and danger-associated signals. Germline mutations in the inflammasome sensor NLRP1 cause Mendelian systemic autoimmunity and skin cancer susceptibility, but its endogenous regulation remains less understood. Here we use a proteomics screen to uncover dipeptidyl dipeptidase DPP9 as a novel interacting partner with human NLRP1 and a related inflammasome regulator, CARD8. DPP9 functions as an endogenous inhibitor of NLRP1 inflammasome in diverse primary cell types from human and mice. DPP8/9 inhibition via small molecule drugs and CRISPR/Cas9-mediated genetic deletion specifically activate the human NLRP1 inflammasome, leading to ASC speck formation, pyroptotic cell death, and secretion of cleaved interleukin-1 $\beta$ . Mechanistically, DPP9 interacts with a unique autoproteolytic domain (Function to Find Domain (FIIND)) found in NLRP1 and CARD8. This scaffolding function of DPP9 and its catalytic activity act synergistically to maintain NLRP1 in its inactive state and repress downstream inflammasome activation. We further identified a single patient-derived germline missense mutation in the NLRP1 FIIND domain that abrogates DPP9 binding, leading to inflammasome hyperactivation seen in the Mendelian autoinflammatory disease Autoinflammation with Arthritis and

Dyskeratosis. These results unite recent findings on the regulation of murine Nlrp1b by Dpp8/9 and uncover a new regulatory mechanism for the NLRP1 inflammasome in primary human cells. Our results further suggest that DPP9 could be a multifunctional inflammasome regulator involved in human autoinflammatory diseases.

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DOI: 10.1074/jbc.RA118.004350

PMCID: PMC6295727 [Available on 2019-12-07]

PMID: 30291141

133. Biochem Genet. 2018 Oct 3. doi: 10.1007/s10528-018-9889-y. [Epub ahead of print]

Clinical and Demographic Evaluation According to MEFV Genes in Patients with Familial Mediterranean Fever.

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The present study examined the relationship between clinical findings and mutation analyses in children with Familial Mediterranean Fever (FMF) in the inner Black Sea region of Turkey. This retrospective, cross-sectional study included patients with FMF who were evaluated between 2007 and 2015. FMF was diagnosed according to the Tel Hashomer criteria. FMF mutations were analyzed using a Real-time PCR System (Roche Diagnostics, Mannheim, Germany), and patients were classified into three groups according to allele status. The most common symptom was abdominal pain (99%, n = 197). The most frequent mutations were M694V and R202Q. Chest pain was reported more often in patients homozygous for M694V (61.4%). Although fever, abdominal pain, and arthritis were more commonly



observed with the M694V mutation, chest pain was the most common symptom in R202Q carriers (n = 10, 32.3%). Proteinuria was observed in 42 (21.2%) patients, frequently accompanied by the M694V mutation (28.6%). The most common mutations in children with FMF in Turkey were M694V and R202Q. Recurrent abdominal pain and arthritis/arthralgia were commonly observed in patients with M694V and R202Q mutations. Moreover, chest pain was commonly seen with the R202Q mutation. Thus, R202Q might be a disease-causing mutation in FMF patients.

DOI: 10.1007/s10528-018-9889-y

PMID: 30284126

134. Orv Hetil. 2018 Oct;159(40):1625-1636. doi: 10.1556/650.2018.31270.

[Recent advances in gout: pathogenesis, diagnosis, comorbidities, treatment].

[Article in Hungarian; Abstract available in Hungarian from the publisher]

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After a "silence" period for decades, a great body of new information has become available about the pathogenesis, diagnosis and treatment of gout. New data on purine metabolism and urate transporters have been published. It has become evident that gout is an autoinflammatory disease involving the inflammasome and interleukin-1. With respect to diagnosis, microscopic evaluation of the urate crystal is still the gold standard, however, sensitive imaging techniques (ultrasound, modern computed tomography methods) are able to visualize crystal deposition and tophus formation. Tophus size may also be monitored over time. We see a renaissance of non-pharmacological, lifestyle-related treatment modalities. Pharmacotherapy includes the resolution of attacks and urate-lowering maintenance therapy. In 2016, two recent series of recommendations have been published. Treat-to-target therapy aiming at urate levels  $\leq 360 \mu\text{mol/l}$  is crucial.

Urate-lowering therapy includes xanthine oxidase inhibitors (allopurinol, febuxostat). However, a number of novel compounds (urate transporter inhibitors, recombinant uricase, interleukin-1 inhibitors) are under development or before introduction to gout treatment. Comorbidities should be considered throughout the follow-up of gout patients. Orv Hetil. 2018; 159(40): 1625-1636.

Publisher: Absztrakt: Több évtizedes „szünetet” követően az utóbbi években számos új adat jelent meg a köszvény patogenezise, diagnosztikája és terápiája vonatkozásában. Megismertük a húgysavanyagcsere újabb vonatkozásait, az uráttranszporterekkel kapcsolatos legfrissebb adatokat. Nyilvánvalóvá vált, hogy a köszvény autoinflammatoricus betegség, melynek kialakulásában az inflammasoma és az interleukin-1 kiemelt szerepet játszik. A diagnosztikában ma is a legfontosabb a mononátrium-urát kristály kimutatása, de érzékenyebb képalkotókkal (ultrahang, modern komputertomográfiás technikák) a kristálylerakódás és a tophusképződés is kimutatható, sőt a tophusok mérete is követhető. Újra reneszánszukat élik a különböző életmódbeli, diétás megfontolások, amelyek a gyógyszeres kezelés fontos kiegészítői. A gyógyszeres kezelés alapja a rohamoldás és a fenntartó kezelés, melyekre vonatkozóan 2016-ban két új ajánlás is megjelent. Ezek lényege a célértékre ( $\leq 360 \mu\text{mol/l}$  húgysavszint) való törekvés. A húgysavszintcsökkentés középpontjában ma is a xantin-oxidáz-gátlók (allopurinol, febuxostat) állnak. Ugyanakkor számos új molekula (uráttranszporter-gátlók, rekombináns urikázok, interleukin-1-gátlók) áll fejlesztés alatt, sőt bevezetés előtt. A beteg kezelése és gondozása során kiemelt figyelmet kell fordítanunk a köszvény társbetegségeire is. Orv Hetil. 2018; 159(40): 1625–1636.

DOI: 10.1556/650.2018.31270

PMID: 30277413

135. BMJ Case Rep. 2018 Sep 30;2018. pii: bcr-2018-225802. doi: 10.1136/bcr-2018-225802.

A delayed diagnosis: recurrent fever and beta thalassaemia.

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Familial Mediterranean fever and beta-thalassaemia are two genetic disorders, with a largely common geographical distribution. However, they have not much else in common, as the first is an autoinflammatory disorder, while the other is a haemoglobinopathy. We describe a patient with known beta-thalassaemia intermedia who presented with recurrent fevers and he was diagnosed with familial Mediterranean fever 2 years later. We discuss whether there is an association between the two disorders and the cognitive biases that lead to the delay in the diagnosis of familial Mediterranean fever.

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DOI: 10.1136/bcr-2018-225802

PMID: 30275024

Conflict of interest statement: Competing interests: None declared.

136. Cold Spring Harb Mol Case Stud. 2018 Oct 1;4(5). pii: a002758. doi: 10.1101/mcs.a002758. Print 2018 Oct.

Combination of exome sequencing and immune testing confirms Aicardi-Goutières syndrome type 5 in a challenging pediatric neurology case.

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Exome sequencing is increasingly being used to help diagnose pediatric neurology cases when clinical presentations are not specific. However, interpretation of equivocal results that include variants of uncertain significance remains a challenge. In those cases, follow-up testing and clinical correlation can help clarify the clinical relevance of the molecular findings. In this report, we describe the diagnostic odyssey of a 4-year-old girl who presented with global developmental delay and seizures, with leukodystrophy seen on MRI. Clinical evaluation, MRI, and comprehensive metabolic testing were performed, followed by whole-exome sequencing (WES), parental testing, follow-up testing, and retrospective detailed clinical evaluation. WES identified two candidate causative pathogenic variants in SAMHD1, a gene associated with the recessive condition Aicardi-Goutières syndrome (AGS) type 5 (OMIM 612952): a previously reported pathogenic variant NM\_015474 c.602T>A (p.I201N), maternally inherited, and a rare missense variant of uncertain significance, c.1293A>T(p.L431F). Analysis of type I interferon-related biomarkers demonstrated that the patient has an interferon signature characteristic of AGS. Retrospective detailed clinical evaluation showed that the girl has a phenotype consistent with AGS5, a rare neurological condition. These results further define the phenotypic spectrum associated with specific SAMHD1 variants, including heterozygous variants in AGS carriers, and support the idea that autoinflammatory dysregulation is part of the disease pathophysiology. More broadly, this work highlights the issues and methodology involved in ascribing clinical relevance to interpretation of variants detected by WES.

© 2018 Haskell et al.; Published by Cold Spring Harbor Laboratory Press.

DOI: 10.1101/mcs.a002758

PMCID: PMC6169830

PMID: 30275001

Epub 2018 Sep 7.

Secondary, AA, Amyloidosis.

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Secondary, AA, amyloidosis is a rare systemic complication that can develop in any long-term inflammatory disorder, and is characterized by the extracellular deposition of fibrils derived from serum amyloid A (SAA) protein. SAA is an acute-phase reactant synthesized largely by hepatocytes under the transcriptional regulation of proinflammatory cytokines. The kidney is the major involved organ with proteinuria as first clinical manifestation; renal biopsy is the commonest diagnostic investigation. Targeted anti-inflammatory treatment promotes normalization of circulating SAA levels preventing amyloid deposition and renal damage. Novel therapies aimed at promoting clearance of existing amyloid deposits soon may be an effective treatment approach.

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DOI: 10.1016/j.rdc.2018.06.004

PMID: 30274625

138. J Allergy Clin Immunol. 2019 Jan;143(1):359-368. doi: 10.1016/j.jaci.2018.09.009.  
Epub 2018 Sep 29.

Unexpected relevant role of gene mosaicism in patients with primary immunodeficiency diseases.

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**BACKGROUND:** Postzygotic de novo mutations lead to the phenomenon of gene mosaicism. The 3 main types are called somatic, gonadal, and gonosomal mosaicism, which differ in terms of the body distribution of postzygotic mutations.

Mosaicism has been reported occasionally in patients with primary immunodeficiency diseases (PIDs) since the early 1990s, but its real involvement has not been systematically addressed.

**OBJECTIVE:** We sought to investigate the incidence of gene mosaicism in patients with PIDs.

**METHODS:** The amplicon-based deep sequencing method was used in the 3 parts of the study that establish (1) the allele frequency of germline variants ( $n = 100$ ), (2) the incidence of parental gonosomal mosaicism in families with PIDs with de novo mutations ( $n = 92$ ), and (3) the incidence of mosaicism in families with PIDs with



moderate-to-high suspicion of gene mosaicism (n = 36). Additional investigations evaluated body distribution of postzygotic mutations, their stability over time, and their characteristics.

**RESULTS:** The range of allele frequency (44.1% to 55.6%) was established for germline variants. Those with minor allele frequencies of less than 44.1% were assumed to be postzygotic. Mosaicism was detected in 30 (23.4%) of 128 families with PIDs, with a variable minor allele frequency (0.8% to 40.5%). Parental gonosomal mosaicism was detected in 6 (6.5%) of 92 families with de novo mutations, and a high incidence of mosaicism (63.9%) was detected among families with moderate-to-high suspicion of gene mosaicism. In most analyzed cases mosaicism was found to be both uniformly distributed and stable over time.

**CONCLUSION:** This study represents the largest performed to date to investigate mosaicism in patients with PIDs, revealing that it affects approximately 25% of enrolled families. Our results might have serious consequences regarding treatment and genetic counseling and reinforce the use of next-generation sequencing-based methods in the routine analyses of PIDs.

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DOI: 10.1016/j.jaci.2018.09.009

PMID: 30273710

139. J Dermatol. 2018 Sep 28. doi: 10.1111/1346-8138.14666. [Epub ahead of print]

Familial or sporadic porokeratosis as an autoinflammatory keratinization disease.

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DOI: 10.1111/1346-8138.14666

PMID: 30264904

140. Mol Cell Pediatr. 2018 Sep 25;5(1):7. doi: 10.1186/s40348-018-0085-2.

The role of S100 proteins in the pathogenesis and monitoring of autoinflammatory diseases.

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S100A8/A9 and S100A12 are released from activated monocytes and granulocytes and act as proinflammatory endogenous toll-like receptor (TLR)4-ligands. S100 serum concentrations correlate with disease activity, both during local and systemic inflammatory processes. In some autoinflammatory diseases such as familial Mediterranean fever (FMF) or systemic juvenile idiopathic arthritis (SJIA), dysregulation of S100 release may be involved in the pathogenesis. Moreover, S100 serum levels are a valuable supportive tool in the diagnosis of SJIA in fever of unknown origin. Furthermore, S100 levels can be used to monitor disease activity to subclinical level, as their serum concentrations decrease with successful treatment.

DOI: 10.1186/s40348-018-0085-2

PMCID: PMC6156694

PMID: 30255357

141. Expert Opin Ther Targets. 2018 Oct;22(10):879-891. doi: 10.1080/14728222.2018.1526924.

The potential of PTPN22 as a therapeutic target for rheumatoid arthritis.

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**INTRODUCTION:** PTPN22 encodes a lymphoid-specific tyrosine phosphatase (LYP) that is a master regulator of the immune response. This gene is a major susceptibility factor for a wide range of autoimmune conditions, including rheumatoid arthritis (RA) for which it represents the strongest non-HLA contributor to disease risk. A missense PTPN22 allele (R620W) affecting the protein-protein interaction of LYP with other relevant players was described as the functional variant of the association. This review will focus on the role of PTPN22 in the pathogenic mechanisms underlying RA predisposition and discuss the possibility of developing LYP-based treatment strategies with a potential application in clinical practice.

**Areas covered:** This review covers the literature showing how PTPN22 is implicated in signalling pathways involved in the autoimmune and autoinflammatory processes underlying RA. Insights obtained from studies aimed at developing novel selective LYP suppressors for treating RA are summarized. **Expert opinion:** Targeting key risk factors during the early steps of the disease may represent a good strategy to accomplish complete disease remission. As cumulating evidences suggest that PTPN22 R620W is a gain-of-function variant, a growing interest in developing LYP inhibitors has arisen. The potential efficacy and possible application of such compounds are discussed.

DOI: 10.1080/14728222.2018.1526924

PMID: 30251905

142. Biochim Biophys Acta Mol Basis Dis. 2018 Nov;1864(11):3805-3823. doi: 10.1016/j.bbadis.2018.08.034. Epub 2018 Aug 29.

Type 2 diabetes - An autoinflammatory disease driven by metabolic stress.

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Type 2 diabetes has traditionally been viewed as a metabolic disorder characterised by chronic high glucose levels, insulin resistance, and declining insulin secretion from the pancreas. Modern lifestyle, with abundant nutrient supply and reduced physical activity, has resulted in dramatic increases in the rates of obesity-associated disease conditions, including diabetes. The associated excess of nutrients induces a state of systemic low-grade chronic inflammation that results from production and secretion of inflammatory mediators from the expanded pool of activated adipocytes. Here, we review the mechanisms by which obesity induces adipose tissue dysregulation, detailing the roles of adipose tissue secreted factors and their action upon other cells and tissues central to glucose homeostasis and type 2 diabetes. Furthermore, given the emerging importance of adipokines, cytokines and chemokines in disease progression, we suggest that type 2 diabetes should now be viewed as an autoinflammatory disease, albeit one that is driven by metabolic dysregulation.

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DOI: 10.1016/j.bbadis.2018.08.034

PMID: 30251697 [Indexed for MEDLINE]

143. Front Immunol. 2018 Sep 10;9:2012. doi: 10.3389/fimmu.2018.02012. eCollection 2018.

Increased Risk for Malignancies in 131 Affected CTLA4 Mutation Carriers.

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Background: Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) is a negative immune regulator on the surface of T cells. In humans, heterozygous germline mutations in CTLA4 can cause an immune dysregulation syndrome. The phenotype comprises a broad spectrum of autoinflammatory, autoimmune, and immunodeficient features. An increased frequency of malignancies in primary immunodeficiencies is known, but their incidence in CTLA-4 insufficiency is unknown. Methods: Clinical manifestations and details of the clinical history were assessed in a worldwide cohort of 184 CTLA4 mutation carriers. Whenever a malignancy was reported, a malignancy-specific questionnaire was filled. Results: Among the 184 CTLA4 mutation carriers, 131 were considered affected, indicating a penetrance of 71.2%. We documented 17 malignancies, which amounts to a cancer prevalence of 12.9% in affected CTLA4 mutation carriers. There were ten lymphomas, five gastric cancers, one multiple myeloma, and one metastatic melanoma. Seven lymphomas and three gastric cancers were EBV-associated. Conclusion: Our findings demonstrate an elevated cancer risk for patients with CTLA-4 insufficiency. As more than half of the cancers were EBV-associated, the failure to control oncogenic viruses seems to be part of the CTLA-4-insufficient phenotype. Hence, lymphoproliferation

and EBV viral load in blood should be carefully monitored, especially when immunosuppressing affected CTLA4 mutation carriers.

DOI: 10.3389/fimmu.2018.02012

PMCID: PMC6140401

PMID: 30250467

144. Arthritis Res Ther. 2018 Sep 24;20(1):214. doi: 10.1186/s13075-018-1712-y.

Metabolomic alterations associated with Behçet's disease.

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**BACKGROUND:** The diagnosis of Behçet's disease (BD) remains challenging due to the lack of diagnostic biomarkers. This study aims to identify potential serum metabolites associated with BD and its disease activity.

**METHODS:** Medical records and serum samples of 24 pretreated BD patients, 12 post-treated BD patients, and age-matched healthy controls (HC) were collected

for metabolomics and lipidomics profiling using UPLC-QTOF-MS and UPLC-QTOF-MSE approaches. Additionally, serum samples from an independent cohort of BD patients, disease controls including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Takayasu's arteritis (TA), Crohn's disease (CD) patients, and HC were collected for further validation of two potential biomarkers using UPLC-QTOFMS analysis.

**RESULTS:** Unsupervised principal component analysis (PCA) showed a clear separation of metabolomics profiles of BD patients from HC. Statistical analysis of the data revealed differential metabolites between BD patients and HC. The serum levels of some phosphatidylcholines (PCs) were found to be significantly lower in BD patients, while the levels of several polyunsaturated fatty acids (PUFAs) were increased markedly in the BD group compared with HC. Furthermore, the serum level of two omega-6 PUFAs, linoleic acid (LA) and arachidonic acid (AA), were dramatically decreased in patients with remission. A validation cohort confirmed that the serum LA and AA levels in BD patients were significantly higher than those in HC and patients with RA, SLE, TA, and CD. In addition, receiver operating characteristic (ROC) analysis indicated good sensitivity and specificity.

**CONCLUSIONS:** The serum metabolomics profiles in BD patients are altered. Serum LA and AA are promising diagnostic biomarkers for BD.

DOI: 10.1186/s13075-018-1712-y

PMCID: PMC6154820

PMID: 30249301

145. Clin Rheumatol. 2018 Sep 22. doi: 10.1007/s10067-018-4302-0. [Epub ahead of print]

Correction to: Long-term efficacy and safety of golimumab in the treatment of multirefractory Behçet's disease.

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#### Erratum for

Clin Rheumatol. 2017 Sep;36(9):2063-2069.

In the original version of this article the author name Gerardo Di Scala was originally presented incorrectly as 'Di Scala Gerardo'; this has been corrected in this article.

DOI: 10.1007/s10067-018-4302-0

PMID: 30242638

146. Pediatr Rheumatol Online J. 2018 Sep 21;16(1):60. doi: 10.1186/s12969-018-0277-2.

Towards a new set of classification criteria for PFAPA syndrome.

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**BACKGROUND:** Diagnosis of Periodic Fever, Aphthous stomatitis, Pharyngitis and Cervical Adenitis (PFAPA) syndrome is currently based on the modified Marshall's criteria, but no validated evidence based classification criteria for PFAPA has been established so far.

**METHODS:** A multistep process, based on the Delphi and Nominal Group Technique was conducted. After 2 rounds of e-mail Delphi survey involving 21 experts in autoinflammation we obtained a list of variables that were discussed in an International Consensus Conference. Variables reaching the 80% of consensus between participants were included in the new classification criteria. In the second phase the new classification criteria and the modified Marshall's criteria were applied on a cohort of 80 pediatric PFAPA patients to compare their performance.

**RESULTS:** The Delphi Survey was sent to 22 participants, 21 accepted to participate. Thirty variables were obtained from the survey and have been discussed at the Consensus Conference. Through the Nominal Group Technique we

obtained a new set of classification criteria. These criteria were more restrictive in respect to the modified Marshall's criteria when applied on our cohort of patients.

**CONCLUSION:** Our work led us to identify a new set of classification criteria for PFAPA syndrome, but they resulted to be too restrictive to be applied in daily clinical practice for the diagnosis of PFAPA.

DOI: 10.1186/s12969-018-0277-2

PMCID: PMC6151014

PMID: 30241480 [Indexed for MEDLINE]

147. Medicine (Baltimore). 2018 Sep;97(38):e12305. doi: 10.1097/MD.00000000000012305.

Subclinical inflammation in a case of menstruation-induced familial Mediterranean fever: A case report.

Hara K(1), Endo Y(1), Ishida M(1), Fujita Y(1), Tsuji S(1), Takatani A(1), Shimizu T(1), Sumiyoshi R(1), Igawa T(1), Umeda M(1), Fukui S(1), Nishino A(1), Kawashiri SY(1), Iwamoto N(1), Ichinose K(1), Tamai M(1), Nakamura H(1), Origuchi T(1), Migita K(2), Kawakami A(1), Koga T(1).

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**RATIONALE:** Because most patients with familial Mediterranean fever (FMF) have attacks without any prodromal symptoms, and since it is suggested that patients with FMF have subclinical inflammation even during remission, a daily continuous administration of colchicine is recommended for patients with FMF even during remission. However, it is possible that intermittent colchicine therapy only during FMF attacks prevents the attacks completely in patients with FMF with expectable attacks.

**PATIENT CONCERNS:** A 31-year-old Japanese woman suffered high fever and arthralgia lasting for 2 to 3 days after each menstrual period's start. She was admitted to our hospital, and colchicine was administered immediately after her next period's start, and the febrile attack was completely prevented.

DIAGNOSES: We eventually diagnosed typical FMF.

INTERVENTIONS: Her remission has been maintained by intermittent colchicine therapy.

OUTCOMES: The genetic analysis revealed the G304R heterozygous mutation in exon 2 of the MEFV gene. Cytokine analysis suggested subclinical inflammation during the remission period.

LESSONS: This case suggests that taking an extensive medical history (including the relationship between fever attack and menstruation) is important in the diagnosis of female patients with FMF. This case also suggests that a continuous administration of colchicine may have to be considered to regulate subclinical inflammation even in patients with FMF with completely expectable attacks.

DOI: 10.1097/MD.00000000000012305

PMCID: PMC6160243

PMID: 30235678 [Indexed for MEDLINE]

148. *Pediatr Radiol*. 2019 Jan;49(1):23-36. doi: 10.1007/s00247-018-4246-1. Epub 2018 Sep 17.

Imaging findings of sterile pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome: differential diagnosis and review of the literature.

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Pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome is a rare autosomal-dominant autoinflammatory disease of incomplete penetrance and variable expression. PAPA syndrome is the result of a mutation in the proline serine threonine phosphatase-interacting protein 1 (PSTPIP1/CD2BP1) gene located on chromosome 15, which results in an abnormal overproduction of the pro-inflammatory cytokine interleukin-1 $\beta$  (IL-1). This syndrome clinically manifests as early onset of recurrent episodes of acute aseptic inflammation of the joints, generally occurring in the first two decades of life, followed by manifestation of characteristic skin lesions in the third decade, after an obvious decline in the joint symptoms. Although uncommon, the potential clinical implications of PAPA syndrome warrant an appropriate diagnosis in a timely fashion.

DOI: 10.1007/s00247-018-4246-1

PMID: 30225645

149. Case Rep Pediatr. 2018 Aug 26;2018:3514645. doi: 10.1155/2018/3514645. eCollection 2018.

Tocilizumab for the Treatment of Mevalonate Kinase Deficiency.

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Mevalonate kinase deficiency (MKD) is a severe autoinflammatory disease caused by recessive mutations in MVK resulting in reduced function of the enzyme mevalonate kinase, involved in the cholesterol/isoprenoid pathway. MKD presents with periodic episodes of severe systemic inflammation, poor quality of life, and life-threatening sequelae if inadequately treated. We report the case of a 12-year-old girl with MKD and severe autoinflammation that was resistant to IL-1 and TNF- $\alpha$  blockade. In view of this, she commenced intravenous tocilizumab (8 mg/kg every 2 weeks), a humanised monoclonal antibody targeting the IL-6 receptor (IL-6R) that binds to membrane and soluble IL-6R, inhibiting IL-6-mediated signaling. She reported immediate cessation of fever and marked improvement in her energy levels following the first infusion; after the fifth dose, she was in complete clinical and serological remission, now sustained for 24 months. This is one of the first reported cases of a child with MKD treated successfully with tocilizumab and adds to the very limited experience of this treatment for MKD. IL-6 blockade could therefore be an important addition to the armamentarium for the treatment of this rare monogenic autoinflammatory disease.

DOI: 10.1155/2018/3514645

PMCID: PMC6129367

PMID: 30225156

150. Ann Dermatol Venereol. 2018 Dec;145(12):733-734. doi: 10.1016/j.annder.2018.08.004. Epub 2018 Sep 13.

[Inflammasome, interleukin-1, autoinflammatory diseases and neutrophilic dermatosis].

[Article in French]

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DOI: 10.1016/j.annder.2018.08.004

PMID: 30219413

151. J Autoimmun. 2018 Nov;94:16-32. doi: 10.1016/j.jaut.2018.08.009. Epub 2018 Sep 13.

Autophagy: A new concept in autoimmunity regulation and a novel therapeutic option.

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Nowadays, pharmacologic treatments of autoinflammatory diseases are largely palliative rather than curative. Most of them result in non-specific immunosuppression, which can be associated with broad disruption of natural and induced immunity with significant and sometimes serious unwanted injuries. Among the novel strategies that are under development, tools that modulate the immune system to restore normal tolerance mechanisms are central. In these approaches, peptide therapeutics constitute a class of agents that display many physicochemical advantages. Within this class of potent drugs, the phosphopeptide P140 is very promising for treating patients with lupus, and likely also patients with other chronic inflammatory diseases. We discovered that P140 targets autophagy, a finely orchestrated catabolic process, involved in the regulation of inflammation and in the biology of immune cells. In vitro, P140 acts directly on a particular form of autophagy called chaperone-mediated autophagy, which seems to be hyperactivated in certain subsets of lymphocytes in lupus and in other autoinflammatory settings. In lupus, the "correcting" effect of P140 on autophagy results in a weaker signaling of autoreactive T cells, leading to a significant

improvement of pathophysiological status of treated mice. These findings also demonstrated ex vivo in human cells, open novel avenues of therapeutic intervention in pathological conditions, in which specific and not general targeting is highly pursued in the context of the new action plans for personalized medicines.

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DOI: 10.1016/j.jaut.2018.08.009

PMID: 30219390

152. Nat Rev Rheumatol. 2018 Oct;14(10):603-618. doi: 10.1038/s41584-018-0081-x.

Mechanisms, biomarkers and targets for adult-onset Still's disease.

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Adult-onset Still's disease (AoSD) is a rare but clinically well-known, polygenic, systemic autoinflammatory disease. Owing to its sporadic appearance in all adult age groups with potentially severe inflammatory onset accompanied by a broad spectrum of disease manifestation and complications, AoSD is an unsolved challenge for clinicians with limited therapeutic options. This Review provides a comprehensive insight into the complex and heterogeneous nature of AoSD, describing biomarkers of the disease and its progression and the cytokine signalling pathways that contribute to disease. The efficacy and safety of biologic therapeutic options are also discussed, and guidance for treatment

decisions is provided. Improving the approach to AoSD in the future will require much closer cooperation between paediatric and adult rheumatologists to establish common diagnostic strategies, treatment targets and goals.

DOI: 10.1038/s41584-018-0081-x

PMID: 30218025

153. *Mod Rheumatol*. 2018 Oct 25:1-5. doi: 10.1080/14397595.2018.1523701. [Epub ahead of print]

Involvement of midkine in autoimmune and autoinflammatory diseases.

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Midkine (MK) is a heparin-binding growth factor that markedly expressed during embryogenesis but downregulated to inconsiderable levels in healthy adults. However, MK is upregulated during tissue repair and in many pathologic conditions, mostly malignancies and inflammatory diseases. MK promotes a number of functions in target cells such as migration, proliferation, survival, growth, reproduction and repair, angiogenesis, and gene expression. It acts as a pro-inflammatory cytokine and contributes to chronic inflammation via promoting chemotaxis and tissue infiltration of neutrophils and macrophages. Furthermore, MK upregulated the production of various inflammatory mediators (i.e. interleukin (IL) 6 and IL8). Recent studies have demonstrated strong evidence that MK is involved in the onset and progression of autoimmune rheumatic diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and Sjögren's syndrome (SS) and other autoimmune conditions such as multiple sclerosis (MS). Additionally, it has been shown that MK is overexpressed in two major clinically defined forms of inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), which are classified as autoinflammatory diseases. Taken



together, MK is involved in the pathogenesis of autoimmune and autoinflammatory diseases and may serve as an indicator and biomarker in these conditions. Furthermore, MK inhibitors are expected to contribute in the management of these diseases.

DOI: 10.1080/14397595.2018.1523701

PMID: 30217121

154. Nervenarzt. 2018 Oct;89(10):1095-1105. doi: 10.1007/s00115-018-0597-y.

[Neuroimmunology and rheumatology: overlap and differential diagnoses].

[Article in German]

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Multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) are chronic inflammatory diseases of the central nervous system (CNS). They may cause inflammation in the brain, spinal cord and optic nerve. Both conditions must be differentiated from CNS manifestations of other systemic autoimmune diseases such as systemic lupus erythematosus (SLE), Sjögren's syndrome, autoinflammatory diseases and sarcoidosis, since amongst others myelitis and optic nerve inflammation may also occur in these conditions. Nevertheless, coexistence of MS or NMOSD with rheumatic disorders such as SLE or Sjögren's syndrome has also been reported especially in NMOSD. Since the therapeutic approach is different it is important to determine a clear diagnosis. In addition some drugs used in rheumatic disease such as anti-tumor necrosis factor biologics may induce inflammatory disease of the CNS and should be avoided in MS. An interdisciplinary approach between neuroimmunology and rheumatology is important for optimal care and treatment in such patients.

DOI: 10.1007/s00115-018-0597-y

PMID: 30215132

155. Autoimmun Rev. 2018 Nov;17(11):1115-1123. doi: 10.1016/j.autrev.2018.06.001. Epub 2018 Sep 11.

Mechanistic immunological based classification of rheumatoid arthritis.

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The classical autoimmunity paradigm in rheumatoid arthritis (RA) is strongly supported by immunogenetics suggesting follicular helper T-cell responses driving high titre specific autoantibodies that pre-dates disease onset. Using the immunological disease continuum model of inflammation against self with "pure" adaptive and innate immune disease at opposite boundaries, we propose a novel immune mechanistic classification describing the heterogeneity within RA. Mutations or SNPs in autoinflammatory genes including MEFV and NOD2 are linked to seronegative RA phenotypes including some so called palindromic RA cases. However, just as innate and adaptive immunity are closely functionally integrated, some ACPA+ RA cases have superimposed "autoinflammatory" features including abrupt onset attacks, severe attacks, self-limiting attacks, relevant autoinflammatory mutations or SNPs and therapeutic responses to autoinflammatory pathway therapies including colchicine and IL-1 pathway blockade. An emergent feature from this classification that non-destructive RA phenotypes, both innate

and adaptive, have disease epicentres situated in the extracapsular tissues. This mixed innate and adaptive immunopathogenesis may be the key to understanding severe disease flares, resistant disease subsets that are unresponsive to standard therapy and for therapies that target the autoinflammatory component of disease that are not currently considered by expert therapeutic recommendations.

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DOI: 10.1016/j.autrev.2018.06.001

PMID: 30213700 [Indexed for MEDLINE]

156. Wounds. 2018 Aug;30(8):216-223.

Is PASH Syndrome a Biofilm Disease?: A Case Series and Review of the Literature.

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**INTRODUCTION:** When occurring together, pyoderma gangrenosum, severe acne, and hidradenitis suppurativa have been described as PASH syndrome. Due to the chronic autoinflammatory state existing in affected patients, PASH syndrome has been attributed to the dysregulation of wound healing.

**CASE REPORTS:** Two cases are presented that demonstrate the paradigmatic clinical features of PASH syndrome and its potential link as an expanding spectrum of bacterial biofilm disorder.

**CONCLUSIONS:** As reported herein, based on biofilm's clinical presentation and resistance to proper wound healing, it could serve as the common denominator and may redirect clinicians' treatment pathways in the near future.

PMID: 30212364 [Indexed for MEDLINE]

157. Pediatr Ann. 2018 Sep 1;47(9):e347-e353. doi: 10.3928/19382359-20180806-01.

## Evaluation of Prolonged and Recurrent Unexplained Fevers.

Statler VA, Marshall GS.

Fever is a common symptom in children. Some children may present to their primary care physician with undifferentiated fever; that is, fever for which there is no obvious source from the history or physical examination. Undifferentiated fevers may be prolonged or recurrent. Distinguishing between the two is helpful for narrowing the differential diagnosis, which can be broad and include infections and inflammatory diseases and, rarely, malignancies and autoinflammatory disorders. The evaluation of such children requires a step-wise approach. Taking a detailed history, performing a thorough physical examination, and reviewing a fever and symptom diary is crucial in recognizing clues that may ultimately lead to a diagnosis. Some children who look good and whose fever disappears may never have a diagnosis, whereas referral to a specialist may be prudent for others. [Pediatr Ann. 2018;47(9):e347-e353].

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DOI: 10.3928/19382359-20180806-01

PMID: 30208193 [Indexed for MEDLINE]

158. Eur J Hum Genet. 2018 Nov;26(11):1564-1565. doi: 10.1038/s41431-018-0242-z. Epub 2018 Sep 11.

Reply to Sönmez et al.

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DOI: 10.1038/s41431-018-0242-z

PMCID: PMC6189082

PMID: 30206351

159. J Am Acad Dermatol. 2019 Jan;80(1):291-295. doi: 10.1016/j.jaad.2018.08.043. Epub 2018 Sep 8.

Recurrent fevers, progressive lipodystrophy, and annular plaques in a child.

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KEY TEACHING POINTS.

Published by Elsevier Inc.

DOI: 10.1016/j.jaad.2018.08.043

PMID: 30205133

160. Arch Argent Pediatr. 2018 Oct 1;116(5):e679-e683. doi: 10.5546/aap.2018.e679.

[Chronic recurrent multifocal osteomyelitis: pediatric clinical case].

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Chronic recurrent multifocal osteomyelitis has recently been classified as an autoinflammatory disorder characterized by episodes of systemic inflammation including serological signs of inflammation occurring in the absence of autoantibodies or pathogen agents. The insidious onset of pain with swelling and tenderness localized over the affected bones are the main manifestations. The metaphysis and epiphyses of the long bones, clavicle and vertebrae are affected. We report a male patient aged 2 years and 2 months with osteomyelitis with lytic destruction in two different single sites with a year difference between the episodes. Histological examination of the bone showed inflammation and chronic osteomyelitis, excluding the existence of infectious osteomyelitis, neoplasm and myeloproliferative disease. Clinical symptoms improved under treatment with nonsteroidal anti-inflammatory drugs. Considering chronic recurrent multifocal osteomyelitis may shorten time to diagnosis in order to avoid potentially unnecessary prolonged courses of intravenous antibiotics, complementary studies and multiple biopsies.

Publisher: La osteomielitis crónica multifocal recurrente fue recientemente clasificada dentro de las enfermedades autoinflamatorias, caracterizadas por episodios de inflamación sistémica, que incluyen indicadores serológicos de inflamación, en ausencia de autoanticuerpos o agentes patógenos. La característica clínica es la aparición insidiosa de dolor, tumefacción y sensibilidad localizada sobre el hueso afectado, principalmente, en la metáfisis y epífisis de los huesos largos, clavícula y también vértebras. Son episodios autolimitados y recurrentes. Se presenta a un paciente de 2 años y 2 meses con afectación ósea tipo osteolítica en dos focos aislados con un año de diferencia entre ambos episodios. La biopsia ósea fue compatible con osteomielitis crónica y se descartó patología de origen infeccioso, neoplásico y enfermedad proliferativa. Presentó buena respuesta al tratamiento con antiinflamatorios. El conocimiento de esta entidad como diagnóstico diferencial evita el tratamiento antibiótico prolongado, estudios complementarios y biopsias óseas, considerando

los criterios diagnósticos y recurrencia de los episodios.

Sociedad Argentina de Pediatría.

DOI: 10.5546/aap.2018.e679

PMID: 30204998

161. Arch Argent Pediatr. 2018 Oct 1;116(5):e649-e654. doi: 10.5546/aap.2018.eng.e649.

Gastrointestinal evaluation in colchicine-treated familial Mediterranean fever patients with chronic abdominal pain: cases series.

[Article in English, Spanish; Abstract available in Spanish from the publisher]

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Publisher: El objetivo de este estudio fue evaluar a los pacientes con fiebre mediterránea familiar (familial Mediterranean fever, FMF) y dolor abdominal crónico resistentes al tratamiento con colchicina. Se incluyó a 48 pacientes diagnosticados en nuestro consultorio de reumatología pediátrica que tenían dolor abdominal a pesar del tratamiento con colchicina. A todos los pacientes se los derivó a un gastroenterólogo pediátrico. Se registraron las características del dolor, tales como aparición, duración y frecuencia; se planificó una endoscopia digestiva para obtener un diagnóstico diferencial. Se determinó la presencia de una mutación del gen MEFV en 46 pacientes. La mediana de la duración del tratamiento fue de 2,8 años. Aproximadamente el 60% de los pacientes tenían dolor abdominal todos los días o de dos a tres veces a la semana; en el 73% de los casos, duró menos de tres horas. A 41 pacientes se les realizó una endoscopia digestiva alta. La gastroduodenitis es un hallazgo frecuente en los pacientes con FMF y dolor abdominal persistente a pesar del tratamiento. Los pacientes con los puntajes más altos de severidad de la enfermedad tenían inflamación digestiva grave.

DOI: 10.5546/aap.2018.eng.e649

PMID: 30204991

162. Rheumatology (Oxford). 2019 Jan 1;58(1):182-184. doi: 10.1093/rheumatology/key283.

Expanding clinical spectrum of autosomal dominant pyrin-associated autoinflammatory disorder caused by the heterozygous MEFV p.Thr577Asn variant.

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DOI: 10.1093/rheumatology/key283

PMID: 30203097

163. Trends Microbiol. 2019 Jan;27(1):75-85. doi: 10.1016/j.tim.2018.08.007. Epub 2018 Sep 7.

A Balancing Act: MDA5 in Antiviral Immunity and Autoinflammation.

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Induction of interferons during viral infection is mediated by cellular proteins that recognise viral nucleic acids. MDA5 is one such sensor of virus presence and is activated by RNA. MDA5 is required for immunity against several classes of viruses, including picornaviruses. Recent work showed that mutations in the IFIH1 gene, encoding MDA5, lead to interferon-driven autoinflammatory diseases. Together with observations made in cancer cells, this suggests that MDA5 detects cellular RNAs in addition to viral RNAs. It is therefore important to understand the properties of the RNAs which activate MDA5. New data indicate that RNA length and secondary structure are features sensed by MDA5. We review these developments and discuss how MDA5 strikes a balance between antiviral immunity and autoinflammation.

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DOI: 10.1016/j.tim.2018.08.007

PMID: 30201512

164. Orphanet J Rare Dis. 2018 Sep 6;13(1):156. doi: 10.1186/s13023-018-0902-7.

The patient journey to diagnosis and treatment of autoinflammatory diseases.

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**BACKGROUND:** Limited data are available on the experiences of patients with autoinflammatory diseases (AIDs) and their families along the path to diagnosis and treatment. We sought to describe these experiences in patients with AIDs

including tumor necrosis factor receptor-associated periodic syndrome (TRAPS), mevalonate kinase deficiency/hyperimmunoglobulin D syndrome (MKD/HIDS), and familial Mediterranean fever (FMF).

**METHODS:** Ninety-minute, semi-structured qualitative interviews and 5-day written/video diaries were used to gather information on the experiences of patients with AIDs and their families.

**RESULTS:** Twelve families of patients from the US (TRAPS [n = 4], MKD/HIDS [n = 5], FMF [n = 5]) participated in this study from August to November 2015. The study included two families with multiple afflicted siblings. Patients' ages ranged from 1 to 28 years. Most parents reported realizing that something was seriously wrong with their child after medical emergencies and/or hospitalizations, which initiated the difficult path to diagnosis. For most, the process included multiple specialist visits, extensive and repeated testing, and many misdiagnoses. Over time, 92% of parents reported losing confidence in the healthcare system's ability to find an answer to their child's symptoms, while they also struggled with unsupportive school personnel and dismissive friends and relatives. Patients and their parents reported holding on to memories of "what life was like" before the onset of symptoms and mourning their subsequent loss of "normalcy." Even after diagnosis, patients and parents continued to feel uncertain about what to expect in the future.

**CONCLUSIONS:** All families emphasized the need for efficient early diagnosis of AIDs. Initiatives that improve the speed and accuracy of diagnosis, provide more comprehensive patient education, and support patients and families through the illness have the potential to significantly improve the quality of life of patients with AIDs and their families. Healthcare providers should be aware of the impact of the long diagnostic journey on families and work to create an environment of trust and collaboration in the face of a difficult and prolonged diagnostic process.

DOI: 10.1186/s13023-018-0902-7

PMCID: PMC6127942

PMID: 30189864

165. J Allergy Clin Immunol. 2018 Nov;142(5):1444-1446. doi: 10.1016/j.jaci.2018.08.020. Epub 2018 Sep 4.

Novel cytoskeletal mutations with immunodeficiency: Why is the raven like a writing desk?

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DOI: 10.1016/j.jaci.2018.08.020

PMID: 30189245

166. *Pediatr Dermatol*. 2018 Nov;35(6):e420-e421. doi: 10.1111/pde.13660. Epub 2018 Sep 6.

Neonatal urticaria: Could it be CAPS?

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A neonatal boy presented with a persistent urticarial rash. Initial investigations showed raised inflammatory markers and evidence of systemic inflammation. A working diagnosis of cryopyrin-associated periodic syndrome (CAPS) was made, and the patient responded extremely well to Anakinra. Molecular genetic testing revealed a somatic mutation (affecting 12.5% of cells) in the NLRP3 gene, accounting for the persistent inflammatory state but milder phenotype as seen in our patient.

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DOI: 10.1111/pde.13660

PMID: 30187963 [Indexed for MEDLINE]

167. Clin Sci (Lond). 2018 Sep 5;132(17):1901-1924. doi: 10.1042/CS20171498. Print 2018 Sep 14.

The classification, genetic diagnosis and modelling of monogenic autoinflammatory disorders.

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Monogenic autoinflammatory disorders are an increasingly heterogeneous group of conditions characterised by innate immune dysregulation. Improved genetic sequencing in recent years has led not only to the discovery of a plethora of conditions considered to be 'autoinflammatory', but also the broadening of the clinical and immunological phenotypic spectra seen in these disorders. This review outlines the classification strategies that have been employed for monogenic autoinflammatory disorders to date, including the primary innate immune pathway or the dominant cytokine implicated in disease pathogenesis, and highlights some of the advantages of these models. Furthermore, the use of the term 'autoinflammatory' is discussed in relation to disorders that cross the innate and adaptive immune divide. The utilisation of next-generation sequencing (NGS) in this population is examined, as are potential in vivo and in vitro methods of modelling to determine pathogenicity of novel genetic findings. Finally, areas where our understanding can be improved are highlighted, such as phenotypic variability and genotype-phenotype correlations, with the aim of identifying areas of future research.

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DOI: 10.1042/CS20171498

PMCID: PMC6123071

PMID: 30185613

168. Genet Test Mol Biomarkers. 2018 Sep;22(9):561-567. doi: 10.1089/gtmb.2018.0058. Epub 2018 Sep 5.

Utilizing Whole-Exome Sequencing to Characterize the Phenotypic Variability of Sickle Cell Disease.

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**BACKGROUND:** Sickle cell disease (SCD) is a monogenic disease that has wide variety of phenotypes with both and environmental factors contributing to its severity.

**METHODS:** We performed whole-exome sequencing (WES) in 22 Saudi SCD patients to identify variants that could explain differences in disease phenotypes. All variants, except those that were benign and likely benign, described in the ClinVar database, were considered in our analysis. Gene-based association testing using sequence kernel association optimal unified test (SKAT-O) with small sample adjustment was performed to evaluate the effect of multiple variants in genes on SCD phenotypes.

**RESULTS:** The mean age of participants was 28 (range, 10-48 years). All patients were homozygous for the sickle cell mutation. The Benin haplotype was present in 15 patients and the Arab-Indian haplotype in 7 patients. One patient who had both SCD and CHARGE association was heterozygous for pathogenic mutation p.Arg987Ter in the CHD7 gene. One SCD individual who had a stroke was a carrier of the pathogenic variant p.Asp36Tyr in the VKORC1 gene which is, associated with warfarin resistance. Two patients with steady hemoglobin levels of 7.5 and 7.1 g/dL were carriers of the pathogenic mutation p.Gly140Ser in the RPL5 gene

that is associated with Diamond-Blackfan anemia. None of the patients were transfusion dependent. A heterozygous pathogenic mutation in the LDLR gene associated with autosomal dominant familial hypercholesterolemia was present in one patient with deep venous thrombosis, although their cholesterol level was normal. One individual with stroke was a carrier for the p.Arg284Ter variant in the NLRP12 gene, which is associated with familial cold autoinflammatory syndrome 2. Another patient with stroke and a pulmonary embolism was heterozygous for the p.Pro106Leu variant of the MPL gene, which has been associated with thrombocytosis. Coding variants in the GOLGB1, ENPP1, and PON1 genes showed no association with stroke in our study. SKAT-O analysis did not explain SCD heterogeneity.

CONCLUSION: WES provided limited information to explain the severity of SCD. Whole genome sequencing, epigenetic studies, and assessment of environmental factors might expand our knowledge of SCD heterogeneity.

DOI: 10.1089/gtmb.2018.0058

PMID: 30183354 [Indexed for MEDLINE]

169. Harefuah. 2018 Aug;157(8):538.

[Familial Mediterranean Fever - FMF By Prof. Alon Pras, Prof. Avi Livne and Prof. Yehuda Shoenfeld].

[Article in Hebrew]

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PMID: 30175574

170. Curr Treat Options Neurol. 2018 Sep 3;20(10):43. doi: 10.1007/s11940-018-0526-1.

Cryopyrin-Associated Periodic Fever Syndrome and the Nervous System.

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**PURPOSE OF REVIEW:** The purpose of this review is to highlight the molecular and clinical characteristics of the cryopyrin-associated periodic fever syndrome (CAPS) and its management. CAPS is an autosomal dominantly inherited autoinflammatory disorder associated with mutations in the NLRP3 gene, which ultimately lead to excessive production of interleukin-1 $\beta$  (IL-1 $\beta$ ) and systemic inflammation. Typical systemic features include fever, urticarial rash and arthralgia, and ultimately amyloidosis. There are also multiple neurological manifestations including, but not restricted to, headache, sensorineural hearing loss, aseptic meningitis, myalgia and optic nerve involvement.

**RECENT FINDINGS:** Since the recognition of CAPS as a single disease entity and discovery of the underlying causative gene, there has been a major breakthrough in terms of its treatment by pharmacological IL-1 $\beta$  inhibition. Highly targeted therapies against IL-1 have been shown to be remarkably effective in the treatment of CAPS and make early diagnosis of this condition crucial. It is hoped that starting pharmacological intervention in a timely manner will prove neuroprotective. There are three drugs licensed for treatment of CAPS; canakinumab, anakinra and rilonacept. The former two are widely used: canakinumab is a fully humanised anti-IL-1 $\beta$  monoclonal antibody administered as a subcutaneous injection once every 8 weeks starting at a dose of 150 mg in patients weighing more than 40 kg. Anakinra is a recombinant form of the IL-1 receptor antagonist and the adult daily dose is 100 mg subcutaneously. CAPS is a highly debilitating disorder characterised by unregulated IL-1 $\beta$  production driven by autosomal dominantly inherited mutations in the NLRP3 gene. Effective therapies targeted against IL-1 are now available and are vital to prevent long-term complications.

DOI: 10.1007/s11940-018-0526-1

PMCID: PMC6132776

PMID: 30175395

171. Eur J Med Genet. 2018 Aug 29. pii: S1769-7212(18)30317-3. doi: 10.1016/j.ejmg.2018.08.013. [Epub ahead of print]

Familial Mediterranean fever (FMF) phenotype in patients homozygous to the MEFV M694V mutation.

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The clinical presentation of familial Mediterranean fever (FMF) is remarkably variable, ranging from a quiescent to a severe and disabling disease. The M694V mutation is one of approximately 300 published genetic variations in the FMF gene. While some studies have reported a more severe phenotype for the homozygous M694V mutation, studies dedicated solely to featuring the phenotype of homozygous M694V genotype are meager. The objective of the study was to present a comprehensive characterization of the homozygous M694V mutation associated phenotype, compared to the phenotypes of other FMF genotypes. For that aim, we compared between the demographic and clinical characteristics of 57 FMF patients, homozygous for the M694V MEFV mutation, and 56 patients with other MEFV genotypes. A questionnaire, detailing demographic and clinical features was completed for each patient based on an interview, physical examination and



medical file data. Compared with the control group, the double M694V MEFV mutation group comprised more patients with severe disease (89.4 vs. 32.1%,  $p < 0.0001$ ) and affected with FMF-related comorbidities (29.8 vs. 12.5%,  $p = 0.0373$ ). The mean frequency of attacks per year was higher for patients with the double M694V MEFV mutation, before and during colchicine treatment ( $23.6 \pm 9.3$  vs.  $15.6 \pm 11.7$ ,  $p = 0.0001$  and  $7.2 \pm 7.8$  vs.  $3.5 \pm 5.5$ ,  $p = 0.0007$ , respectively); and the mean dose of colchicine used was higher ( $1.9 \pm 0.48$  vs.  $1.48 \pm 0.54$  mg/day,  $p = 0.0001$ ). Among the genotypes tested, homozygosity to the M694V MEFV mutation was found to be associated with the most grievous phenotype in the clinical spectrum of FMF.

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DOI: 10.1016/j.ejmg.2018.08.013

PMID: 30171907

172. Int Immunol. 2018 Aug 31. doi: 10.1093/intimm/dxy059. [Epub ahead of print]

Dysregulation of immunoproteasomes in autoinflammatory syndromes.

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Immunoproteasomes degrade ubiquitin-coupled proteins and play a role in creating peptides for presentation by MHC class I proteins. Studies of gene-deficient mice in which each immunoproteasomal subunit was affected have demonstrated that dysfunction of immunoproteasomes leads to immunodeficiency, i.e., reduced expression of MHC class I and attenuation of CD8 T cell responses. Recent studies, however, have uncovered a new type of autoinflammatory syndrome characterized by fever, nodular erythema and progressive partial lipodystrophy that is caused by genetic mutations in immunoproteasome subunits. These mutations disturbed the assembly of immunoproteasomes, which led to reduced proteasomal activity and thus accumulation of ubiquitin-coupled proteins. Those findings suggest that immunoproteasomes function as anti-inflammatory machinery in humans. The discovery of a new type of autoinflammatory syndrome caused by dysregulated

immunoproteasomes provides novel insights into the important roles of immunoproteasomes in inflammation as well as the spectrum of autoinflammatory diseases.

DOI: 10.1093/intimm/dxy059

PMID: 30169676

173. *Pediatr Dermatol*. 2018 Nov;35(6):e337-e340. doi: 10.1111/pde.13619. Epub 2018 Aug 30.

Chronic urticaria in infants as the first manifestation of autoinflammatory disease.

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We report two unrelated infants in whom chronic urticaria was the first clinical manifestation of cryopyrin-associated periodic syndrome, which should be suspected in infants with early-onset chronic urticaria, especially if there is a neutrophil-rich infiltrate in the skin biopsy. Early diagnosis of cryopyrin-associated periodic syndrome may lead to early and successful treatment with anti-interleukin-1 medications.

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DOI: 10.1111/pde.13619

PMID: 30168189 [Indexed for MEDLINE]

174. Hautarzt. 2018 Sep;69(9):761-772. doi: 10.1007/s00105-018-4250-2.

[Schnitzler syndrome].

[Article in German]

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Schnitzler syndrome is a very rare acquired systemic disease with many similarities to hereditary autoinflammatory syndromes. The main characteristics are generalized exanthema and a monoclonal gammopathy with IgM. Other clinical features include fever, muscle, bone and/or joint pain, and lymphadenopathy. About 15-20% of patients with Schnitzler syndrome develop lymphoproliferative diseases and, in rare cases, amyloid A (AA) amyloidosis can occur if the disease is not treated. Activation of the innate immune system, especially interleukin(IL)-1 $\beta$ , is central in the pathogenesis of the disease. Consequently, complete control of disease symptoms can be achieved in 80% of patients by treatment with the IL-1 receptor antagonist anakinra.

DOI: 10.1007/s00105-018-4250-2

PMID: 30167710

175. BMJ Open. 2018 Aug 30;8(8):e021037. doi: 10.1136/bmjopen-2017-021037.

Clinical and multi-omics cross-phenotyping of patients with autoimmune and autoinflammatory diseases: the observational TRANSIMMUNOM protocol.

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**INTRODUCTION:** Autoimmune and autoinflammatory diseases (AIDs) represent a socioeconomic burden as the second cause of chronic illness in Western countries. In this context, the TRANSIMMUNOM clinical protocol is designed to revisit the nosology of AIDs by combining basic, clinical and information sciences. Based on classical and systems biology analyses, it aims to uncover important phenotypes that cut across diagnostic groups so as to discover biomarkers and identify novel therapeutic targets.

**METHODS AND ANALYSIS:** TRANSIMMUNOM is an observational clinical protocol that aims to cross-phenotype a set of 19 AIDs, six related control diseases and healthy volunteers . We assembled a multidisciplinary cohort management team tasked with (1) selecting informative biological (routine and omics type) and clinical parameters to be captured, (2) standardising the sample collection and shipment circuit, (3) selecting omics technologies and benchmarking omics data providers, (4) designing and implementing a multidisease electronic case report form and an omics database and (5) implementing supervised and unsupervised data analyses.

**ETHICS AND DISSEMINATION:** The study was approved by the institutional review board of Pitié-Salpêtrière Hospital (ethics committee Ile-De-France 48-15) and done in accordance with the Declaration of Helsinki and good clinical practice. Written informed consent is obtained from all participants before enrolment in the study. TRANSIMMUNOM's project website provides information about the protocol (<https://www.transimmunom.fr/en/>) including experimental set-up and tool developments. Results will be disseminated during annual scientific committees appraising the project progresses and at national and international scientific conferences.

**DISCUSSION:** Systems biology approaches are increasingly implemented in human pathophysiology research. The TRANSIMMUNOM study applies such approach to the pathophysiology of AIDs. We believe that this translational systems immunology approach has the potential to provide breakthrough discoveries for better understanding and treatment of AIDs.

**TRIAL REGISTRATION NUMBER:** NCT02466217; Pre-results.

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DOI: 10.1136/bmjopen-2017-021037

PMCID: PMC6119447

PMID: 30166293

Conflict of interest statement: Competing interests: None declared.

176. Br J Clin Pharmacol. 2018 Aug 30. doi: 10.1111/bcp.13748. [Epub ahead of print]

Anti-IL-7 receptor  $\alpha$  monoclonal antibody (GSK2618960) in healthy subjects - a randomized, double-blind, placebo-controlled study.

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AIM: Interleukin (IL)-7 signalling modulates T cell activity and is implicated in numerous autoimmune diseases. The present study investigated the safety, pharmacokinetics, target engagement, pharmacodynamics and immunogenicity of GSK2618960, an IL-7 receptor- $\alpha$  subunit (CD127) monoclonal antibody.

METHODS: A double-blind (sponsor-unblind) study of a single intravenous infusion of either GSK2618960 (0.6 mg kg<sup>-1</sup> or 2.0 mg kg<sup>-1</sup>) or placebo was carried out in 18 healthy subjects over 24 weeks.

RESULTS: GSK2618960 was well tolerated; there were no serious or significant adverse events. The observed half-life was 5 ( $\pm$ 1) days (2.0 mg kg<sup>-1</sup>), with nonlinear pharmacokinetics. Full receptor occupancy (>95%) was observed until day 8 (0.6 mg kg<sup>-1</sup>) and day 22 (2.0 mg kg<sup>-1</sup>). Maximal inhibition of IL-7-mediated signal transducer and activator of transcription 5 (STAT5) phosphorylation was observed in 5/6 subjects until day 22 (2.0 mg kg<sup>-1</sup>). Mean circulating IL-7 and soluble receptor (CD127) levels were increased above baseline during days 2 and 15 (0.6 mg kg<sup>-1</sup>) and days 2 and 22 (2.0 mg kg<sup>-1</sup>). No meaningful changes were observed in absolute numbers or proportions of immune cell populations or inflammatory cytokine profiles (IL-6, tumour necrosis factor- $\alpha$ , interferon- $\gamma$ , IL-2). Persistent antidrug antibodies (ADAs) were detected in 5/6 subjects administered a dose of 0.6 mg kg<sup>-1</sup> (neutralizing in 2/6) and in 6/6 subjects administered 2.0 mg kg<sup>-1</sup> (neutralizing in 5/6).

CONCLUSION: GSK2618960 was well tolerated and blocked IL-7 receptor signalling upon full target engagement. Although there was no discernible impact on peripheral T cell subsets in healthy subjects, GSK2618960 may effectively modulate the autoinflammatory activity of pathogenic T cells in diseased tissue. A relatively short half-life is likely the result of target-mediated rather than ADA-mediated clearance.

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DOI: 10.1111/bcp.13748

PMID: 30161291

177. Bratisl Lek Listy. 2018;119(8):490-493. doi: 10.4149/BLL\_2018\_089.

Evaluation of pentraxin-3 in familial Mediterranean fever patients during attack and attack-free periods.

Gok M, Sirkeci O, Kara M, Sakin YS, Tanoglu A, Sirkeci EE, Oztin H, Duzenli T, Kaplan M, Yazgan Y, Ipcioglu OM.

INTRODUCTION: Pentraxin-3 (PTX-3) is a prototype of pentraxin proteins that have been shown to be involved in acute phase response. In this study, we aimed to investigate the relationship between PTX-3 levels and familial Mediterranean fever (FMF) disease, and to evaluate PTX-3 as a novel diagnostic marker of FMF.

**METHOD:** Forty-three male patients diagnosed with FMF and 42 healthy individuals were included in the study. Patients with other inflammatory diseases and patients who used drugs having anti-inflammatory properties were excluded from the research. Blood samples were obtained during both attack and attack-free periods.

**RESULTS:** Patient attack periods were confirmed by combining physical examination and elevation of acute phase reactants. Acute phase reactants were significantly higher in attack versus attack-free periods ( $p < 0.01$ ), however PTX-3 levels were not significantly different between the two periods. Additionally, PTX-3 levels in FMF patients were higher than in controls in both attack ( $917.29 \pm 725.29$  vs  $451.83 \pm 291.95$ ,  $p < 0.01$ ) and attack-free periods ( $748.23 \pm 487.53$  vs  $451.83 \pm 291.95$ ,  $p < 0.01$ ).

**CONCLUSION:** In this study, we showed that PTX-3 levels, in both FMF attack and attack-free periods, were significantly higher than in the control group.

Finally, PTX-3 may be a promising biomarker for FMF diagnosis and may predict FMF attacks (Tab. 2, Fig. 2, Ref. 18).

DOI: 10.4149/BLL\_2018\_089

PMID: 30160156

178. Bratisl Lek Listy. 2018;119(7):425-428. doi: 10.4149/BLL\_2018\_077.

Mitochondrial DNA copy number alterations in familial mediterranean fever patients.

Erdem HB, Ceylan AC, Sahin I, Sever-Erdem Z, Citli S, Tatar A.

**OBJECTIVES AND BACKGROUND:** Familial Mediterranean Fever (FMF) is characterized by recurrent fever episodes as a result of inflammation of serous membranes. Changes in the number of different mtDNA copy number variations, detected in FMF patients, who developed amyloidosis, might be an important parameter in the understanding of the pathophysiology of the disease.

**METHODS:** Changes in the mtDNA copy number between 50 patients with FMF, who had M694V homozygote mutation and amyloidosis, and 50 healthy controls, who had not any MEFV mutation or FMF clinical finding, were examined. The 22 MEFV mutations were analyzed by Pyromark Q24 system. Quantitative analysis was performed on RT-PCR. The level of mtDNA was calculated using the delta Ct ( $\Delta Ct$ ) of average Ct of mtDNA and nDNA ( $\Delta Ct = Ct \text{ mtDNA} - Ct \text{ nDNA}$ ) in the same well as an exponent of 2



(2ΔCt).

RESULTS: A significant decrease in the amount of mtDNA was detected in FMF patients with M694V homozygous mutation carriers, who developed amyloidosis compared to the control group ( $p < 0.001$ ).

CONCLUSION: In this study, mitochondrial dysfunction, which has been identified through changes in the mitochondrial genome in many diseases, was identified by showing that the copy number variations of mtDNA in leukocytes also decreased for FMF disease (Tab. 3, Fig. 1, Ref. 21).

DOI: 10.4149/BLL\_2018\_077

PMID: 30160131 [Indexed for MEDLINE]

179. Clin Rheumatol. 2018 Dec;37(12):3449-3454. doi: 10.1007/s10067-018-4274-0. Epub 2018 Aug 29.

A Chinese case series of Yao syndrome and literature review.

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Yao syndrome (YAOS), formerly named NOD2-associated autoinflammatory disease, is a periodic disease characterized by fever, dermatitis, polyarthritis, distal extremity swelling, and gastrointestinal and sicca-like symptoms associated with specific NOD2 sequence variants. All patients in the literature were Caucasians. Herein, we report the first case series of YAOS in China to further expand the clinical and genetic characteristics of this disorder. A retrospective review of

patients who were diagnosed with YAOS at our tertiary medical center was conducted. Three Han Chinese women with YAOS were included. Recurrent fever occurred in all patients and each febrile episode lasted several days to several weeks, and asymptomatic intervals ranged from several weeks to several months. Two patients experienced intermittent arthritis/arthralgia and abdominal pain, and one had sicca-like symptoms. None had dermatitis. Three variants in NOD2 were identified, including Q902K, R541P, and Y514H. The patients' symptoms significantly improved after treatment with glucocorticoids and/or sulfasalazine. YAOS exists in the Chinese population, and it may be a global disorder. Our patients appear to exhibit somewhat distinct clinical phenotypes from those in the Caucasian population, and three novel NOD2 variants have been identified in the disease.

DOI: 10.1007/s10067-018-4274-0

PMID: 30159790

180. Nat Commun. 2018 Aug 29;9(1):3506. doi: 10.1038/s41467-018-05861-7.

Nrf2 negatively regulates STING indicating a link between antiviral sensing and metabolic reprogramming.

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The transcription factor Nrf2 is a critical regulator of inflammatory responses. If and how Nrf2 also affects cytosolic nucleic acid sensing is currently unknown. Here we identify Nrf2 as an important negative regulator of STING and suggest a link between metabolic reprogramming and antiviral cytosolic DNA sensing in human cells. Here, Nrf2 activation decreases STING expression and responsiveness to STING agonists while increasing susceptibility to infection with DNA viruses. Mechanistically, Nrf2 regulates STING expression by decreasing STING mRNA stability. Repression of STING by Nrf2 occurs in metabolically reprogrammed cells following TLR4/7 engagement, and is inducible by a cell-permeable derivative of the TCA-cycle-derived metabolite itaconate (4-octyl-itaconate, 4-OI). Additionally, engagement of this pathway by 4-OI or the Nrf2 inducer sulforaphane is sufficient to repress STING expression and type I IFN production in cells from patients with STING-dependent interferonopathies. We propose Nrf2 inducers as a future treatment option in STING-dependent inflammatory diseases.

DOI: 10.1038/s41467-018-05861-7

PMCID: PMC6115435

PMID: 30158636 [Indexed for MEDLINE]

181. Proc Natl Acad Sci U S A. 2018 Sep 11;115(37):E8775-E8782. doi: 10.1073/pnas.1809853115. Epub 2018 Aug 28.

Human iPSC-derived trigeminal neurons lack constitutive TLR3-dependent immunity that protects cortical neurons from HSV-1 infection.

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Herpes simplex virus type 1 (HSV-1) encephalitis (HSE) is the most common sporadic viral encephalitis in Western countries. Some HSE children carry inborn errors of the Toll-like receptor 3 (TLR3)-dependent IFN- $\alpha/\beta$ - and - $\lambda$ -inducing pathway. Induced pluripotent stem cell (iPSC)-derived cortical neurons with TLR3 pathway mutations are highly susceptible to HSV-1, due to impairment of cell-intrinsic TLR3-IFN immunity. In contrast, the contribution of cell-intrinsic immunity of human trigeminal ganglion (TG) neurons remains unclear. Here, we describe efficient in vitro derivation and purification of TG neurons from human iPSCs via a cranial placode intermediate. The resulting TG neurons are of sensory identity and exhibit robust responses to heat (capsaicin), cold (icilin), and inflammatory pain (ATP). Unlike control cortical neurons, both control and TLR3-deficient TG neurons were highly susceptible to HSV-1. However, pretreatment of control TG neurons with poly(I:C) induced the cells into an anti-HSV-1 state. Moreover, both control and TLR3-deficient TG neurons developed resistance to HSV-1 following pretreatment with IFN- $\beta$  but not IFN- $\lambda$ . These data indicate that TG neurons are vulnerable to HSV-1 because they require preemptive stimulation of the TLR3 or IFN- $\alpha/\beta$  receptors to induce antiviral immunity, whereas cortical neurons possess a TLR3-dependent constitutive resistance that is sufficient to block incoming HSV-1 in the absence of prior antiviral signals. The lack of constitutive resistance in TG neurons in vitro is consistent with their exploitation as a latent virus reservoir in vivo. Our results incriminate deficiencies in the constitutive TLR3-dependent response of cortical neurons in the pathogenesis of HSE.

DOI: 10.1073/pnas.1809853115

PMCID: PMC6140487 [Available on 2019-03-11]

PMID: 30154162 [Indexed for MEDLINE]

Conflict of interest statement: Conflict of interest statement: L.W.E. and G.A.S. are coauthors on a 2017 paper [Pomeranz LE (2017) J Neurosci 37:4128–4144], in which they independently provided unpublished reagents/analytic tools.

182. Pediatr Allergy Immunol. 2018 Dec;29(8):863-872. doi: 10.1111/pai.12976.

Targeted next-generation sequencing for genetic diagnosis of 160 patients with primary immunodeficiency in south China.

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**BACKGROUND:** Primary immunodeficiency disorders (PID) is a group of heterogeneous diseases mainly characterized by severe and recurrent infections and an increased susceptibility to lymphoproliferative, atopic, and autoimmune conditions. The clinical diagnosis should preferably be complemented by a genetic diagnosis. To date, PID-related reports from China seldom attempt to make a genetic test for their patients.

**METHODS:** Our study aimed to evaluate demographic data, clinical manifestations, and molecular diagnosis of PID patients from southern China. Moreover, by comparison with previous reports, we provide a picture of the current status of PID in mainland China. A total number of 160 pediatric PID patients (106 males and 54 females) were enrolled, and targeted next-generation sequencing was conducted using 269 PID-related genes and subsequently confirmed by Sanger sequencing and familial segregation analysis.

**RESULT:** The autoinflammatory disease group was the most common subcategory of PID (20%), followed by immune dysregulation (17.5%) and combined immunodeficiencies (16.2%). Antibody deficiency disorders were identified in only 11.9% of the cohort. The putative causative gene was identified in 70 patients (43.8%), and an X-linked pattern was found in 45.7% of the genetically diagnosed patients.

**CONCLUSION:** The current study provides the first collective study of PID phenotypes and genotypes in south China and provides a strong argument for the diagnostic application of targeted next-generation sequencing panels in patients with suspected PID.

DOI: 10.1111/pai.12976

PMID: 30152884

183. Ocul Immunol Inflamm. 2018 Aug 27:1-7. doi: 10.1080/09273948.2018.1511810. [Epub ahead of print]

The Presence of Uveitis Is Associated with a Sustained Response to the Interleukin (IL)-1 Inhibitors Anakinra and Canakinumab in Behçet's Disease.

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**PURPOSE:** To identify factors associated with sustained response to interleukin (IL)-1 inhibition among demographic, clinical and therapeutic data in patients with Behçet disease (BD).

**METHODS:** BD patients treated with anakinra or canakinumab were enrolled. Patients were divided into two groups according to the clinical response: group 1 included subjects showing a treatment duration of at least 52 weeks and no secondary inefficacy during the first follow-up year; the remaining patients were included in the group 2. Demographic, clinical and therapeutic data were analyzed to identify significant differences between groups.

**RESULTS:** Eighteen patients were included in group 1 and 18 patients in group 2. A better response to IL-1 inhibitors was significantly more common among patients

with BD-related uveitis ( $p = 0.006$ ) and patients with a longer disease duration ( $p = 0.03$ ).

CONCLUSION: IL-1 blockade is effective in BD, especially in the subset of patients presenting eye involvement and in those with long-lasting disease.

DOI: 10.1080/09273948.2018.1511810

PMID: 30148652

184. J Immunol Res. 2018 Jul 17;2018:5954897. doi: 10.1155/2018/5954897. eCollection 2018.

Influence of Biological Therapeutics, Cytokines, and Disease Activity on Depression in Rheumatoid Arthritis.

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Purpose: Rheumatoid arthritis (RA) is an often debilitating autoinflammatory disease. Patients with rheumatoid arthritis are often troubled by co-occurring depression or other psychological manifestations. RA patients have a variety of treatment options available, including biologicals that inhibit cytokines or immune cells. If these cytokines influence the psychological symptoms, then the use of cytokine inhibitors should modulate these symptoms.

Methods: A cohort of 209 individuals was recruited. This group included 82 RA patients, 22 healthy subjects, 32 depressed control subjects, and 73 subjects with systemic lupus erythematosus. Of the RA patients, 51% were on a biological therapeutic. ELISA was used to measure cytokine levels. A variety of



psychological assessments were used to evaluate depression, anxiety, sleep, fatigue, and relationship status. Clinical values were obtained from medical records.

Results: IL-10 concentration was associated with depressive symptoms in the RA patients, healthy controls, and the lupus patients. In the patients with primary depression, depressive symptoms were associated with IL-6 and TNF-alpha. In RA patients, Tocilizumab use was associated with decreased depressive symptoms. 14 RA patients who were not using biologicals began using them by a one-month follow-up. In these patients, there was no significant change to any value except for fatigue.

Conclusions: A variety of both biological and social factors influences depressive symptoms in RA. IL-10 and IL-6 are likely to be involved, since IL-10 concentration was associated with depression and Tocilizumab decreased depressive symptoms in the RA patients. The roles of these cytokines are different in RA and lupus, as high IL-10 in RA is associated with increased depressive symptoms, but high IL-10 in the lupus patients is associated with decreased depression. IL-6 was also associated with depressive symptoms in the patients with primary depression. These results strongly indicate that disease activity, including cytokine levels, has a strong impact on depressive symptoms.

DOI: 10.1155/2018/5954897

PMCID: PMC6083532

PMID: 30148175 [Indexed for MEDLINE]

185. Med Mycol Case Rep. 2018 Feb 6;20:28-32. doi: 10.1016/j.mmcr.2018.02.001. eCollection 2018 Jun.

Tracheal, laryngeal and pulmonary mucormycosis followed by organizing pneumonia in a patient with Adult Onset Still's Disease.

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We report a case of tracheal, laryngeal and pulmonary mucormycosis in a patient receiving immunosuppressive medication for an autoinflammatory fever syndrome. Mucormycosis was confirmed by histopathology from tracheal specimens and molecular evidence of *Lichtheimia*. A surgical approach was not possible because of the multifocal disease pattern and the extent of tracheal involvement. The patient was successfully treated with liposomal amphotericin B followed by posaconazole maintenance therapy. After 9 months, recurrent pulmonary mucormycosis was suspected but emerged as organizing pneumonia without evidence of active fungal infection.

DOI: 10.1016/j.mmcr.2018.02.001

PMCID: PMC6105918

PMID: 30148059

186. Mod Rheumatol. 2018 Oct 18:1-5. doi: 10.1080/14397595.2018.1514999. [Epub ahead of print]

HLA-DQB1 DPB1 alleles in Japanese patients with adult-onset Still's disease.

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**OBJECTIVE:** HLA class II alleles are major determinants of genetic predisposition to rheumatic diseases. Predisposing effects of HLA had been suggested in AOSD, however, ethnic differences may account for variations in AOSD association with HLA. We determined the contribution of HLA-DQB1, DPB1 alleles to susceptibility to Adult-onset Still's disease (AOSD) in the Japanese population.

**METHODS:** HLA-DQB1 and DPB1 alleles were analyzed in 87 Japanese patients with AOSD and 413 Japanese healthy subjects.

**RESULTS:** We found significant association between HLA-DQB1\*06:02 ( $P_c = 0.010$ , odds ratio: 2.54) and AOSD, whereas there was no association between the DQB1\*06:02 allele and disease phenotypes of AOSD. Moreover, we did not find a predisposing effect of the HLA-DPB1 allele to AOSD. Haplotype analysis showed that presence of DRB1\*15:01-DQB1\*06:02 was associated with Japanese patients with AOSD. However, conditional logistic regression tests were unable to demonstrate independent association between DRB1\*1501 or DQB1\*0602 and AOSD.

**CONCLUSIONS:** Our results show significant association between AOSD and the HLA DQB1\*06:02 allele, and between the DRB1\*1501-DQB1\*06:02 haplotype and AOSD susceptibility. These findings suggest that genetic susceptibility to AOSD depends on the genotype combinations of HLA DRB1 and DQB1 alleles.

DOI: 10.1080/14397595.2018.1514999

PMID: 30136608

187. Front Immunol. 2018 Aug 6;9:1801. doi: 10.3389/fimmu.2018.01801. eCollection 2018.

Lymphocyte Autophagy in Homeostasis, Activation, and Inflammatory Diseases.

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Erratum in

Front Immunol. 2018 Nov 16;9:2627.

Autophagy is a catabolic mechanism, allowing the degradation of cytoplasmic content via lysosomal activity. Several forms of autophagy are described in mammals. Macroautophagy leads to integration of cytoplasmic portions into vesicles named autophagosomes that ultimately fuse with lysosomes.

Chaperone-mediated autophagy is in contrast the direct translocation of protein in lysosomes. Macroautophagy is central to lymphocyte homeostasis. Although its role is controversial in lymphocyte development and in naive cell survival, it seems particularly involved in the maintenance of certain lymphocyte subtypes. Its importance in memory B and T cells biology has recently emerged. Moreover, some effector cells like plasma cells rely on autophagy for survival. Autophagy is central to glucose and lipid metabolism, and to the maintenance of organelles like mitochondria and endoplasmic reticulum. In addition macroautophagy, or individual components of its machinery, are also actors in antigen presentation by B cells, a crucial step to receive help from T cells, this crosstalk favoring their final differentiation into memory or plasma cells. Autophagy is deregulated in several autoimmune or autoinflammatory diseases like systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, and Crohn's disease. Some treatments used in these pathologies impact autophagic activity, even if the causal link between autophagy regulation and the efficiency of the treatments has not yet been clearly established. In this review, we will first discuss the mechanisms linking autophagy to lymphocyte subtype survival and the signaling pathways involved. Finally, potential impacts of autophagy modulation in lymphocytes on the course of these diseases will be approached.

DOI: 10.3389/fimmu.2018.01801

PMCID: PMC6087746

PMID: 30127786

188. Mol Pain. 2018 Jan-Dec;14:1744806918799127. doi: 10.1177/1744806918799127. Epub 2018 Aug 20.

Autoinflammatory and autoimmune contributions to complex regional pain syndrome.

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Complex regional pain syndrome (CRPS) is a highly enigmatic syndrome typically developing after injury or surgery to a limb. Severe pain and disability are common among those with chronic forms of this condition. Accumulating evidence suggests that CRPS may involve both autoinflammatory and autoimmune components. In this review article, evidence for dysfunction of both the innate and adaptive immune systems in CRPS is presented. Findings from human studies in which cytokines and other inflammatory mediators were measured in the skin of affected limbs are discussed. Additional results from studies of mediator levels in animal models are evaluated in this context. Similarly, the evidence from human, animal, and translational studies of the production of autoantibodies and the potential targets of those antibodies is reviewed. Compelling evidence of autoinflammation in skin and muscle of the affected limb has been collected from CRPS patients and laboratory animals. Cytokines including IL-1 $\beta$ , IL-6, TNF $\alpha$ , and others are reliably identified during the acute phases of the syndrome. More recently, autoimmune contributions have been suggested by the discovery of self-directed pain-promoting IgG and IgM antibodies in CRPS patients and model animals. Both the autoimmune and the autoinflammatory components of CRPS appear to be regulated by neuropeptide-containing peripheral nerve fibers and the sympathetic nervous system. While CRPS displays a complex neuroimmunological pathogenesis, therapeutic interventions could be designed targeting autoinflammation, autoimmunity, or the neural support for these phenomena.

DOI: 10.1177/1744806918799127

PMCID: PMC6125849

PMID: 30124090

189. J Invest Dermatol. 2019 Jan;139(1):146-156. doi: 10.1016/j.jid.2018.07.025. Epub 2018 Aug 16.

A Critical Role of the IL-1 $\beta$ -IL-1R Signaling Pathway in Skin Inflammation and Psoriasis Pathogenesis.

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The IL-1 signaling pathway has been shown to play a critical role in the pathogenesis of chronic, autoinflammatory skin diseases such as psoriasis. However, the exact cellular and molecular mechanisms have not been fully understood. Here, we show that IL-1 $\beta$  is significantly elevated in psoriatic lesional skin and imiquimod-treated mouse skin. In addition, IL-1R signaling appears to correlate with psoriasis disease progression and treatment response. IL-1 signaling in both dermal  $\gamma\delta$  T cells and other cells such as keratinocytes is essential to an IMQ-induced skin inflammation. IL-1 $\beta$  induces dermal  $\gamma\delta$  T cell proliferation and IL-17 production in mice. In addition, IL-1 $\beta$  stimulates keratinocytes to secrete chemokines that preferentially chemoattract peripheral CD27- CCR6+IL-17 capable of producing  $\gamma\delta$  T cells ( $\gamma\delta$ T17). Further studies showed that endogenous IL-1 $\beta$  secretion is regulated by skin commensals to maintain dermal  $\gamma\delta$ T17 homeostasis in mice. Mouse skin associated with *Corynebacterium* species, bacteria enriched in human psoriatic lesional skin, has increased IL-1 $\beta$  and dermal  $\gamma\delta$ T17 cell expansion. Thus, the IL-1 $\beta$ -IL-1R signaling pathway may contribute to skin inflammation and psoriasis pathogenesis via the direct

regulation of dermal IL-17-producing cells and stimulation of keratinocytes for amplifying inflammatory cascade.

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DOI: 10.1016/j.jid.2018.07.025

PMID: 30120937

190. Mol Biol (Mosk). 2018 Jul-Aug;52(4):699-704. doi: 10.1134/S0026898418040171.

[In silico Search for Tubulin Polymerization Inhibitors].

[Article in Russian]

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Cytostatic colchicine is widely used in the treatment of Familial Mediterranean fever, but it has several side effects. For finding new, more effective drugs with higher affinity and diminish side effects we carried out virtual screening of potential inhibitors of the main target of colchicine, the polymerization of tubulin by evaluating affinity 25745 compounds, structurally related to the colchicine. We have identified 11 commercially available compounds with higher affinity to tubulin. Compounds with highest binding scores include trimethoxybenzene and its derivatives; these compounds bind to the same site in similar orientation. Information provided can form the basis for design of new cytostatics.

DOI: 10.1134/S0026898418040171

PMID: 30113036

191. Isr Med Assoc J. 2018 Jul;20(7):438-441.

Prompt Clinical Response to Secukinumab in Patients with Axial Spondyloarthritis: Real Life Observational Data from Three Italian Referral Centers.

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**BACKGROUND:** Clinical research is needed to identify patients with axial spondyloarthritis (axSpA) who are more likely to be responsive to interleukin (IL)-17 inhibition.

**OBJECTIVES:** To evaluate short-term efficacy of secukinumab in the management of axSpA.

**METHODS:** Twenty-one patients (7 males, 14 females) with axSpA were consecutively treated with secukinumab. Laboratory and clinical assessments were based on erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP, and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Data were recorded at baseline and at a 3 month follow-up visit.

**RESULTS:** The study was comprised of 21 patients. Both BASDAI and ASDAS-CRP showed a statistically significant reduction between the baseline and the 3 month visit ( $P < 0.0001$  and  $P = 0.0005$ , respectively). During the laboratory assessment, ESR showed a significant decrease ( $P = 0.008$ ) while CRP improvement did not reach statistical significance ( $P = 0.213$ ). No statistical significance was observed between patients treated with secukinumab 150 mg vs. 300 mg in BASDAI ( $P=0.99$ ),



ASDAS-CRP (P = 0.69), ESR (P = 0.54), and CRP (P = 0.56). No significant differences emerged between the BASDAI (P = 0.15), ASDAS-CRP (P = 0.09), and CRP (P = 0.15) rates in biologic-naïve patients and those previously failing tumor necrosis factor- $\alpha$  inhibition. Conversely, ESR decrease was significantly higher in the biologic-naïve subgroup (P = 0.01). No adverse events were reported. CONCLUSIONS: Secukinumab has proven remarkable short-term effectiveness, regardless of the biologic treatment line. A dosage of 150 mg proved to be appropriate in the clinical and laboratory management of axSpA.

PMID: 30109794

192. Autoimmun Rev. 2018 Oct;17(10):990-1001. doi: 10.1016/j.autrev.2018.04.006. Epub 2018 Aug 11.

Recommendations and barriers to vaccination in systemic lupus erythematosus.

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Patients with Systemic Lupus Erythematosus (SLE) pose a unique dilemma pertaining to immunization against common pathogens. SLE patients are usually not immunized with vaccines based on the fear of either precipitating infection in this immunosuppressed patient population (with live vaccines) or aggravating autoimmunity and hence lupus flares (with any vaccines). However, elevated vulnerability to infection makes patients with SLE precisely the population that needs protection from vaccine-preventable diseases. A summary of guidelines from the Centers for Disease Control and Prevention, professional societies, review articles and expert opinions regarding use of individual vaccines applicable to adults with SLE is presented in this review.

Published by Elsevier B.V.

DOI: 10.1016/j.autrev.2018.04.006

PMCID: PMC6150817 [Available on 2019-10-01]

PMID: 30103044 [Indexed for MEDLINE]

193. Intern Med. 2018 Dec 1;57(23):3351-3355. doi: 10.2169/internalmedicine.1099-18. Epub 2018 Aug 10.

First Nationwide Survey of 199 Patients with Amyloid A Amyloidosis in Japan.

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**Objective** To clarify the underlying diseases, clinical manifestations, and treatment strategies for Amyloid A (AA) amyloidosis (AAA) in Japanese patients.

**Methods** We conducted a survey on Japanese patients with AAA treated between January 1, 2012, and December 31, 2014. Results A total of 199 patients with AAA were included in the present study. The underlying diseases of AAA were rheumatoid arthritis (60.3%), uncharacterized inflammatory disorders (11.1%), neoplasms (7.0%), other rheumatic diseases (6.5%), inflammatory bowel diseases (4.5%), chronic infection (4.5%), Castleman's disease (4.0%), and autoinflammatory diseases (2.0%). The clinical manifestations at the diagnosis of AAA were moderate to severe renal dysfunction (46.2%), moderate to severe proteinuria (30.7%), intractable diarrhea (32.2%), melena (4.5%), paralytic ileus (3.5%), heart failure (11.6%), cardiac conduction disturbances (10.1%), arrhythmia (5.5%), and hypothyroidism (11.6%). Diagnostic biopsies were performed most frequently in the gastrointestinal tract (66.3%), followed by the kidneys (22.1%), heart (5.5%), abdominal fat (4.0%), and others (3.0%). Biologics were used to treat 97 patients with AAA (48.7%). Tocilizumab (TCZ) was administered to 66 patients, with 95.5% showing good responses. Anti-TNF agents were administered

to 27 patients, with 74.1% showing good responses. The treatment effects of TCZ were significantly superior to those of anti-TNF agents ( $p<0.007$ ). Conclusion The most common underlying diseases of AAA were rheumatic diseases. Uncharacterized inflammatory disorders and neoplasms were also frequently observed in patients with AAA. Renal and gastrointestinal manifestations were common and important for the diagnosis of AAA, with cardiac manifestations also being of significance. Biologics, particularly TCZ, were effective therapeutic modalities.

DOI: 10.2169/internalmedicine.1099-18

PMCID: PMC6306533

PMID: 30101921

194. Ann Rheum Dis. 2018 Nov;77(11):1558-1565. doi: 10.1136/annrheumdis-2017-212515. Epub 2018 Aug 12.

Consensus proposal for taxonomy and definition of the autoinflammatory diseases (AIDs): a Delphi study.

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Autoinflammatory diseases (AIDs) are a relatively new family of disorders, defined about 19 years ago. Some of them are hereditary and some are not. The names given to these diseases do not follow any systematic guidelines, and sometimes the same disorder carries several names. The aim of this study is to refine the definition of AIDs and to provide some conventions for their naming. We focused mainly on monogenetic AIDs. Delphi technique, which enables consensus among a group of experts through internet and mail communication and questionnaires, was employed. After achieving 100% consensus among six members of a steering committee, the questionnaire containing AID definitions and the agreed-upon conventions were sent to 26 physicians and researchers working in the field of AIDs in order to gain broader support for the committee's proposals. The committee proposed the following definition for AIDs: "Autoinflammatory diseases are clinical disorders caused by defect(s) or dysregulation of the innate immune system, characterized by recurrent or continuous inflammation (elevated acute phase reactants-APR) and the lack of a primary pathogenic role for the adaptive immune system (autoreactive T-cells or autoantibody production)." Several rules were defined for guiding the naming of these diseases among which are: abandoning eponyms and preferring the name of the gene over its encoded protein. The new definition for AIDs allows inclusion of clinical disorders mainly associated with defects in the innate immune system. The new conventions propose names with clinical meaning and in some cases even clues for treatment.

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DOI: 10.1136/annrheumdis-2017-212515

PMID: 30100561

Conflict of interest statement: Competing interests: For EB-C, MG, AG, DLK, HJL, IT: Nothing to disclose for this manuscript. NR received honoraria for consultancy of speaker's bureau from the following pharmaceutical companies since last 5 years: Abbott, AbbVie, Amgen, Biogenidec, Astellas, Alter, AstraZeneca, Baxalta Biosimilars, Boehringer, BMS, CD Pharma, Celgene, CrescendoBio, EMD

Serono, Hoffman La Roche, Italfarmaco, Janssen, MedImmune, Medac, Novartis, Novo Nordisk, Pfizer, Rewind Arms, R Pharma, Sanofi Aventis, Servier, Sinergie, Takeda, Vertex, UCB Biosciences GmbH. The Gaslini Hospital, which is the public Hospital where NR works as full time public employee, has received contributions from the following industries: Abbott, BMS, 'Francesco Angelini', GlaxoSmithKline (GSK), Hoffman La Roche, Italfarmaco, Janssen, Novartis, Pfizer, Sanofi Aventis, Schwarz Biosciences, Sobi, Xoma, Wyeth. This money has been reinvested for the research activities of the hospital in a fully independent manner without any commitment with third parties.

195. Vaccine. 2018 Sep 11;36(38):5796-5802. doi: 10.1016/j.vaccine.2018.07.074. Epub 2018 Aug 9.

Autoimmune diseases after hepatitis B immunization in adults: Literature review and meta-analysis, with reference to 'autoimmune/autoinflammatory syndrome induced by adjuvants' (ASIA).

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**BACKGROUND:** To assess if hepatitis B vaccination in adults is causally associated with autoimmune diseases. Such causation has been claimed based mainly on case reports and uncontrolled studies, and a syndrome 'Autoimmune/autoinflammatory Disorder Induced by Adjuvants' (ASIA) has been claimed to be linked to immunization, particularly hepatitis B vaccination.

**METHODS:** Review of peer-reviewed literature from January 1990 to March 2017 identifying controlled studies with documented incidence of autoimmune diseases occurring after hepatitis B vaccinations in adults. From 1297 studies identified, 259 were further assessed and 49 reviewed further; 19 relevant papers reporting 21 results are reviewed here, and 14 results included in a meta-analysis.

**RESULTS:** Overall no association between hepatitis B vaccination and the onset of autoimmune diseases was seen. The overall odds ratio was 1.06, with 95%

confidence limits of 0.93-1.21, with non-significant heterogeneity. Only one study showed a significant excess risk between hepatitis B immunisation and autoimmune disease.

CONCLUSIONS: Despite multiple case reports, there is no reliable scientific evidence of autoimmune diseases being caused by hepatitis B vaccinations.

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DOI: 10.1016/j.vaccine.2018.07.074

PMID: 30100071 [Indexed for MEDLINE]

196. Clin Rheumatol. 2018 Aug 11. doi: 10.1007/s10067-018-4228-6. [Epub ahead of print]

Comparative efficacy between adalimumab and infliximab in the treatment of non-infectious intermediate uveitis, posterior uveitis, and panuveitis: a retrospective observational study of 107 patients.

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To compare the efficacy of adalimumab (ADA) and infliximab (IFX) in patients with non-infectious intermediate uveitis, posterior uveitis, and panuveitis.

Demographic, clinical, instrumental, and therapeutic data from patients enrolled were collected at the start of treatment, at 12-month follow-up, and at the last follow-up assessment. One hundred seven patients (46 females, 187 eyes) were enrolled, 66 (61.7%) treated with ADA and 41 (38.3%) with IFX. Bilateral involvement was observed in 80 cases. The mean follow-up was  $26.45 \pm 21.71$  months for ADA patients and  $56.60 \pm 56.04$  months for IFX patients. The overall decrease of uveitis frequency during the first 12 months of treatment was 66.7% in the IFX group and 84.2% in the ADA group, compared to the previous 12 months ( $p = 0.09$ ). A significantly higher corticosteroid dosage was found among patients treated with ADA at the last follow-up visit ( $p = 0.008$ ). The percentage of patients co-administered with corticosteroids was significantly higher among ADA patients both at the 12-month visit ( $p = 0.03$ ) and at the last visit ( $p = 0.0004$ ). The frequency of uveitic macular edema (UME) was significantly higher among patients treated with ADA compared to those treated with IFX at the 12-month assessment ( $p = 0.015$ ) and at the last follow-up visit ( $p = 0.011$ ); central macular thickness was significantly higher in ADA group compared to the IFX group at the last follow-up assessment ( $p = 0.04$ ). ADA and IFX have shown a similar efficacy in controlling uveitis relapses, but IFX showed a more pronounced corticosteroid sparing effect and a significantly higher capacity in resolving UME compared to ADA.

DOI: 10.1007/s10067-018-4228-6

PMID: 30099655

197. Rheumatol Int. 2018 Oct;38(10):1833-1840. doi: 10.1007/s00296-018-4122-1. Epub 2018 Aug 11.

A retrospective study comparing the phenotype and outcomes of patients with

polyarteritis nodosa between UK and Turkish cohorts.

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There is a need for better definition of polyarteritis nodosa (PAN) subphenotypes and the influence of ethnicity and geography. This study is aimed to study the demographic and clinical features of PAN cohorts from the UK and Turkey (TR) and to compare and contrast disease characteristics. A retrospective survey of databases from two vasculitis centres between 1990 and 2016 for PAN patients fulfilling the EMEA Vasculitis Classification algorithm. All paediatric-onset adult patients met the Ankara 2008 (EULAR/PReS endorsed) criteria for childhood PAN. Those with typical angiographic and/or histopathologic findings consistent with PAN were included. 93 (M/F: 51/42) patients (UK: 47, TR: 46) were included. Three were HBV-related, 20 (21.5%) had paediatric onset and 16 (16.5%), cutaneous PAN. TR patients had younger age of disease onset 44 (28.5-59.0) vs. 24.5 (11.8-40.5),  $p = 0.002$ . Twelve (26%) of TR patients had monogenic disease (Familial Mediterranean Fever association ( $n = 7$ ), deficiency of adenosine deaminase 2, DADA2, ( $n = 5$ )). No difference was found in phenotype between paediatric and adult onset patients except for frequency of cutaneous lesions ( $p = 0.002$ ). During a median 67.5 (32-126) months follow-up, 13 patients died (12.7% in UK vs. 15.2% in Turkish cohorts). No difference was found between two cohorts in relation to relapse rate, death and vasculitis damage index. This study defined a diagnosis of PAN according to the EMEA algorithm. The TR group had a younger age of disease onset and more cases of monogenic disease; however, disease extent, relapse rate, damage index and death rates were similar between groups.



198. Orphanet J Rare Dis. 2018 Aug 9;13(1):132. doi: 10.1186/s13023-018-0878-3.

Health-related quality of life in children with PFAPA syndrome.

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**BACKGROUND:** Conventionally, PFAPA syndrome is considered as a benign disease compared to other recurrent fevers because it completely passes before adulthood. However, in our clinical practice, fever episodes have a huge impact on daily activities.

**METHODS:** Observational cohort study using the Pediatric Quality of Life Inventory (PedsQL™ 4.0) Generic Core and Fatigue Scales. PedsQL™ uses a modular approach to measure the HRQOL in children with acute and chronic health conditions. We used pediatric FMF patients as the control group.

**RESULTS:** We included 33 children with PFAPA and compared them to 27 FMF patients matched for age: preschool-age children (2 to 7 years) and school-age children and youths (8 to 18 years). PedsQL™ self-reported scores of children with PFAPA were systematically lower than those of FMF peers for general quality of life and physical and psychosocial functioning (significant only in the preschool-age group). PedsQL™ self-reported fatigue scores of children with PFAPA were significantly lower than those of FMF peers for both preschoolers and school-age children and youths. Parent proxy-reports were not significantly different, even though scores were systematically lower for the parents of PFAPA children.

**CONCLUSION:** Our study demonstrates, for the first time, that the wellbeing of PFAPA children is poor, with a major impact on psychosocial functioning and increased fatigue. The quality of life of PFAPA children appears to be even lower than that of FMF patients, for whom a lower than normal HRQOL has already been

demonstrated.

DOI: 10.1186/s13023-018-0878-3

PMCID: PMC6085641

PMID: 30092788

199. Avicenna J Med Biotechnol. 2018 Jul-Sep;10(3):178-182.

Association between rs6759298 and Ankylosing Spondylitis in Iranian Population.

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**Background:** Ankylosing Spondylitis (AS) is a chronic autoinflammatory Spondyloarthropathy (SpA) which is characterized by sacroiliitis, which progresses to the axial skeleton. It seems that non-Human Leukocyte Antigen (HLA) and also HLA-B27 are associated with the susceptibility and pathogenesis of the disease. The recent Ge-nome-Wide Association Studies (GWASs) have reported intergenic rs6759298 to be associated with AS etiology. The aim of this study was investigation of the rs6759298 polymorphism in Iranian AS patients. In addition, probable correlations with clinical indices and manifestations were considered. **Methods:** This study included 403 patients with AS. The control group consisted of 506 healthy individuals who were matched for sex, age, and ethnicity with AS group. Genotyping of rs6759298 was determined using the Amplification-Refractory Mutation System-Polymerase Chain Reaction (ARMS-PCR). **Results:** The GG genotype and G allele were found to be significantly more prevalent in the patient group in comparison to the control group [(p=2×10<sup>-6</sup> and 7.44×10<sup>-9</sup>; OR (95% CI) =2.16 (1.56-2.98) and 1.73 (1.43-2.08)], respectively. **Conclusion:** No associations were found between patients with three genotypes and

any disease manifestations or clinical indices. This investigation confirmed a highly significant association of rs6759298 with disease susceptibility, with no effect on disease progress or clinical presentations. Since rs6759298 belongs to the 2p15 gene desert, further studies would elucidate the exact role of this polymorphism in the pathogenesis of AS.

PMCID: PMC6064007

PMID: 30090213

Conflict of interest statement: Conflict of Interest The authors declare that there is no conflict of interest.

200. Rheumatol Int. 2018 Aug 7. doi: 10.1007/s00296-018-4123-0. [Epub ahead of print]

Is age associated with disease severity and compliance to treatment in children with familial Mediterranean fever?

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Familial Mediterranean Fever (FMF) is the most common monogenic autoinflammatory disease in the world. The disease characteristics may vary in different age groups. In this study, we aimed to compare disease characteristics and treatment compliance according to the age of pediatric FMF patients. This is a single-center, cross-sectional study. Between August and October 2016, patients

who were diagnosed with FMF, participated to the study. 378 pediatric FMF patients were enrolled in the study. Among those, age at symptom onset was  $\leq 5$  years in 69%, 6-11 years in 26% and  $\geq 12$  years in 5%. Patients older than 12 years old at symptom onset, had significantly less frequent fever attacks than the patients from other age groups. Patients younger than 5 years old at symptom onset had significantly higher international severity scoring system for FMF (ISSF) than other patients. And M694V homozygosity was significantly more frequent in patients with younger age at symptom onset. Patients younger than 5 years old were using their drugs more regularly than the other age groups ( $p = 0.002$ ). Drug compliance was 90.5% in patients  $\leq 5$  years, 64.4% in patients 6-11 years, 58.3% in patients  $\geq 12$  years. The disease characteristics of FMF may differ between patients with different age at symptom onset. Younger age at disease onset seems to be related with more severe course; thus these patients should be followed-up more closely. In addition, treatment compliance which is critical for prevention of amyloidosis in FMF should be questioned especially in adolescent patients.

DOI: 10.1007/s00296-018-4123-0

PMID: 30088045

201. Front Immunol. 2018 Jul 24;9:1647. doi: 10.3389/fimmu.2018.01647. eCollection 2018.

DICER1: A Key Player in Rheumatoid Arthritis, at the Crossroads of Cellular Stress, Innate Immunity, and Chronic Inflammation in Aging.

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Loss-of-function or knockout mouse models have established a fundamental role for the RNase III enzyme DICER1 in development and tissue morphogenesis and/or homeostasis. These functions are currently assumed to result mainly from the DICER1-dependent biogenesis of microRNAs which exhibit important gene expression regulatory properties. However, non-canonical DICER1 functions have recently emerged. These include interaction with the DNA damage response (DDR) pathway and the processing of cytotoxic non-coding RNAs, suggesting that DICER1 might also participate in the regulation of major cellular processes through miRNA-independent mechanisms. Recent findings indicated that reduced Dicer1 expression, which correlates with worsened symptoms in mouse models of joint inflammation, is also noted in fibroblast-like synoviocytes (FLS) harvested from rheumatoid arthritis (RA) patients, as opposed to FLS cultured from biopsies of osteoarthritic patients. In addition, low DICER1 levels are associated with the establishment of cellular stress and its associated responses, such as cellular senescence. Senescent and/or stressed cells are associated with an inflammatory secretome (cytokines and chemokines), as well as with "find-me" and "eat-me" signals which will attract and activate the innate immune compartment (NK cells, macrophages, and neutrophils) to be eliminated. Failure of this immunosurveillance mechanism and improper restauration of homeostasis could lead to the establishment of a systemic and chronic inflammatory state. In this review, we suggest that reduced DICER1 expression contributes to a vicious cycle during which accumulating inflammation and premature senescence, combined to inadequate innate immunity responses, creates the appropriate conditions for the initiation and/or progression of autoimmune-autoinflammatory diseases, such as RA.

DOI: 10.3389/fimmu.2018.01647

PMCID: PMC6066587

PMID: 30087677

202. Biomed Pharmacother. 2018 Nov;107:155-167. doi: 10.1016/j.biopha.2018.07.174. Epub 2018 Aug 4.

Synergistic antiproliferative and differentiating effect of 2,4-monofurfurylidene-tetra-O-methylsorbitol and 4,6-dimethyl-2-(3,4,5-trimethoxyphenylamino)pyrimidine on primary and immortalized keratinocytes.

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Psoriasis is one of the most common chronic autoinflammatory skin disease, associated with hyperproliferation and abnormal differentiation of keratinocytes, inflammation, and angiogenesis. The available treatments for psoriasis are not curative and may have numerous side effects, and topical administration is preferred over systemic therapy due to the reduced systemic burden of the drug. Thus, novel and more efficacious formulations of anti-inflammatory and/or differentiating compounds for topical application could be very useful for the disease management and for improving the quality of life of the patients. Here we evaluated the potential as anti-psoriatic of an equimolar mixture of two compounds, 2,4-Monofurfurylidene-tetra-O-methylsorbitol (Compound A) and 4,6-dimethyl-2-(3,4,5-trimethoxyphenylamino)pyrimidine (Compound B), that, used individually, are known to possess immunomodulating properties (Compound A) and keratolytic and anti-inflammatory activity (Compound B). Human immortalized keratinocyte cell line (HaCaT cells) and primary human keratinocyte cells from adult donor (HEKa) were used as in vitro experimental models. We show that the mix A + B exhibits antiproliferative activity and induces terminal differentiation more efficiently than compounds A and B used individually. We confirm that the compound B is the active ingredient of the mixture and the mainly responsible for anti-psoriatic activity, but the mix A + B is more effective and possesses lower cytotoxicity than the compound B alone. This could be ascribable to the association with compound A, that is known to possess, in addition to the immunomodulating ability, antioxidant and antiradical action. Our results indicate that mix A + B could be a suitable candidate for a new cosmeceutical formulation for topical treatment of psoriasis.

203. Rheumatology (Oxford). 2018 Dec 1;57(12):2140-2144. doi: 10.1093/rheumatology/key218.

Familial Mediterranean fever in Chinese adult patients.

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**Objectives:** FMF is the most frequent monogenic auto-inflammatory disease worldwide. There have been hardly any cases reported in the Chinese population. We aimed to describe the first cohort of adult FMF patients in China.

**Methods:** We evaluated all the adult patients suffering from FMF referred to our centre from April 2015 through March 2017. Patients were diagnosed clinically according to the Tel Hashomer criteria. Whole exome sequencing was performed in each patient.

**Results:** A total of 11 adult patients were diagnosed as FMF in our centre. The mean age of onset was 29.4 years (s.d. 18.2). All patients were of Chinese Han ethnicity with no positive family history. All patients had intermittent febrile episodes. During attacks, seven patients had generalized abdominal pain, three experienced chest pain, four developed arthritis and none reported erysipelas-like skin changes. No patient had evidence of AA amyloidosis. Every patient carried at least one variant in the MEFV gene. All patients had good response to colchicine.

**Conclusion:** Our study is the first to suggest the presence of FMF in the Chinese adult population. The late onset, often atypical and mild clinical manifestations and absence of AA amyloidosis in our patients might be related to low-penetrance and heterozygous MEFV variants. Our results await to be confirmed on larger Chinese populations.

DOI: 10.1093/rheumatology/key218

PMID: 30085313

204. Isr Med Assoc J. 2018 Aug;20(8):517-521.

Correlation of Serum Amyloid-A Levels, Clinical Manifestations, Treatment, and Disease Activity in Patients with Behçet's Disease.

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**BACKGROUND:** Behçet's disease (BD) is an inflammatory disorder potentially leading to life- and sight-threatening complications. No laboratory marker correlating with disease activity or predicting the occurrence of disease manifestations is currently available.

**OBJECTIVES:** To determine an association between serum amyloid-A (SAA) levels and disease activity via the BD Current Activity Form (BDCAF), to evaluate disease activity in relation to different SAA thresholds, to examine the association between single organ involvement and the overall major organ involvement with different SAA thresholds, and to assess the influence of biologic therapy on SAA levels.

**METHODS:** We collected 95 serum samples from 64 BD patients. Related demographic, clinical, and therapeutic data were retrospectively gathered.

**RESULTS:** No association was identified between SAA levels and BD disease activity (Spearman's  $\rho = 0.085$ ,  $P = 0.411$ ). A significant difference was found in the mean BDCAF score between patients presenting with SAA levels  $< 200$  mg/L and those



with SAA levels > 200 mg/L (P = 0.027). SAA levels > 200 mg/L were associated with major organ involvement (P = 0.008). A significant association was found between SAA levels > 150 mg/dl and ocular (P = 0.008), skin (P = 0.002), and mucosal (P = 0.012) manifestations. Patients undergoing biologic therapies displayed more frequently SAA levels < 200 mg/L vs. patients who were not undergoing biologic therapies (P = 0.012).

**CONCLUSIONS:** Although SAA level does not represent a biomarker for disease activity, it might be a predictor of major organ involvement and ocular disease relapse at certain thresholds in patients with BD.

PMID: 30084580

205. Turk Pediatri Ars. 2018 Mar 1;53(1):31-36. doi: 10.5152/TurkPediatriArs.2018.5818. eCollection 2018 Mar.

Comparison of familial Mediterranean fever and juvenile idiopathic arthritis patients according to family origin.

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**Aim:** Familial Mediterranean fever is an inherited condition that is more prevalent in some regions of Turkey. Juvenile idiopathic arthritis is the most common chronic arthritis of childhood. There is lack of studies on the frequency of mentioned conditions across different regions of Turkey. We aimed to compare the Familial Mediterranean fever and juvenile idiopathic arthritis patients according to their family origin.

**Material and Methods:** Patients with diagnosis of familial Mediterranean fever and juvenile idiopathic arthritis followed up at the Division of Pediatric Rheumatology were assessed. Data regarding the family origin of patients were noted from their medical records. Both groups were compared according to their origins.

**Results:** A total of 704 patients with Familial Mediterranean fever, 204 patients

with juvenile idiopathic arthritis were enrolled. The main age of the patients at the study time was  $12.3 \pm 4.4$  years and  $12.1 \pm 4.8$  years, respectively. The frequency of familial Mediterranean fever was significantly higher in subjects with the origin of Black Sea and Central Anatolia regions (z score 2.69, and 3.69, respectively). Juvenile idiopathic arthritis was significantly more common in subjects from Marmara and Southeastern Anatolia regions (z score -4.11 and -2.54, respectively).

Conclusion: The familial Mediterranean fever is more common among subjects from the Black Sea and Central Anatolia regions of Turkey, especially Kastamonu, Sivas and Tokat provinces. Whereas, patients with juvenile idiopathic arthritis more commonly originate from Marmara and Southeastern Anatolia regions of Turkey.

DOI: 10.5152/TurkPediatriArs.2018.5818

PMCID: PMC6070219

PMID: 30083072

Conflict of interest statement: Conflict of Interest: No conflict of interest was declared by the authors.

206. Eur J Clin Invest. 2018 Nov;48(11):e13013. doi: 10.1111/eci.13013. Epub 2018 Aug 23.

Influence of baseline modified Rheumatic Disease Comorbidity Index (mRDCI) on drug survival and effectiveness of biological treatment in patients affected with Rheumatoid arthritis, Spondyloarthritis and Psoriatic arthritis in real-world settings.

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AIM: To assess the impact of baseline modified Rheumatic Disease Comorbidity Index (mRDCI) a simple comorbidity count, on overall survival of treatments with biological drugs in patients affected with Rheumatoid Arthritis (RA), Spondyloarthritis (SpA) and Psoriatic Arthritis (PsA) in real-world settings.

METHODS: Patients (nr. 635) with RA (nr. 214), SpA (nr. 213) and PsA (nr. 208) starting a first biological drug were retrospectively analysed. mRDCI was scored at baseline, and disease characteristics were recorded at entry and at last observation. Drug retention was analysed using Kaplan-Meier curves. Cox regression models were used to estimate the association of baseline mRDCI with drug discontinuation and clinical outcomes, the achievement of clinical remission based on 28 joint-Disease Activity Score (DAS28) <2.6 for RA and PsA, and on Ankylosing Spondylitis-C-reactive protein Disease Activity Score (ASDAS-CRP) <1.3 for SpA.

RESULTS: Baseline mRDCI significantly correlated with the number of biological drug switches ( $\rho$  0.26). Persistence on biologic therapy was significantly higher in patients with mRDCI=0 (96.4%), than in those with mRDCI  $\geq$ 2 (83.9%). Patients without comorbidities showed significantly higher drug survival rate in PsA ( $P = 0.0001$ ) or SpA ( $P = 0.02$ ), but not in RA. mRDCI was also found to be a predictor of definitive drug discontinuation (HR: 1.53) and of failure to achieve remission in RA (HR: 0.66) or PsA (HR: 0.77), and in SpA (HR: 0.43).

CONCLUSIONS: This study provided evidence that baseline mRDCI negatively impacts the persistence on biologic treatments and clinical outcomes in patients with RA, SpA and PsA in real-life settings.

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DOI: 10.1111/eci.13013

PMID: 30079593

207. Vet Immunol Immunopathol. 2018 Aug;202:153-163. doi: 10.1016/j.vetimm.2018.07.001. Epub 2018 Jul 7.

Identification of genetic variation in equine collagenous lectins using targeted resequencing.

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Collagenous lectins are a family of soluble pattern recognition receptors that play an important role in innate immune resistance to infectious disease. Through recognition of carbohydrate motifs on the surface of pathogens, some collagenous lectins can activate the lectin pathway of complement, providing an effective means of host defense. Genetic polymorphisms in collagenous lectins have been shown in several species to predispose animals to a variety of infectious diseases. Infectious diseases are an important cause of morbidity in horses, however little is known regarding the role of equine collagenous lectins. Using a high-throughput, targeted re-sequencing approach, the relationship between genetic variation in equine collagenous lectin genes and susceptibility to disease was investigated. DNA was isolated from tissues obtained from horses submitted for post-mortem examination. Animals were divided into two populations, those with infectious or autoinflammatory diseases ( $n = 37$ ) and those without ( $n = 52$ ), and then subdivided by dominant pathological process for a total of 21 pools, each containing 4-5 horses. DNA was extracted from each horse and pooled in equimolar amounts, and the exons, introns, upstream (approximately 50 kb) and downstream (approximately 3 kb) regulatory regions for the 11 equine collagenous lectin genes and related MASP genes were targeted for re-sequencing. A custom target capture kit was used to prepare a sequencing library, which was sequenced on an Illumina MiSeq. After implementing quality control filters, 4559 variants were identified. Of these, 92 were present in the coding regions (43 missense, 1 nonsense, and 48 synonymous), 1414 in introns, 3029 in the upstream region, and 240 in the downstream region. In silico analysis of the missense short nucleotide variants identified 12 mutations with potential to disrupt collagenous lectin protein structure or function, 280 mutations located within predicted transcription factor binding sites, and 95 mutations located within predicted microRNA binding elements. Analysis of allelic association identified 113 mutations that segregated between the infectious/autoinflammatory and non-infectious populations. The variants discovered in this experiment represent potential genetic contributors to disease susceptibility of horses, and will

serve as candidates for further population-level genotyping. This study contributes to the growing body of evidence that pooled, high-throughput sequencing is a viable strategy for cost-effective variant discovery.

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DOI: 10.1016/j.vetimm.2018.07.001

PMID: 30078590

208. J Cell Physiol. 2018 Dec;233(12):9209-9222. doi: 10.1002/jcp.26949. Epub 2018 Aug 5.

The MicroRNA-326: Autoimmune diseases, diagnostic biomarker, and therapeutic target.

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MicroRNAs (miRNAs) are uniquely regulated in healthy, inflamed, activated, cancerous, or other cells and tissues of a pathological state. Many studies confirm that immune dysregulation and autoimmune diseases with inflammation are correlated with various miRNA expression changes in targeted tissues and cells in innate or adaptive immunity. In this review, we will explain the history and classification of epigenetic changes. Next, we will describe the role of miRNAs

changes, especially mir-326 in autoimmunity, autoinflammatory, and other pathological conditions. A systematic search of MEDLINE, Embase, and Cochrane Library was presented for all related studies from 1899 to 2017 with restrictions in the English language. In recent years, researchers have concentrated on mostly those roles of miRNA that are correlated with the inflammatory and anti-inflammatory process. Latest studies have proposed a fundamental pathogenic role in cancers and autoinflammatory diseases. Studies have described the role of microRNAs in autoimmunity and autoinflammatory diseases, cancers, and so on. The miRNA-326 expression plays a significant role in autoimmune and other types of diseases.

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DOI: 10.1002/jcp.26949

PMID: 30078204

209. Ann Rheum Dis. 2018 Nov;77(11):1599-1605. doi: 10.1136/annrheumdis-2018-213725. Epub 2018 Aug 4.

In silico validation of the Autoinflammatory Disease Damage Index.

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**INTRODUCTION:** Autoinflammatory diseases can cause irreversible tissue damage due to systemic inflammation. Recently, the Autoinflammatory Disease Damage Index (ADDI) was developed. The ADDI is the first instrument to quantify damage in familial Mediterranean fever, cryopyrin-associated periodic syndromes, mevalonate kinase deficiency and tumour necrosis factor receptor-associated periodic syndrome. The aim of this study was to validate this tool for its intended use in a clinical/research setting.

**METHODS:** The ADDI was scored on paper clinical cases by at least three physicians per case, independently of each other. Face and content validity were assessed by requesting comments on the ADDI. Reliability was tested by calculating the intraclass correlation coefficient (ICC) using an 'observer-nested-within-subject' design. Construct validity was determined by correlating the ADDI score to the Physician Global Assessment (PGA) of damage and disease activity. Redundancy of individual items was determined with Cronbach's alpha.

**RESULTS:** The ADDI was validated on a total of 110 paper clinical cases by 37 experts in autoinflammatory diseases. This yielded an ICC of 0.84 (95% CI 0.78 to 0.89). The ADDI score correlated strongly with PGA-damage ( $r=0.92$ , 95% CI 0.88 to 0.95) and was not strongly influenced by disease activity ( $r=0.395$ , 95% CI 0.21 to 0.55). After comments from disease experts, some item definitions were refined. The interitem correlation in all different categories was lower than 0.7, indicating that there was no redundancy between individual damage items.

**CONCLUSION:** The ADDI is a reliable and valid instrument to quantify damage in individual patients and can be used to compare disease outcomes in clinical studies.

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DOI: 10.1136/annrheumdis-2018-213725

Conflict of interest statement: Competing interests: Novartis Pharma financially supported meetings with the methodologist. PAB: consultancy/speaking fees from Novartis, Roche, SOBI, UCB. FdB: Novartis, Novimmune, Hoffmann-La Roche, SOBI, AbbVie. LC: speaker's fee from Novartis and SOBI. MC: consultancy fees for Novartis, SOBI and Abbvie. KLD: consultancy work for SOBI and Novartis; donations, honorariums and unrestricted grants have been received by the Autoinflammatory Alliance from SOBI, Novartis and Regeneron. RG: consultant for Abbvie. RGM: study support from SOBI, Novartis, Regeneron. VH: honorariums and educational grants from Novartis; honorariums from SOBI. MH: consultant for Novartis. HMM: consultant for Novartis and SOBI; speaker for Novartis. TK: research grant by Novartis; speaker's bureau by Roche, BMS, Novartis and SOBI. JKD: consultant/speaker for Novartis and SOBI, and has received grant support from SOBI and Novartis. RML: ad board and consultant for Abbvie and Novartis. PQ: investigator, consultant and speaker's bureau for Novartis and SOBI. MG: consultant for and unrestricted grants to Eurofever and speaker's fee from SOBI and Novartis. YU: grant/research support from Novartis; consultant for Novartis; speaker's bureau of Abbvie, Neopharm, Novartis, Roche. JF: consultant for Novartis. GS: consulting fees for Novartis. FD: attended to Novartis advisory board meeting.

210. Ann Rheum Dis. 2019 Jan;78(1):6-15. doi: 10.1136/annrheumdis-2018-213454. Epub 2018 Aug 4.

Gene editing for inflammatory disorders.

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Technology for precise and efficient genetic editing is constantly evolving and

is now capable of human clinical applications. Autoimmune and inflammatory diseases are chronic, disabling, sometimes life-threatening, conditions that feature heritable components. Both primary genetic lesions and the inflammatory pathobiology underlying these diseases represent fertile soil for new therapies based on the capabilities of gene editing. The ability to orchestrate precise targeted modifications to the genome will likely enable cell-based therapies for inflammatory diseases such as monogenic autoinflammatory disease, acquired autoimmune disease and for regenerative medicine in the setting of an inflammatory environment. Here, we discuss recent advances in genome editing and their evolving applications in immunoinflammatory diseases. Strengths and limitations of older genetic modification tools are compared with CRISPR/Cas9, base editing, RNA editing, targeted activators and repressors of transcription and targeted epigenetic modifiers. Commonly employed delivery vehicles to target cells or tissues of interest with genetic modification machinery, including viral, non-viral and cellular vectors, are described. Finally, applications in animal and human models of inflammatory diseases are discussed. Use of chimeric autoantigen receptor T cells, correction of monogenic diseases with genetically edited haematopoietic stem and progenitor cells, engineering of induced pluripotent stem cells and ex vivo expansion and modification of regulatory T cells for a range of chronic inflammatory diseases are reviewed.

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DOI: 10.1136/annrheumdis-2018-213454

PMID: 30077989

Conflict of interest statement: Competing interests: None declared.

211. J Pharmacol Exp Ther. 2018 Oct;367(1):155-167. doi: 10.1124/jpet.118.250845. Epub 2018 Aug 3.

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome-Metabolic Disease or Disturbed Homeostasis due to Focal Inflammation in the Hypothalamus?

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Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex disease characterized by debilitating fatigue, lasting for at least 6 months, with associated malaise, headaches, sleep disturbance, and cognitive impairment, which severely impacts quality of life. A significant percentage of ME/CFS patients remain undiagnosed, mainly due to the complexity of the disease and the lack of reliable objective biomarkers. ME/CFS patients display decreased metabolism and the severity of symptoms appears to be directly correlated to the degree of metabolic reduction that may be unique to each individual patient. However, the precise pathogenesis is still unknown, preventing the development of effective treatments. The ME/CFS phenotype has been associated with abnormalities in energy metabolism, which are apparently due to mitochondrial dysfunction in the absence of mitochondrial diseases, resulting in reduced oxidative metabolism. Such mitochondria may be further contributing to the ME/CFS symptomatology by extracellular secretion of mitochondrial DNA, which could act as an innate pathogen and create an autoinflammatory state in the hypothalamus. We propose that stimulation of hypothalamic mast cells by environmental, neuroimmune, pathogenic and stress triggers activates microglia, leading to focal inflammation in the brain and disturbed homeostasis. This process could be targeted for the development of novel effective treatments.

DOI: 10.1124/jpet.118.250845

PMID: 30076265

212. Nat Rev Dis Primers. 2018 Aug 2;4(1):11. doi: 10.1038/s41572-018-0009-4.

Cryoglobulinaemia.

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Cryoglobulinaemia refers to the serum presence of cryoglobulins, which are defined as immunoglobulins that precipitate at temperatures <37 °C. Type I

cryoglobulinaemia consists of only one isotype or subclass of monoclonal immunoglobulin, whereas type II and type III are classified as mixed cryoglobulinaemia because they include immunoglobulin G (IgG) and IgM. Many lymphoproliferative, infectious and autoimmune disorders have been associated with mixed cryoglobulinaemia; however, hepatitis C virus (HCV) is the aetiological agent in most patients. The underlying mechanism of the disorder is B cell lymphoproliferation and autoantibody production. Mixed cryoglobulinaemia can cause systemic vasculitis, with manifestations ranging from purpura, arthralgia and weakness to more serious lesions with skin ulcers, neurological and renal involvement. This Primer focuses on mixed cryoglobulinaemia, which has a variable course and a prognosis that is primarily influenced by vasculitis-associated multiorgan damage. In addition, the underlying associated disease in itself may cause considerable mortality and morbidity. Treatment of cryoglobulinaemic vasculitis should be modulated according to the underlying associated disease and the severity of organ involvement and relies on antiviral treatment (for HCV infection), immunosuppression and immunotherapy, particularly anti-CD20 B cell depletion therapies.

DOI: 10.1038/s41572-018-0009-4

PMID: 30072738

213. Eur J Rheumatol. 2018 Dec;5(4):278-280. doi: 10.5152/eurjrheum.2018.17183. Epub 2018 Jul 20.

Recurrence of proteinuria after cessation of tocilizumab in patients with AA amyloidosis secondary to FMF.

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There is no established treatment protocol for amyloid-A (AA) amyloidosis secondary to Familial Mediterranean Fever (FMF). Recently, we reported the efficacy of tocilizumab in 11 amyloidosis cases associated with FMF. In 2 patients of 11, we discontinued the tocilizumab administration owing to the normalization of amyloidosis-related symptoms, but proteinuria re-occurred

eventually. Fortunately, the patients responded to tocilizumab re-treatment. This led us to conclude that physicians should not stop the treatment, even in patients with normalized proteinuria levels.

DOI: 10.5152/eurjrheum.2018.17183

PMCID: PMC6267750

PMID: 30071938

214. Clin Rheumatol. 2018 Jul 31. doi: 10.1007/s10067-018-4225-9. [Epub ahead of print]

Detection of a novel mutation in NLRP3/CIAS1 gene in an Indian child with Neonatal-Onset Multisystem Inflammatory Disease (NOMID).

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Neonatal-Onset Multisystem Inflammatory Disease (NOMID) or Chronic Infantile Neurologic Cutaneous Articular (CINCA) syndrome is a monogenic autoinflammatory disorder characterized by urticarial skin rash, fever, chronic meningitis and joint manifestations. Here we report a case of an Indian male child who presented at the age of 9 months with fever, respiratory distress, urticarial skin rash, arthritis, and neuroregression. Suspecting NOMID/CINCA syndrome, the child's blood was sent to the Jaslok Hospital and Research Centre for mutation analysis of the CIAS1/NLRP3 gene. The DNA was screened for mutations in exon 3 of CIAS1/NLRP3 gene by automated Sanger sequencing. DNA sequencing showed a novel heterozygous c.1813A→G, p.R605G mutation in exon 3 of CIAS1/NLRP3 gene (ref no NM\_001243133.1). His parents tested negative for this mutation. We therefore identified a novel de novo mutation in this family in the CIAS1/NLRP3 gene

responsible for the child's clinical features.

DOI: 10.1007/s10067-018-4225-9

PMID: 30066283

215. Clin Rheumatol. 2018 Jul 30. doi: 10.1007/s10067-018-4230-z. [Epub ahead of print]

On demand use of anakinra for attacks of familial Mediterranean fever (FMF).

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To evaluate the efficacy of on-demand use of anakinra in patients with crFMF. The Gazi FMF cohort was established in the year 2010, and from that date, 689 patients with FMF diagnosed according to the Tel Hashomer criteria were registered. Attack type, duration, severity, and their impact on life were collected either by disease diaries or a mobile phone application (FMF AIDD, AppStore, and Playstore). A retrospective cohort analysis was made from records of patients who have ever been treated with IL-1 inhibitors. A total of 78 patients were treated with IL-1 inhibitors in our cohort. Among these, 15 patients were identified who received on-demand anakinra. Rationale for on-demand use was prominent prodrome or trigger for attacks and patient's personal claim. Six patients were switched from regular use and nine were directly started as on-demand use. All were using background colchicine in maximum tolerated doses. None of the patients had evidence of persistently elevated acute phase reactants or proteinuria. The median duration of on-demand anakinra use was 6 (3-36) months. Pre- and post- on-demand anakinra periods were compared. Patient reported attack severity ( $p = 0.002$ ), duration ( $p = 0.001$ ), frequency ( $p = 0.001$ ), absenteeism ( $p = 0.002$ ), and presenteeism ( $p = 0.002$ ) were



significantly improved. On-demand anakinra prevented progression of prodromes to full-blown attacks which was demonstrated by decrease in the rate of attack/prodrome ratio ( $p = 0.02$ ). On-demand anakinra can be continued in ten subjects on long-term. On-demand anakinra significantly improved FMF attacks in certain patients which suggest this approach would be of benefit in daily practice in selected patients.

DOI: 10.1007/s10067-018-4230-z

PMID: 30062447

216. Front Immunol. 2018 Jul 16;9:1533. doi: 10.3389/fimmu.2018.01533. eCollection 2018.

Long Non-Coding RNAs Play a Role in the Pathogenesis of Psoriatic Arthritis by Regulating MicroRNAs and Genes Involved in Inflammation and Metabolic Syndrome.

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Psoriatic arthritis (PsA) is an inflammatory arthritis, characterized by inflammation of entheses and synovium, leading to joint erosions and new bone formation. It affects 10-30% of patients with psoriasis, and has an estimated prevalence of approximately 1%. PsA is considered to be primarily an autoimmune disease, driven by autoreactive T cells directed against autoantigens present in the skin and in the joints. However, an autoinflammatory origin has recently been proposed. Long noncoding RNAs (lncRNAs) are RNAs more than 200 nucleotides in length that do not encode proteins. lncRNAs play important roles in several biological processes, including chromatin remodeling, transcription control, and post-transcriptional processing. Several studies have shown that lncRNAs are expressed in a stage-specific or lineage-specific manner in immune cells that have a role in the development, activation, and effector functions of immune cells. lncRNAs are thought to play a role in several diseases, including

autoimmune disorders. Indeed, a few lncRNAs have been identified in systemic lupus erythematosus, rheumatoid arthritis, and psoriasis. Although several high-throughput studies have been performed to identify lncRNAs, their biological and pathological relevance are still unknown, and most transcriptome studies in autoimmune diseases have only assessed protein-coding transcripts. No data are currently available on lncRNAs in PsA. Therefore, by microarray analysis, we have investigated the expression profiles of more than 50,000 human lncRNAs in blood samples from PsA patients and healthy controls using Human Clariom D Affymetrix chips, suitable to detect rare and low-expressing transcripts otherwise unnoticed by common sequencing methodologies. Network analysis identified lncRNAs targeting highly connected genes in the PsA transcriptome. Such genes are involved in molecular pathways crucial for PsA pathogenesis, including immune response, glycolipid metabolism, bone remodeling, type 1 interferon, wntless related integration site, and tumor necrosis factor signaling. Selected lncRNAs were validated by RT-PCR in an expanded cohort of patients. Moreover, modulated genes belonging to meaningful pathways were validated by RT-PCR in PsA PBMCs and/or by ELISA in PsA sera. The findings indicate that lncRNAs are involved in PsA pathogenesis by regulating both microRNAs and genes and open new avenues for the identification of new biomarkers and therapeutical targets.

DOI: 10.3389/fimmu.2018.01533

PMCID: PMC6054935

PMID: 30061880

217. Proc Natl Acad Sci U S A. 2018 Aug 14;115(33):E7768-E7775. doi: 10.1073/pnas.1806239115. Epub 2018 Jul 30.

Nitro-fatty acids are formed in response to virus infection and are potent inhibitors of STING palmitoylation and signaling.

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The adaptor molecule stimulator of IFN genes (STING) is central to production of type I IFNs in response to infection with DNA viruses and to presence of host DNA in the cytosol. Excessive release of type I IFNs through STING-dependent

mechanisms has emerged as a central driver of several interferonopathies, including systemic lupus erythematosus (SLE), Aicardi-Goutières syndrome (AGS), and stimulator of IFN genes-associated vasculopathy with onset in infancy (SAVI). The involvement of STING in these diseases points to an unmet need for the development of agents that inhibit STING signaling. Here, we report that endogenously formed nitro-fatty acids can covalently modify STING by nitro-alkylation. These nitro-alkylations inhibit STING palmitoylation, STING signaling, and subsequently, the release of type I IFN in both human and murine cells. Furthermore, treatment with nitro-fatty acids was sufficient to inhibit production of type I IFN in fibroblasts derived from SAVI patients with a gain-of-function mutation in STING. In conclusion, we have identified nitro-fatty acids as endogenously formed inhibitors of STING signaling and propose for these lipids to be considered in the treatment of STING-dependent inflammatory diseases.

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DOI: 10.1073/pnas.1806239115

PMCID: PMC6099880

PMID: 30061387 [Indexed for MEDLINE]

Conflict of interest statement: Conflict of interest statement: F.J.S. declares financial interest in Complexa Inc.

218. J Autoimmun. 2018 Nov;94:99-109. doi: 10.1016/j.jaut.2018.07.013. Epub 2018 Jul 27.

mTOR pathway activation in large vessel vasculitis.

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**BACKGROUND:** Mammalian target of rapamycin complex 1 (mTORC 1) drives the proinflammatory expansion of T helper (TH) type 1, TH17 cells and controls fibroblast proliferation, typical features of large vessel vasculitis (LVV) pathogenesis. Molecular pathways involved in arterial lesions of LVV are unknown.

**METHODS:** We evaluate mTORC pathway activation in vascular aorta lesions and in T cell homeostasis of patients with LVV.

**RESULTS:** Proliferation of both endothelial cells and vascular smooth-muscle cells was shown in vascular lesions in LVV. The vascular endothelium of proliferating aorta vessels from patients with LVV showed indications of activation of the mTORC1 pathway (S6RP phosphorylation). In cultured vascular endothelial cells, sera from patients with LVV stimulated mTORC1 through the phosphorylation of S6RP. mTORC1 activation was found also in Th1 and Th17 cells both systemically and in inflamed vessels. Patients with LVV exhibited a diminished S6RP

phosphorylation in Tregs. Inhibition of mTORC1 pathway with rapamycin, increase Tregs and decrease effector CD4+IFN $\gamma$ +, CD4+IL17+ and CD4+IL21+ T cells in patients with LVV.

CONCLUSIONS: We provided evidence that mTORC1 pathway has a central role in driving T cell inflammation and vascular lesions in LVV. Targeting mTORC pathway may represent a new therapeutic option in patients with LVV.

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DOI: 10.1016/j.jaut.2018.07.013

PMID: 30061014

219. Biosci Rep. 2018 Aug 29;38(4). pii: BSR20171503. doi: 10.1042/BSR20171503. Print 2018 Sep 3.

The role of polymorphic ERAP1 in autoinflammatory disease.

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Autoimmune and autoinflammatory conditions represent a group of disorders characterized by self-directed tissue damage due to aberrant changes in innate and adaptive immune responses. These disorders possess widely varying clinical phenotypes and etiology; however, they share a number of similarities in genetic associations and environmental influences. Whilst the pathogenic mechanisms of disease remain poorly understood, genome wide association studies (GWAS) have implicated a number of genetic loci that are shared between several autoimmune and autoinflammatory conditions. Association of particular HLA alleles with disease susceptibility represents one of the strongest genetic associations. Furthermore, recent GWAS findings reveal strong associations with single nucleotide polymorphisms in the endoplasmic reticulum aminopeptidase 1 (ERAP1)

gene and susceptibility to a number of these HLA-associated conditions. ERAP1 plays a major role in regulating the repertoire of peptides presented on HLA class I alleles at the cell surface, with the presence of single nucleotide polymorphisms in ERAP1 having a significant impact on peptide processing function and the repertoire of peptides presented. The impact of this dysfunctional peptide generation on CD8+ T-cell responses has been proposed as a mechanism of pathogenesis diseases where HLA and ERAP1 are associated. More recently, studies have highlighted a role for ERAP1 in innate immune-mediated pathways involved in inflammatory responses. Here, we discuss the role of polymorphic ERAP1 in various immune cell functions, and in the context of autoimmune and autoinflammatory disease pathogenesis.

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DOI: 10.1042/BSR20171503

PMCID: PMC6131210

PMID: 30054427

220. J Clin Rheumatol. 2018 Jul 25. doi: 10.1097/RHU.0000000000000873. [Epub ahead of print]

Effectiveness of Canakinumab in Colchicine- and Anakinra-Resistant or -Intolerant Adult Familial Mediterranean Fever Patients: A Single-Center Real-Life Study.

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**OBJECTIVE:** We aimed to present our single-center real-life experience of canakinumab use in adult patients with familial Mediterranean fever (FMF).

**METHODS:** Data were derived from the Gazi FMF cohort, which was established in 2010. From that year, all patients with FMF were registered. The impact of FMF on their lives was tracked by either an FMF diary or mobile phone application

(FMF-AIDD, free to download in App Store and Google Play). The records of patients who were treated with canakinumab were reviewed.

**RESULTS:** Twenty-three adult patients with FMF (65% female) were enrolled in this study. The median age was 32 years (min-max, 24-58 years), and the disease duration was 26 years (14-59 years). A total of 86% of patients harbored homozygous or compound heterozygous exon 10 MEFV mutations. Indications for interleukin 1 inhibitor use were colchicine resistance (n = 12) or intolerance (n = 2), amyloidosis (n = 7), and chronic manifestations of the disease (n = 2). All patients used anakinra before. The median duration of canakinumab use was 7 months (min-max, 1-44 months). Pre- and post-canakinumab periods were compared. Attack severity, duration, frequency, C-reactive protein level, and erythrocyte sedimentation rate were significantly improved ( $P \leq 0.01$ ), whereas serum creatinine and alanine aminotransferase levels remained the same ( $P = 0.27$  and  $P = 0.74$ , respectively). Canakinumab achieved complete disease remission in 14 patients (60%). Canakinumab was discontinued in 7 patients. The reasons for discontinuation were pregnancy (n = 2), dominance of axial spondyloarthropathy (n = 2), inflammatory bowel disease, patient's refusal, and weight gain.

**CONCLUSIONS:** Canakinumab is effective in the prevention of FMF bouts without severe adverse effects. Treatment with canakinumab in an individualized dose and interval may be a reasonable choice for colchicine- and anakinra-resistant or -intolerant adult patients with FMF and those with chronic manifestations of disease.

DOI: 10.1097/RHU.0000000000000873

PMID: 30048391

221. Arq Gastroenterol. 2018 Apr-Jun;55(2):175-178. doi: 10.1590/S0004-2803.201800000-31.

SEROLOGICAL SCREENING FOR CELIAC DISEASE IN CHILDREN WITH COLCHICINE-RESISTANT FAMILIAL MEDITERRANEAN FEVER.

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**BACKGROUND:** Familial Mediterranean fever and celiac disease share some common clinical features such as abdominal pain, diarrhea, arthralgia and arthritis.

Also, both of the diseases are associated with many inflammatory and autoimmune diseases. Previous studies have shown the association between familial Mediterranean fever (FMF) and different clinical conditions.

**OBJECTIVE:** We aimed to investigate the relationship between celiac disease and colchicine-resistant familial Mediterranean fever (crFMF) disease.

**METHODS:** This prospective study was conducted at the Department of Pediatric Gastroenterology and Pediatric Rheumatology from October 2015 to August 2016. A total of 24 patients with crFMF were included in the study. We used 60 sex- and age-matched healthy subjects as a control group. Levels of total IgA and tissue transglutaminase (tTG) IgA antibody were measured in both groups. Those with increased level of tTG IgA were tested for anti-endomysium IgA antibodies (EMA). Gastroduodenoscopy and intestinal biopsy were planned for a definite diagnosis of celiac disease in patients with positive EMA.

**RESULTS:** Of the 24 patients in this study, 18 (75.0%) were female. Only 4 (16.6%) of 24 patients were positive for tTG IgA. Patients with positive tTG IgA were then tested for EMA IgA antibodies and none of them had a positive result. Only one (1.6%) subject from the control group was positive for tTG IgA but EMA positivity was not detected.

**CONCLUSION:** We did not found celiac disease in 24 children with crFMF. Since crFMF disease is rarely seen in general population, further studies with more patients are needed to provide more precise interpretation.

DOI: 10.1590/S0004-2803.201800000-31

PMID: 30043869 [Indexed for MEDLINE]

222. Crit Rev Clin Lab Sci. 2018 Sep;55(6):432-442. doi: 10.1080/10408363.2018.1488805. Epub 2018 Jul 23.

Mosaicism in autoinflammatory diseases: Cryopyrin-associated periodic syndromes (CAPS) and beyond. A systematic review.

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Autoinflammatory diseases (AIDs) are conditions related to defective regulation of the innate immune system. Sanger sequencing of the causative genes has long been the reference for confirming the diagnosis. However, for many patients with a typical AID phenotype, the genetic cause remains unknown. A pioneering study in 2005 demonstrated mosaicism in patients with cryopyrin-associated periodic syndromes (CAPS); the authors found somatic mosaicism in 69% of their cohort of Sanger-negative CAPS patients. We aim to address the extent to which mosaicism contributes to the etiology of AIDs and its impact on phenotype. We retrieved English-language publications reporting mosaicism in AIDs by querying PubMed with no restriction on date and we surveyed French reference centers. We provide a comprehensive clinical and genetic picture of mosaicism in AIDs. We estimate that the proportion of CAPS-like patients presenting mosaicism ranges from 0.5% to 19%. We also discuss the possible links between the proportion of mutated alleles and various clinical features. This review reevaluates the contribution of mosaic DNA variants in CAPS. Mosaicism may be more common than anticipated in other AIDs. No significant difference was demonstrated between variant allele frequency and clinical phenotype. Such knowledge has implications for the development of guidelines for genetic diagnosis, genetic counseling of affected families and effective patient care.

DOI: 10.1080/10408363.2018.1488805

PMID: 30035647

223. *Pediatr Clin North Am*. 2018 Aug;65(4):691-709. doi: 10.1016/j.pcl.2018.04.005.

Systemic Juvenile Idiopathic Arthritis.

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Systemic juvenile idiopathic arthritis (sJIA) is a distinctive subtype of juvenile idiopathic arthritis, characterized by fever and arthritis, often accompanied by rash, sometimes by generalized lymphadenopathy, hepatosplenomegaly, and serositis. The diagnosis requires adequate exclusion of infectious, oncologic, autoimmune, and autoinflammatory diseases. Macrophage activation syndrome, a serious and potentially fatal complication of sJIA, requires prompt evaluation and treatment. Newer biologic agents, particularly interleukin-1 and interleukin-6 inhibitors, are highly effective and have transformed the treatment approach by reducing the use of systemic glucocorticoids. Primary care providers have a crucial role in monitoring children with sJIA for disease-related complications and medication-related adverse events.

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DOI: 10.1016/j.pcl.2018.04.005

PMID: 30031494 [Indexed for MEDLINE]

224. *Ann Rheum Dis*. 2018 Nov;77(11):1675-1687. doi: 10.1136/annrheumdis-2018-213524. Epub 2018 Jul 20.

Multi-OMICS analyses unveil STAT1 as a potential modifier gene in mevalonate kinase deficiency.

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**OBJECTIVES:** The objective of the present study was to explain why two siblings carrying both the same homozygous pathogenic mutation for the autoinflammatory disease hyper IgD syndrome, show opposite phenotypes, that is, the first being asymptomatic, the second presenting all classical characteristics of the disease.

**METHODS:** Where single omics (mainly exome) analysis fails to identify culprit genes/mutations in human complex diseases, multiomics analyses may provide solutions, although this has been seldom used in a clinical setting. Here we combine exome, transcriptome and proteome analyses to decipher at a molecular level, the phenotypic differences between the two siblings.

**RESULTS:** This multiomics approach led to the identification of a single gene-STAT1-which harboured a rare missense variant and showed a significant overexpression of both mRNA and protein in the symptomatic versus the asymptomatic sister. This variant was shown to be of gain of function nature, involved in an increased activation of the Janus kinase/signal transducer and activator of transcription signalling (JAK/STAT) pathway, known to play a critical role in inflammatory diseases and for which specific biotherapies presently exist. Pathway analyses based on information from differentially expressed transcripts and proteins confirmed the central role of STAT1 in the proposed regulatory network leading to an increased inflammatory phenotype in the symptomatic sibling.

**CONCLUSIONS:** This study demonstrates the power of a multiomics approach to uncover potential clinically actionable targets for a personalised therapy. In more general terms, we provide a proteogenomics analysis pipeline that takes advantage of subject-specific genomic and transcriptomic information to improve protein identification and hence advance individualised medicine.

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DOI: 10.1136/annrheumdis-2018-213524

PMCID: PMC6225799

PMID: 30030262

Conflict of interest statement: Competing interests: None declared.

225. Front Immunol. 2018 Jul 4;9:1527. doi: 10.3389/fimmu.2018.01527. eCollection 2018.

A Case of Adult-Onset Still's Disease Caused by a Novel Splicing Mutation in TNFAIP3 Successfully Treated With Tocilizumab.

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TNFAIP3 encodes the NF- $\kappa$ B regulatory protein A20. High-penetrance heterozygous mutations in TNFAIP3 cause a haploinsufficiency of A20 (HA20), inadequate inhibition of NF- $\kappa$ B pathway, and an early onset autoinflammatory disorder. However, the clinical phenotype of patients with HA20 varies greatly and clinical diagnoses prior to establishing the genetic cause, included both autoimmune and autoinflammatory conditions. Here, we present the first patient with HA20, who was previously diagnosed with AOSD but was later found to have a novel heterozygous variant in TNFAIP3 and who was successfully treated with anti-IL6 receptor biologic tocilizumab (RoActemra). We discovered a novel heterozygous mutation in TNFAIP3 c.1906C>T, not previously found in ExAC database. Further analysis shows that this single-nucleotide variant at the terminal residue of TNFAIP3 exon 7 produces an alternatively spliced mRNA resulting in p.His636fsTer1. Additional genetic analysis of family members shows that this variant does segregate with the inflammatory clinical phenotypes. Subsequent functional test show that NF- $\kappa$ B activation, measured as intracellular phosphorylation of p65 in CD14 + monocytes, was more enhanced in the patient compared with healthy controls (HC) following stimulation with LPS. This was associated with higher production of inflammatory cytokines by the patients PBMC in response to LPS and ATP and enhanced activation of NLRP3 inflammasome complex. Furthermore, increased activation of NLRP3 inflammasome was evident systemically, since we detected higher levels of ASC specks in patients' sera compared with HC. Finally, we used population genetics data from GnomAD to construct a map of both genetic conservation and most probable disease-causing variants in TNFAIP3 which might be found in future cases of HA20.

DOI: 10.3389/fimmu.2018.01527

PMCID: PMC6039542

PMID: 30022980

226. Intern Emerg Med. 2018 Sep;13(6):839-844. doi: 10.1007/s11739-018-1907-x. Epub 2018 Jul 18.

Recurrent pericarditis: still idiopathic? The pros and cons of a well-honoured term.

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In developed countries, more than 80% of cases of acute pericarditis remain without an established diagnosis after a conventional and standard diagnostic approach. These cases are generally labelled as 'idiopathic', i.e. without a known cause. This lack of information is a matter of concern for both patients and clinicians. Some years ago, this term reflected the state of the art of scientific knowledge on the topic. Advances have changed this point of view, in light of available molecular techniques like polymerase chain reaction able to identify viral cardiotropic agents in pericardial fluid and biopsies.

Furthermore, the remarkable efficacy of interleukin-1 antagonists, a therapy

targeting the innate immune response, suggests clinical and pathogenic similarity between a proportion of patients with idiopathic recurrent pericarditis and classical autoinflammatory diseases. So, it seems useful to discuss the pros and cons of using the term "idiopathic" in light of the new knowledge.

DOI: 10.1007/s11739-018-1907-x

PMID: 30022399

227. Rheumatol Int. 2018 Jul 17. doi: 10.1007/s00296-018-4105-2. [Epub ahead of print]

Familial Mediterranean fever and periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome: shared features and main differences.

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Autoinflammatory diseases are characterized by fever attacks of varying durations, associated with variety of symptoms including abdominal pain, lymphadenopathy, polyserositis, arthritis, etc. Despite the diversity of the clinical presentation, there are some common features that make the differential diagnosis of the autoinflammatory diseases challenging. Familial Mediterranean fever (FMF) is the most commonly seen autoinflammatory conditions, followed by syndrome associated with periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA). In this review, we aim to evaluate disease characteristics that make a diagnosis of FMF and PFAPA challenging, especially in a regions endemic for FMF. The ethnicity of patient, the regularity of the disease attacks, and the involvement of the upper respiratory systems and symphonies could be helpful in differential diagnosis. Current data from the literature suggest the use of biological agents as an alternative for patients with FMF and PFAPA who are non-responder classic treatment options. More controlled studies are needed to evaluate the efficacy and safety of this strategy.

DOI: 10.1007/s00296-018-4105-2



228. Scand J Rheumatol. 2018 Jul 17:1-8. doi: 10.1080/03009742.2018.1464205. [Epub ahead of print]

*Helicobacter pylori* infection is not associated with rheumatoid arthritis.

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**OBJECTIVE:** Rheumatoid arthritis (RA) is an autoinflammatory disease caused by genetic susceptibility and environmental triggers, which include infectious agents. *Helicobacter pylori*, a bacterium that frequently colonizes the stomach, is associated with the development of certain autoinflammatory disorders. This study examined a possible association between *H. pylori* infection and RA.

**METHOD:** This cohort study was performed in the Central Denmark Region. Patients were enrolled from primary healthcare centres after a urea breath test (UBT) for *H. pylori* and followed for a median of 8 years. Nationwide administrative registries provided information about the patients' diagnoses, country of birth, and gender. Comorbidity was determined using the Charlson Comorbidity Index. We compared the prevalence of RA via odds ratios (ORs) and incidences using Cox regression to calculate the hazard ratios (HRs) by comparing *H. pylori*-positive and *H. pylori*-negative individuals and adjusting for confounding variables.

**RESULTS:** A total of 56 000 people diagnosed as *H. pylori* positive or negative had similar rates of comorbidity. No link was found between *H. pylori* and RA. There was no difference in RA prevalence until time of UBT [OR = 0.91, 95% confidence interval (CI) 0.70-1.19] or incidence of new RA cases after UBT (HR = 0.80, 95% CI 0.56-1.13) between *H. pylori*-positive and -negative subjects. Validation via four other RA definitions provided similar results.

**CONCLUSION:** This study found no association between *H. pylori* infection and RA. This result does not support the involvement of *H. pylori* in a gut-joint axis of

importance for RA development.

DOI: 10.1080/03009742.2018.1464205

PMID: 30014755

229. Clin Rheumatol. 2018 Dec;37(12):3397-3403. doi: 10.1007/s10067-018-4214-z. Epub 2018 Jul 17.

Serum IL 4 and its gene polymorphism (rs79071878) in Egyptian children with familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is an autoinflammatory disorder. It is caused by mutations in the MEFV gene encoding the pyrin protein, which regulates the innate inflammatory response. The aim of the current study was to investigate the relationship between serum Interleukin-4 (IL-4) and its gene polymorphism, namely rs79071878, and FMF occurrence, severity, and response to treatment in Egyptian children harboring the disease. Fifty Egyptian children diagnosed as having FMF were included in this study. They were divided equally into two groups according to disease activity. Forty controls, age- and gender-matched, were also included. Serum IL-4 levels were measured by enzyme-linked immunosorbent assay (ELISA). The IL-4 rs79071878 polymorphism was determined by polymerase chain reaction (PCR) analysis. There was no significant difference in genotype distribution of IL-4 gene rs79071878 between patients and controls ( $p = 0.286$ ) and had no correlation with FMF severity or response to colchicine therapy. Serum IL-4 level had no significant difference between children with FMF attack and those in attack-free period compared to controls ( $p = 0.794$ ) and had no correlation with any of demographic, or clinical characteristics, disease severity, or response to colchicine therapy. Serum IL-4 level and its gene polymorphism were not found to have any increase risk of FMF occurrence, disease severity, or response to

treatment in the Egyptian children. Further studies are needed to verify these results.

DOI: 10.1007/s10067-018-4214-z

PMID: 30014360

230. Clin Rheumatol. 2018 Sep;37(9):2305-2321. doi: 10.1007/s10067-018-4209-9. Epub 2018 Jul 16.

From autoinflammation to autoimmunity: old and recent findings.

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Autoimmune diseases and autoinflammatory diseases have a number of similar etiopathogenetic and clinical characteristics, including genetic predisposition and recurrent systemic inflammatory flares. The first phase of ADs involves innate immunity: by means of TLRs, autoantigen presentation, B and T cell recruitment and autoantibody synthesis. The second phase involves adaptive immunity, a self-sustaining process in which immune complexes containing nucleic acids and autoantibodies activate self-directed inflammation. The link between autoimmunity and autoinflammation is IL-1 $\beta$ , which is crucial in connecting the innate immune response due to NLR activation and the adaptive immune responses of T and B cells. In conclusion, although ADs are still considered adaptive immunity-mediated disorders, there is increasing evidence that innate immunity and inflammasomes are also involved. The aim of this review is to highlight the

link between the innate and adaptive immune mechanisms involved in autoimmune diseases.

DOI: 10.1007/s10067-018-4209-9

PMID: 30014358

231. J Allergy Clin Immunol. 2018 Oct;142(4):1370-1373.e8. doi: 10.1016/j.jaci.2018.06.027. Epub 2018 Jul 3.

Calcium and zinc tune autoinflammatory Toll-like receptor 4 signaling by S100A12.

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DOI: 10.1016/j.jaci.2018.06.027

PMID: 30010542

232. Mod Rheumatol. 2018 Oct 18:1-4. doi: 10.1080/14397595.2018.1500874. [Epub ahead of print]

Neonatal onset familial Mediterranean fever.

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**OBJECTIVES:** Familial Mediterranean fever (FMF) is an autosomal recessive disease characterised by recurrent, self-limited attacks of fever with serositis.

Recently, it was shown that FMF patients with early disease onset have more severe disease. The aim of this study was to describe the demographic, clinical and genetic features of FMF patients who had disease onset during the neonatal period.

**METHODS:** Medical records of all patients diagnosed as FMF and had been seen in the outpatient clinic of Paediatric Rheumatology department between January 2013 and January 2014 were retrospectively evaluated. Patients with disease onset during the first month of life were included to the study.

**RESULTS:** Among 317 patients; 19 (12 males) were included to the study. Approximately 60% of the patients had family history of FMF. Homozygous p.M694V mutation was detected in 42% of the cases. Thirteen patients present with attacks of fever and remaining had attacks in the form of restlessness, resembling infantile colic starting in the neonatal period. Majority of these patients developed classical abdominal attacks between the ages of 1 and 2.5 years. The diagnosis of FMF was significantly delayed; the median age at onset of therapy was 3.5 years (range 7 months-17 years).

**CONCLUSION:** Patients with FMF could have complaints even in the neonatal period. Homozygous p.M694V mutation is a prominent mutation in this group of patients. In order to prevent diagnostic delay physicians dealing with these type of patients should be more vigilant.

DOI: 10.1080/14397595.2018.1500874

PMID: 30009667

233. Postepy Dermatol Alergol. 2018 Jun;35(3):231-237. doi: 10.5114/ada.2018.76086. Epub 2018 Jun 18.

Quo vadis, biological treatment for psoriasis and psoriatic arthritis?

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Psoriasis is a chronic autoimmune disease that affects approximately 2-3% of the world's population. Although the cutaneous manifestations of the disease are the most prevalent, psoriasis is also associated with a systemic inflammation and various co-morbidities linked with autoinflammatory processes. One of those processes is psoriatic arthritis, an inflammatory, seronegative spondyloarthropathy that develops in 13.8-30% of psoriatic patients at some point of their lives. Over the past 15 years the therapeutic options for severe and generalized psoriasis have broadened immensely with the introduction of biological agents to everyday practice. We present a quick overview of current biological therapies in the treatment of psoriasis and prospects for forthcoming advancements in biological treatment.

DOI: 10.5114/ada.2018.76086

PMCID: PMC6041715

PMID: 30008638

234. Autoimmun Rev. 2018 Sep;17(9):935-941. doi: 10.1016/j.autrev.2018.04.002. Epub 2018 Jul 11.

Nature versus nurture in the spectrum of rheumatic diseases: Classification of spondyloarthritis as autoimmune or autoinflammatory.

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Spondyloarthritides (SpA) include inflammatory joint diseases with various clinical phenotypes that may also include the axial skeleton and/or entheses. SpA include psoriatic arthritis, reactive arthritis, enteropathic arthritis and ankylosing spondylitis; the latter is frequently associated with extra-articular manifestations, such as uveitis, psoriasis, and inflammatory bowel disease. SpA are associated with the HLA-B27 allele and recognize T cells as key pathogenetic players. In contrast to other rheumatic diseases, SpA affect women and men equally and are not associated with detectable serum autoantibodies. In addition, but opposite to rheumatoid arthritis, SpA are responsive to treatment regimens including IL-23 or IL-17-targeting biologics, yet are virtually unresponsive to steroid treatment. Based on these differences with prototypical autoimmune diseases, such as rheumatoid arthritis or connective tissue diseases, SpA may be better classified among autoinflammatory diseases, with a predominant innate immunity involvement. This would rank SpA closer to gouty arthritis and periodic fevers in the spectrum of rheumatic diseases, as opposed to autoimmune-predominant diseases. We herein provide available literature on risk factors associated with SpA in support of this hypothesis with a specific focus on genetic and environmental factors.

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DOI: 10.1016/j.autrev.2018.04.002

PMID: 30005857 [Indexed for MEDLINE]

235. Colchicine.

Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); 2006-.

Long-term prophylactic maternal doses of colchicine up to 1.5 mg daily produce levels in milk that result in the infant receiving less than 10% of the maternal weight-adjusted dosage. The highest milk levels occur 2 to 4 hours after a dose, so avoiding breastfeeding during this time can minimize the infant dose, although some clinicians simply recommend taking the drug after nursing. No adverse

effects in breastfed infants have been reported in case series and a case-control study and some authors consider colchicine safe during breastfeeding in women being treated for familial Mediterranean fever or rheumatic conditions.[1][2][3][4]

PMID: 30000272

236. Front Immunol. 2018 Jun 26;9:1426. doi: 10.3389/fimmu.2018.01426. eCollection 2018.

Probiotic *Lactobacillus acidophilus* Strain INMIA 9602 Er 317/402 Administration Reduces the Numbers of *Candida albicans* and Abundance of Enterobacteria in the Gut Microbiota of Familial Mediterranean Fever Patients.

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Intestinal microorganisms play a crucial role in health and disease. The disruption of host-microbiota homeostasis has been reported to occur not only during disease development but also as a result of medication. Familial Mediterranean fever (FMF) is an inflammatory genetic disease characterized by elevated systemic reactivity against the commensal gut microbiota and high levels of *Candida albicans* in the gut. This study's major objective was to investigate the effects of commercial probiotic Narine on the relative abundance of gut bacteria (specifically, enterobacteria, lactobacilli, *Staphylococcus aureus*, and enterococci) of *C. albicans* carrier and non-carrier FMF patients in remission.



Our main finding indicates that the probiotic reduces numbers of *C. albicans* and abundance of enterobacteria in male and female patients of *C. albicans* carriers and non-carriers. It has pivotal effect on *Enterococcus faecalis*: increase in male non-carriers and decrease in female ones regardless of *C. albicans* status. No effect was seen for *Lactobacillus* and *S. aureus*. Our data suggest that M694V/V726A pyrin inflammasome mutations leading to FMF disease may contribute to gender-specific differences in microbial community structure in FMF patients. The study's secondary objective was to elucidate the gender-specific differences in the gut's microbial community of FMF patients. The tendency was detected for higher counts of enterobacteria in female FMF subjects. However, the small number of patients of these groups preclude from conclusive statements, pointing at the need for additional investigations with appropriate for statistical analysis groups of subjects involved in the study.

DOI: 10.3389/fimmu.2018.01426

PMCID: PMC6028570

PMID: 29997616

237. Zhonghua Er Ke Za Zhi. 2018 Jul 2;56(7):524-528. doi: 10.3760/cma.j.issn.0578-1310.2018.07.010.

[Clinical and genetic analysis of 11 cases with periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome].

[Article in Chinese; Abstract available in Chinese from the publisher]

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Objective: To investigate the clinical, inflammatory and genetic characteristics of cases with periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome. Methods: Clinical and inflammatory manifestations and gene sequencing of 11 cases with PFAPA were retrospectively analyzed. Inflammatory markers including white blood cell (WBC) , C reactive protein (CRP) , and serum amyloid A (SAA) were compared between febrile period and intermittent period.

Fifteen normal children were taken as healthy controls. The levels of plasma inflammatory cytokines including interleukin(IL)1 $\beta$ , IL-6, IL-17, tumor necrosis factor(TNF)- $\alpha$ , interferon (IFN)- $\gamma$ , and granulocyte-colony stimulating factor(G-CSF) were compared between febrile period and intermittent period with paired-sample t test, and compared between febrile cases and healthy controls with independent t test. Results: A total of 11 cases (7 females and 4 males) were included. The median onset age was 24 (3-60) months, and the median age of diagnosis was 69 (11-151) months. The median febrile duration was 4 (1-8) days, and the intermittent period lasted 1 to 8 weeks. All the cases had periodic fever and pharyngitis/tonsillitis, 7 of whom had combined lymphadenitis, and 5 of whom suffered from oral ulcers. Compared to intermittent-period-status, WBC ((14.7 $\pm$ 4.1)  $\times$ 10<sup>9</sup>/L vs. (8.4 $\pm$ 1.9)  $\times$ 10<sup>9</sup>/L, P<0.05), CRP((24.2 $\pm$ 21.1) vs. (3.3 $\pm$ 2.1)mg/L, P<0.05), SAA ((136.4 $\pm$ 47.7) vs. (7.1 $\pm$ 1.1)mg/L, P<0.05) were significantly elevated in febrile period. Compared to intermittent-period-status and healthy controls, plasma levels of IL-6 ((38 $\pm$ 10) vs. (8 $\pm$ 4) and (8 $\pm$ 5)ng/L, t=6.514 and 6.830 respectively, P<0.05), IFN- $\gamma$  ((132 $\pm$ 43) vs.(49 $\pm$ 21) and (53 $\pm$ 21)ng/L, t=4.069 and 4.276 respectively, P<0.05), G-CSF ((403 $\pm$ 12) vs. (175 $\pm$ 90) and (121 $\pm$ 49)ng/L, t=4.219 and 9.047 respectively, P<0.05) were significantly higher in febrile period, while no differences were found in levels of IL-1 $\beta$ , IL-17 and TNF- $\alpha$ . Gene sequencing found MEFV gene heterozygous variation in 8 cases. Conclusions: PFAPA often manifests as periodic fever, pharyngitis, tonsillitis, aphthous stomatitis and adenitis. Gene sequencing analysis, detection of inflammation markers and cytokines could help with the diagnose of this disease.

Publisher: **目的：**探讨周期性发热-阿弗他口炎-咽炎-淋巴结炎（PFAPA）患儿的临床特征、血浆细胞因子变化及基因变异特点。**方法：**

回顾性分析2015年6月至2017年5月深圳市儿童医院诊断的11例PFAPA患儿的临床资料及基因变异特点，选择15名健康体检的儿童为健康对照组，检测患儿及健康对照组血浆细胞因子白细胞介素（IL）1 $\beta$ 、IL-6、IL-17、肿瘤坏死因子 $\alpha$ （TNF- $\alpha$ ）、 $\gamma$ 干扰素（IFN- $\gamma$ ）、粒细胞集落刺激因子（G-CSF），比较患儿发热期与发热间歇期外周血炎症指标[白细胞（WBC）、C反应蛋白（CRP）、血浆淀粉样蛋白（SAA）]及发热期、间歇期与健康对照组血浆细胞因子，组间比较采用t检验；患儿及父母外周血行免疫基因组外显子检测。**结果：**

11例患儿中男7例，女4例，中位起病年龄24（3~60）月龄，中位诊断年龄69（11~151）月龄，中位发热时长4（1~8）d，发热间歇期1~8周。11例患儿均有周期性发热及咽炎或扁桃体炎，7例有淋巴结炎，5例有口腔溃疡。发热期与间歇期外周血炎症指标：

WBC $[(14.7\pm4.1)\times10(9)/L$ 比 $(8.4\pm1.9)\times10(9)/L$ , $t=4.645$ , $P<0.001$ ], CRP $[(24.2\pm21.1)$ 比 $(3.3\pm2.$

1)  $\text{mg/L}$ , $t=3.286$ , $P=0.040$ ], SAA $[(136.4\pm47.7)$ 比 $(7.1\pm1.1)$   $\text{mg/L}$ , $t=7.172$ , $P<0.001$ ], 组间比较差异均有统

计学意义。血浆细胞因子检测显示，发热期分别与发热间歇期、健康对照组两两比较，

IL-6 $[(38\pm10)$ 比 $(8\pm4)$ 、 $(8\pm5)$   $\text{ng/L}$ ,  $t=6.514$ 、 $6.830$ ]

、IFN- $\gamma$  $[(132\pm43)$ 比 $(49\pm21)$ 、 $(53\pm21)$   $\text{ng/L}$ ,

$t=4.069$ 、 $4.276$ ]、G-CSF $[(403\pm12)$ 比 $(175\pm90)$ 、 $(121\pm49)$   $\text{ng/L}$ ,

$t=4.219$ 、 $9.047$ ]升高，差异有统计学意义（ $P$ 均 $<0.05$ ）。免疫基因组外显子测序显示8例

PFAPA患儿存在MEFV基因杂合变异。结论：

PFAPA临床特征包括周期性发热、咽炎或扁桃体炎、阿弗他口炎及淋巴结炎，当患儿表现为周期性发热伴上述临床症状时需警惕PFAPA，基因测序分析、外周血炎症指标及细胞

因子检测有助于诊断此病。

DOI: 10.3760/cma.j.issn.0578-1310.2018.07.010

PMID: 29996186

238. Acta Dermatovenerol Croat. 2018 Jun;26(2):173-178.

Tumor Necrosis Factor Antagonists in the Treatment of Pyoderma Gangrenosum, Acne, and Suppurative Hidradenitis (PASH) Syndrome.

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The clinical triad of pyoderma gangrenosum (PG), acne and suppurative hidradenitis (HS) has been described under the acronym PASH syndrome and is considered to represent a distinct entity in the group of autoinflammatory diseases. It is a fairly new, only recently recognized disorder with a limited number of reported cases and without defined treatment recommendations. We aimed to summarize currently available data on the use of tumor necrosis factor (TNF) antagonists in the management of PASH syndrome and report on our own experience with the use of adalimumab in a patient presenting with this specific constellation of clinical signs and symptoms. Among the 11 cases identified in the literature, infliximab and adalimumab were the most commonly used agents, both exhibiting favorable effects in the majority of, but not all, patients. This was particularly evident in terms of relatively rapid remission of PG whereas HS lesions seemed to be more resistant to treatment. In our patient, adalimumab monotherapy resulted in a remarkable and sustained remission, although significant improvement of HS lesions was observed only from week 16 of therapy onwards. In summary, TNF antagonists are a promising treatment for PASH; however, conclusions regarding the choice of a specific agent, optimal dosing or use in combination with other treatment modalities cannot yet be drawn.

PMID: 29989876 [Indexed for MEDLINE]

239. Clin Transplant. 2018 Aug;32(8):e13345. doi: 10.1111/ctr.13345. Epub 2018 Jul 22.

Canakinumab treatment in kidney transplant recipients with AA amyloidosis due to familial Mediterranean fever.

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BACKGROUND: Familial Mediterranean fever (FMF) is an autoinflammatory disease

characterized by recurrent serosal inflammation with fever, which can result in amyloid deposition. Anti-interleukin-1 drugs emerge as a therapeutic option for colchicine-resistant patients. In this study, we aimed to document our experience with canakinumab use in kidney transplant recipients who developed AA amyloidosis due to FMF.

**METHODS:** A total of nine patients with FMF amyloidosis treated with canakinumab were enrolled. Laboratory and clinical data were collected from the patient files, electronic database of the hospital and with interviews.

**RESULTS:** Five of the patients were male and four were female (median age: 33, range: 27-62 years). All of the patients had rapid or gradual disappearance of FMF attacks. The following changes in the laboratory parameters were observed before and after the treatment: C-reactive protein:  $18.31 \pm 13.58$  mg/L vs  $9.98 \pm 11.66$  mg/L, creatinine clearance:  $45.27 \pm 21.5$  mL/min vs  $50.71 \pm 22.48$  mL/min, and 24-hour proteinuria:  $2381.8 \pm 3910.4$  mg vs  $710.0 \pm 1117.5$  mg; there were no statistically significant differences on those parameters. One patient developed a reaction to injection while another showed symptoms of Cytomegalovirus pneumonia.

**CONCLUSION:** Canakinumab can be considered as a safe and efficient drug in preventing the FMF attacks in kidney transplant recipients.

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DOI: 10.1111/ctr.13345

PMID: 29981275

240. Clin Rheumatol. 2018 Oct;37(10):2811-2817. doi: 10.1007/s10067-018-4194-z. Epub 2018 Jul 7.

Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in Behçet's disease: which and when to use?

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Behçet's disease (BD) is an uncommon autoimmune/autoinflammatory disease. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were investigated in many diseases as a marker of inflammation. In this study, we investigated NLR and PLR in patients with BD as a marker of disease activity and its association with different clinical manifestations. The study included 23 BD patients; their mean age was ( $32.5 \pm 6.76$ ) and M:F ratio was 16:7. Complete blood picture was done for all patients. NLR and PLR were compared in both active and inactive BD patients and its relation with different clinical manifestations was assessed. NLR was higher in active BD patients than in inactive BD patients ( $P < 0.01$ ). Although both NLR and PLR were correlated with Behçet's Disease Current Activity Form (BDCAF), the correlation of NLR with BDCAF was much stronger than that of PLR. NLR was associated with some mucocutaneous lesions. Both NLR and PLR were associated with articular and GIT manifestations, but also NLR showed more significant results. In our studied patients, both NLR and PLR were not informative about any ongoing ocular activity ( $P > 0.05$ ). Both ratios were not affected by the presence of neurologic deficits nor previous vascular events ( $P > 0.05$ ). NLR was superior to PLR as an indicator of disease activity. NLR was closely related to skin manifestations while PLR was not. In our study, both were not considered reliable in representing ocular activity.

DOI: 10.1007/s10067-018-4194-z

PMID: 29980877

241. Genes Immun. 2018 Jul 6. doi: 10.1038/s41435-018-0030-3. [Epub ahead of print]

Adults with septic shock and extreme hyperferritinemia exhibit pathogenic immune variation.

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Post-hoc subgroup analysis of the negative trial of interleukin-1 $\beta$  receptor antagonist (IL1RA) for septic shock suggested that patients with features of macrophage activation syndrome (MAS) experienced a 50% relative risk reduction for mortality with treatment. Here we seek a genetic basis for this differential response. From 1341 patients enrolled in the ProCESS trial of early goal directed therapy for septic shock, we selected 6 patients with MAS features and the highest ferritin, for whole exome sequencing (mean 24,030.7 ng/ml,  $\pm$ SEM 7,411.1). In total 11 rare (minor allele frequency <5%) pathogenic or likely pathogenic variants causal for the monogenic disorders of Familial Hemophagocytic Lymphohistiocytosis, atypical Hemolytic Uremic Syndrome, Familial Mediterranean Fever, and Cryopyrin-associated Periodic Fever were identified. In these conditions, seven of the identified variants are currently targeted with IL1RA and four with anti-C5 antibody. Gene-targeted precision medicine may benefit this subgroup of patients with septic shock and pathogenic immune variation.

DOI: 10.1038/s41435-018-0030-3

PMCID: PMC6320733

PMID: 29977033

242. Nature. 2018 Jul;559(7713):269-273. doi: 10.1038/s41586-018-0287-8. Epub 2018 Jul 4.

Targeting STING with covalent small-molecule inhibitors.

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Aberrant activation of innate immune pathways is associated with a variety of diseases. Progress in understanding the molecular mechanisms of innate immune pathways has led to the promise of targeted therapeutic approaches, but the development of drugs that act specifically on molecules of interest remains challenging. Here we report the discovery and characterization of highly potent and selective small-molecule antagonists of the stimulator of interferon genes (STING) protein, which is a central signalling component of the intracellular DNA sensing pathway<sup>1,2</sup>. Mechanistically, the identified compounds covalently target the predicted transmembrane cysteine residue 91 and thereby block the activation-induced palmitoylation of STING. Using these inhibitors, we show that the palmitoylation of STING is essential for its assembly into multimeric complexes at the Golgi apparatus and, in turn, for the recruitment of downstream signalling factors. The identified compounds and their derivatives reduce STING-mediated inflammatory cytokine production in both human and mouse cells. Furthermore, we show that these small-molecule antagonists attenuate pathological features of autoinflammatory disease in mice. In summary, our work uncovers a mechanism by which STING can be inhibited pharmacologically and demonstrates the potential of therapies that target STING for the treatment of autoinflammatory disease.

DOI: 10.1038/s41586-018-0287-8

PMID: 29973723

243. Int J Rheum Dis. 2018 Jul;21(7):1458-1462. doi: 10.1111/1756-185X.13329.

Multifocal osteolysis with chylous polyserositis and intrathoracic vein thrombosis: a diagnostic challenge for rheumatologists.

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Vanishing bone disease with multisystemic involvement may mimic systemic autoimmune or autoinflammatory diseases. We present a 19-year-old man who was hospitalized due to chest pain following a progressive osteolysis of the bony thorax. The disease later expanded into the pleura, peritoneum and pericardium in a form of massive chylous polyserositis. The patient also developed thrombosis of multiple central veins, which in turn worsened the chylothorax by increasing the pressure in the thoracic duct. This is the first case of vanishing bone disease complicated by triple chylous effusions and central vein thrombosis.

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DOI: 10.1111/1756-185X.13329

PMID: 29968326 [Indexed for MEDLINE]

244. Drugs. 2018 Jul;78(11):1073-1083. doi: 10.1007/s40265-018-0942-2.

The Future of IL-1 Targeting in Kidney Disease.

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Interleukin (IL)-1 $\alpha$  and IL-1 $\beta$  are proinflammatory cytokines that play a role in many diseases such as rheumatoid arthritis, juvenile rheumatoid arthritis, gout, and periodic inflammatory syndromes, including familial Mediterranean fever and Muckle-Wells syndrome. Drugs targeting IL-1 such as recombinant IL-1Ra (anakinra), neutralizing anti-IL-1 $\beta$  antibodies (canakinumab) and IL-1 $\beta$  traps (rilonacept) are in clinical use to treat these diseases. Additionally, experimental evidence suggests a role of IL-1 in kidney disease and hypertension and targeting IL-1 showed promising results in high cardiovascular risk patients, hemodialysis and renal transplantation patients. We now summarize knowledge on the potential role of IL-1 targeting in patients with kidney disease.

DOI: 10.1007/s40265-018-0942-2

PMID: 29968152

245. Toxicol Appl Pharmacol. 2018 Sep 15;355:93-102. doi: 10.1016/j.taap.2018.06.022. Epub 2018 Jun 28.

Flavonoids interfere with NLRP3 inflammasome activation.

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NOD-like receptor (NLR) family, pyrin domain-containing 3 (NLRP3) inflammasome is a component of innate immunity, and is responsible for producing mature IL-1 $\beta$  and -18. Several flavonoids were found to affect inflammasome pathway, but the mechanism of action is still obscure. To elucidate the effects on NLRP3 inflammasome pathway and to determine the structure-activity relationships, NLRP3 inflammasome in differentiated THP-1 cells was activated via treatment with monosodium urate (MSU) crystals. Levels of mature IL-1 $\beta$ , NLRP3 inflammasome

components and apoptosis-associated speck-like protein containing a CARD (caspase recruitment domain) (ASC) oligomerization were investigated and the mechanisms of action were also elucidated. Among the 56 flavonoids initially tested, only flavone, 2',4'-dihydroxyflavone, 3',4'-dichloroflavone, 4',5,7-trihydroxyflavone (apigenin), 3,4',5,7-tetrahydroxyflavone (kaempferol) and 3,3',4',5,7-pentahydroxyflavone (quercetin) significantly inhibited IL-1 $\beta$  production at 10  $\mu$ M. Apigenin, kaempferol and 3',4'-dichloroflavone inhibited ASC oligomerization without affecting the ASC level in cell lysates. Apigenin also inhibited absent in melanoma 2 (AIM2) inflammasome-related pathway, but not NLR family CARD domain-containing protein 4 (NLRC4) inflammasome activation. The action of apigenin on NLRP3 inflammasome activation is mediated partly via inhibition of phosphorylation of spleen tyrosine kinase/protein tyrosine kinase 2 (Syk/Pyk2) pathway. Furthermore, orally administered apigenin (100 mg/kg) strongly reduced the number of neutrophils and monocytes in MSU-induced peritonitis in mice. The present study, for the first time, demonstrated the structure-activity profiles of flavonoids in NLRP3 inflammasome activation and mechanisms of cellular action. Certain flavonoids including apigenin are expected to ameliorate the inflammatory symptoms in autoinflammatory diseases associated with NLRP3 inflammasome activation.

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DOI: 10.1016/j.taap.2018.06.022

PMID: 29960001

246. EMBO J. 2018 Aug 1;37(15). pii: e98506. doi: 10.15252/emboj.201798506. Epub 2018 Jun 29.

RNase H2, mutated in Aicardi-Goutières syndrome, promotes LINE-1 retrotransposition.

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Long INterspersed Element class 1 (LINE-1) elements are a type of abundant retrotransposons active in mammalian genomes. An average human genome contains ~100 retrotransposition-competent LINE-1s, whose activity is influenced by the combined action of cellular repressors and activators. TREX1, SAMHD1 and ADAR1 are known LINE-1 repressors and when mutated cause the autoinflammatory disorder Aicardi-Goutières syndrome (AGS). Mutations in RNase H2 are the most common cause of AGS, and its activity was proposed to similarly control LINE-1 retrotransposition. It has therefore been suggested that increased LINE-1 activity may be the cause of aberrant innate immune activation in AGS Here, we establish that, contrary to expectations, RNase H2 is required for efficient LINE-1 retrotransposition. As RNase H1 overexpression partially rescues the defect in RNase H2 null cells, we propose a model in which RNase H2 degrades the LINE-1 RNA after reverse transcription, allowing retrotransposition to be completed. This also explains how LINE-1 elements can retrotranspose efficiently without their own RNase H activity. Our findings appear to be at odds with LINE-1-derived nucleic acids driving autoinflammation in AGS.

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DOI: 10.15252/embj.201798506

PMCID: PMC6068448

PMID: 29959219

247. Immunity. 2018 Jul 17;49(1):80-92.e7. doi: 10.1016/j.immuni.2018.05.008. Epub 2018 Jun 26.

# Iron Drives T Helper Cell Pathogenicity by Promoting RNA-Binding Protein PCBP1-Mediated Proinflammatory Cytokine Production.

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Iron deposition is frequently observed in human autoinflammatory diseases, but its functional significance is largely unknown. Here we showed that iron promoted proinflammatory cytokine expression in T cells, including GM-CSF and IL-2, via regulating the stability of an RNA-binding protein PCBP1. Iron depletion or Pcbp1 deficiency in T cells inhibited GM-CSF production by attenuating Csf2 3' untranslated region (UTR) activity and messenger RNA stability. Pcbp1 deficiency or iron uptake blockade in autoreactive T cells abolished their capacity to induce experimental autoimmune encephalomyelitis, an animal model for multiple sclerosis. Mechanistically, intracellular iron protected PCBP1 protein from caspase-mediated proteolysis, and PCBP1 promoted messenger RNA stability of Csf2 and Il2 by recognizing UC-rich elements in the 3' UTRs. Our study suggests that iron accumulation can precipitate autoimmune diseases by promoting proinflammatory cytokine production. RNA-binding protein-mediated iron sensing may represent a simple yet effective means to adjust the inflammatory response to tissue homeostatic alterations.

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DOI: 10.1016/j.immuni.2018.05.008

PMID: 29958803

248. Transpl Int. 2018 Oct;31(10):1181-1184. doi: 10.1111/tri.13312. Epub 2018 Jul 13.

Transplantation within the era of anti-IL-1 therapy: case series of five patients with familial Mediterranean fever-related amyloidosis.

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DOI: 10.1111/tri.13312

PMID: 29957882

249. Inflammation. 2018 Oct;41(5):1945-1954. doi: 10.1007/s10753-018-0838-z.

IL-1 $\beta$  Enhances Wnt Signal by Inhibiting DKK1.

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Aberrant endochondral bone formation in the physis is a unique bone lesion in neonatal-onset multisystem inflammatory disease (NOMID), also called chronic infantile neurologic cutaneous articular (CINCA), the most severe of the cryopyrin-associated periodic syndrome (CAPS) diseases, which are interleukin-1 $\beta$  (IL-1 $\beta$ )-related monogenic autoinflammatory diseases. The wingless (Wnt) pathway plays an important role in osteoblast differentiation. In this study, we explored the potential role of IL-1 $\beta$  on the expression of WNT genes and the Wnt antagonist Dickkopf-1 (DKK1). The expression of WNT and DKK1 in fibroblast-like synoviocytes (FLS), which are articular resident cells, was quantified by quantitative PCR and enzyme-linked immunosorbent assay. Additionally, we used T cell factor (TCF) reporter assays to evaluate the activity of the canonical Wnt signal pathway in the presence or absence of the supernatant of cultured FLS treated with or without IL-1 $\beta$  and IL-6. Anti-DKK1 antibodies were used to neutralize DKK1. The expression of both canonical and non-canonical WNT genes as well as DKK1 was observed in FLS. The supernatant of cultured FLS suppressed the luciferase activity of the TCF reporter, and this effect was reduced by its pre-treatment with an anti-DKK1 antibody. Both IL-1 $\beta$  and IL-6 significantly reduced DKK1 production. Furthermore, the supernatant of FLS cultured with IL-1 $\beta$  or IL-6 showed a reduced inhibitory effect on Wnt signaling, compared with the supernatant of untreated FLS. These data suggest that IL-1 $\beta$ , like IL-6, dampens DKK1 production, and thereby promotes Wnt signal activation. Therefore, increased levels of IL-1 $\beta$  may contribute to the dysregulation of endochondral ossification in NOMID/CINCA.

DOI: 10.1007/s10753-018-0838-z

PMID: 29956067

250. Case Rep Vet Med. 2017 Aug 8;2017:4275305. doi: 10.1155/2017/4275305. eCollection 2017.

Autoinflammatory Reaction in Dogs Treated for Cancer via G6PD Inhibition.

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Glucose-6-phosphate dehydrogenase (G6PD) is an oncoprotein that is overexpressed in cancer cells to provide the NADPH required for their increased anabolism. NADPH, sourced from G6PD fuels nucleotide biosynthesis, maintains redox potential of thioredoxin and glutathione and drives the mevalonate pathway that powers many of the basic mechanisms by which cancer cells escape host control. G6PD is thus a target for cancer treatment being addressed by many groups around the world. We have discovered that systemic inhibition of G6PD by high dose dehydroepiandrosterone (DHEA) causes a severe autoinflammatory response in dogs, which does not occur in mice or rats. Since dogs more closely model the human adrenal androgen system than do common laboratory animals, this finding is relevant to the design of G6PD-inhibiting drugs for humans. The autoinflammatory reaction observed closely resembles mevalonate kinase deficiency (MKD), a rare autosomal recessive disease in humans characterized by recurrent febrile attacks, arthralgia, skin rash, and aphthous ulcers of mucocutaneous tissues. In a manner comparable to animal models of MKD, the reconstitution of protein geranylgeranylation blocked the autoinflammatory reaction caused by systemic G6PD inhibition. This autoinflammatory response to systemic G6PD inhibition represents an unexpected result that must be taken into consideration when targeting this oncoprotein.

DOI: 10.1155/2017/4275305

PMCID: PMC6005277

PMID: 29955429

251. RMD Open. 2018 Jun 4;4(1):e000694. doi: 10.1136/rmdopen-2018-000694. eCollection 2018.

Polymyalgia rheumatica: an autoinflammatory disorder?

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DOI: 10.1136/rmdopen-2018-000694

PMCID: PMC6018871

PMID: 29955386

Conflict of interest statement: Competing interests: None declared.

252. Free Radic Biol Med. 2018 Sep;125:44-52. doi:  
10.1016/j.freeradbiomed.2018.06.011. Epub 2018 Jun 25.

How the phagocyte NADPH oxidase regulates innate immunity.

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The phagocyte NADPH oxidase is a multi subunit protein complex that generates reactive oxygen species at cell membranes and within phagosomes. It is essential for host defence as evidenced by the severe immunodeficiency syndrome caused by a loss of one of the subunits. This is known as chronic granulomatous disease (CGD). However, the phagocyte NADPH oxidase also has a key role to play in regulating immunity and it is notable that chronic granulomatous disease is also characterised by autoimmune and autoinflammatory manifestations. This is because reactive oxygen species play a role in regulating signalling through their ability to post-translationally modify amino acid residues such as cysteine and methionine. In this review, I will outline the major aspects of innate immunity that are regulated by the phagocyte NADPH oxidase, including control of transcription, autophagy, the inflammasome and type 1 interferon signalling.

Copyright © 2018. Published by Elsevier Inc.

DOI: 10.1016/j.freeradbiomed.2018.06.011

PMID: 29953922

253. Med Monatsschr Pharm. 2017 May;40(5):218-20.

[in process]

[Article in German]

Saußele T.

PMID: 29952152 [Indexed for MEDLINE]

254. Rheumatol Int. 2018 Aug;38(8):1571-1576. doi: 10.1007/s00296-018-4092-3. Epub 2018 Jun 27.

C3 glomerulopathy in NLRP12-related autoinflammatory disorder: case-based review.

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Autoinflammatory diseases (AIDs) are a recently described group of conditions caused by mutations in multiple genes that code for proteins of the innate immune system. Cryopyrin-associated periodic syndromes (CAPS) are autoinflammatory diseases comprising three clinically overlapping disorders: familial cold urticarial syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID). CAPS have been associated with

gain-of-function variations in NLRP3 (NOD-like receptor family, pyrin containing domain-3). However, a new class of autoinflammatory disease resembling FCAS or MWS has been described in patients with NLRP12 mutations. Here, we report a 6-year-old boy diagnosed with AID who developed an unexpected C3 glomerulopathy during attacks and carried a novel variation in NLRP12. Following treatment with IL (interleukin) 1 targeting agents, all symptoms and inflammation resolved. This is the first case in the literature affected by both autoinflammatory disease and C3 glomerulopathy.

DOI: 10.1007/s00296-018-4092-3

PMID: 29951964 [Indexed for MEDLINE]

255. J Am Dent Assoc. 2018 Sep;149(9):794-800. doi: 10.1016/j.adaj.2018.04.025. Epub 2018 Jun 23.

Dental treatment of a rare case of pyoderma gangrenosum with aggressive periodontal disease.

Carmagnola D, Pispero A, Canciani E, Dellavia C, Barbieri C, Lodi G, Varoni EM.

**BACKGROUND AND OVERVIEW:** Pyoderma gangrenosum (PG) is a rare neutrophil-mediated autoinflammatory dermatosis that can involve the oral mucosa. Dental surgery is a potential triggering factor for the onset of PG lesions. The authors describe and discuss the dental management of a rare case of aggressive periodontitis in a patient with PG, from multiple tooth extractions to prosthetic rehabilitation, including administration of systemic steroid prophylaxis before surgery to prevent the potential onset of PG-related lesions.

**CASE DESCRIPTION:** A 22-year-old man who had a diagnosis of PG and who had aggressive periodontal disease underwent dental extractions, gingivoplastic surgery, and prosthetic rehabilitation. The patient received 8 milligrams of betamethasone intramuscularly 20 minutes before the oral surgery. The tissues healed perfectly, and no adverse effects were reported.

**CONCLUSIONS AND PRACTICAL IMPLICATIONS:** For minor oral surgery, prophylactic corticosteroids might help reduce the risk of developing PG-related lesions. The clinician should plan the prosthetic devices to be as atraumatic as possible.

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DOI: 10.1016/j.adaj.2018.04.025

PMID: 29945713

256. J Postgrad Med. 2018 Jul-Sep;64(3):170-173. doi: 10.4103/jpgm.JPGM\_23\_18.

Chronic nonbacterial osteomyelitis from a tertiary care referral center.

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Chronic nonbacterial osteomyelitis (CNO) is a little known autoinflammatory bone disorder primarily affecting children and sometimes young adults. Diagnosis is often delayed due to its varied and nonspecific initial symptoms. Very few cases are reported from India. The aim of this report is to increase the awareness of this disease among physicians, orthopedic surgeons, and rheumatologists. Four male patients were diagnosed with CNO in the past 3 years. The age at onset varied from 9 to 23 years with a median diagnostic delay of 3.5 years. All patients presented with recurrent bony pain with or without localized swelling over the affected bones. Two patients had previously undergone open surgical procedures with bone biopsies and three patients had received at least one course of antibiotics. Two patients responded well to nonsteroidal anti-inflammatory drugs alone, one patient required a short course of glucocorticoids, and another patient required methotrexate to control disease activity. This case series includes males, onset at a relatively later age in most, and a longer diagnostic delay. Thus, in addition to children and adolescents, CNO should be suspected in young adults presenting with recurrent bony pain with or without localized swelling.

DOI: 10.4103/jpgm.JPGM\_23\_18

PMCID: PMC6066617

PMID: 29943737

Conflict of interest statement: There are no conflicts of interest

257. J Bone Miner Res. 2018 Nov;33(11):2071-2080. doi: 10.1002/jbmr.3532. Epub 2018 Jul 30.

Unique Variant of NOD2 Pediatric Granulomatous Arthritis With Severe 1,25-Dihydroxyvitamin D-Mediated Hypercalcemia and Generalized Osteosclerosis.

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Pediatric granulomatous arthritis (PGA) refers to two formerly separate entities: autosomal dominant Blau syndrome (BS) and its sporadic phenocopy early-onset sarcoidosis (EOS). In 2001 BS and in 2005 EOS became explained by heterozygous mutations within the gene that encodes nucleotide-binding oligomerization domain-containing protein 2 (NOD2), also called caspase recruitment domain-containing protein 15 (CARD15). NOD2 is a microbe sensor in leukocyte cytosol that activates and regulates inflammation. PGA is characterized by a triad of autoinflammatory problems (dermatitis, uveitis, and arthritis) in early childhood, which suggests the causal NOD2/CARD15 mutations are activating defects. Additional complications of PGA were recognized especially when NOD2 mutation analysis became generally available. However, in PGA, hypercalcemia is only briefly mentioned, and generalized osteosclerosis is not reported, although NOD2 regulates NF- $\kappa$ B signaling essential for osteoclastogenesis and osteoclast function. Herein, we report a 4-year-old girl with PGA uniquely complicated by severe 1,25(OH)<sub>2</sub> D-mediated hypercalcemia, nephrocalcinosis, and compromised

renal function together with radiological and histopathological features of osteopetrosis (OPT). The classic triad of PGA complications was absent, although joint pain and an antalgic gait accompanied wrist, knee, and ankle swelling and soft non-tender masses over her hands, knees, and feet. MRI revealed tenosynovitis in her hands and suprapatellar effusions. Synovial biopsy demonstrated reactive synovitis without granulomas. Spontaneous resolution of metaphyseal osteosclerosis occurred while biochemical markers indicated active bone turnover. Anti-inflammatory medications suppressed circulating 1,25(OH)<sub>2</sub>D, corrected the hypercalcemia, and improved her renal function, joint pain and swelling, and gait. Mutation analysis excluded idiopathic infantile hypercalcemia, type 1, and known forms of OPT, and identified a heterozygous germline missense mutation in NOD2 common in PGA (c.1001G>A, p.Arg334Gln). Thus, radiological and histological findings of OPT and severe hypercalcemia from apparent extrarenal production of 1,25(OH)<sub>2</sub>D can complicate NOD2-associated PGA. Although the skeletal findings seem inconsequential, treatment of the hypercalcemia is crucial to protect the kidneys. © 2018 American Society for Bone and Mineral Research.

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DOI: 10.1002/jbmr.3532

PMID: 29933504

258. Medicine (Baltimore). 2018 Jun;97(25):e11149. doi: 10.1097/MD.00000000000011149.

Case report: successful treatment of refractory SAPHO syndrome with the JAK inhibitor tofacitinib.

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**INTRODUCTION:** Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome is an autoinflammatory disorder without standardized treatment. Janus kinase (JAK) inhibitors can block a range of cytokines and might possess significant anti-inflammatory activity. Here, we report the first case of efficacious treatment of refractory SAPHO syndrome with the JAK inhibitor tofacitinib.

**CASE PRESENTATION:** A 44-year-old woman presented with arthralgia in the right wrist and complained of having difficulty in doing housework. Symptoms were unresponsiveness to nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, and tumor necrosis factor inhibitors. A diagnosis of SAPHO syndrome was made based on previous dermatological and osteoarticular manifestations and bone scintigraphy findings. Oral treatment with tofacitinib at 5 mg twice daily in combination with the basic methotrexate treatment was initiated. After 4 weeks of using tofacitinib, the patient reported marked improvement of symptoms and also reported being competent in completing housework.

**CONCLUSIONS:** The efficacy of JAK inhibitors in treating refractory SAPHO syndrome should be noted.

DOI: 10.1097/MD.00000000000011149

PMCID: PMC6024477

PMID: 29924019 [Indexed for MEDLINE]

259. Drug Des Devel Ther. 2018 Jun 8;12:1633-1643. doi: 10.2147/DDDT.S114532. eCollection 2018.

The role of IL-1 inhibition in systemic juvenile idiopathic arthritis: current status and future perspectives.

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The pathogenesis, clinical course, and response to treatment in systemic juvenile

idiopathic arthritis (SJIA) differ from other types of juvenile idiopathic arthritis and are similar to other interleukin-1 (IL-1)-mediated diseases. The main cytokine involved in the pathogenesis of SJIA is IL-1 $\beta$ , which can be neutralized by targeted anti-IL-1 therapy. In SJIA, no antibodies have been found and there is growing evidence that it is mainly an autoinflammatory and not an autoimmune disease. Before the era of biologic therapy, treatment of SJIA was primarily based on long-term treatment with high doses of glucocorticosteroids (GCS). The side effects of GCS could have a significant impact on the outcome of the disease and could cause long-term damage. Treatment with anti-IL-1 agents early in the disease course has revolutionized the management principles of SJIA. However, not all SJIA patients respond equally well to anti-IL-1 therapy, and it has been shown that age at the onset of disease, duration of the disease, number of affected joints, neutrophil count, and ferritin level can predict the response to anti-IL-1 therapy. In particular, an elevated ferritin level should prompt testing for macrophage activation syndrome (MAS), the most severe complication of SJIA. Anti-IL-1 therapy has been shown to be effective also in patients with MAS. Although anti-IL-1 agents are currently not recommended as first-line treatment, there is growing evidence that anti-IL-1 agents introduced at the beginning of SJIA could enable lower doses and a shorter duration of GCS therapy, change the long-term disease outcome, and even influence molecular disease patterns. There are currently three anti-IL-1 agents available: anakinra, canakinumab, and rilonacept. In this review, we present the current knowledge on the pathogenesis of SJIA, the rationale for anti-IL-1 treatment, and future perspectives on the treatment of SJIA.

DOI: 10.2147/DDDT.S114532

PMCID: PMC5996857

PMID: 29922038 [Indexed for MEDLINE]

Conflict of interest statement: Disclosure The authors report no conflicts of interest in this work.

260. Curr Opin Rheumatol. 2018 Sep;30(5):506-513. doi: 10.1097/BOR.0000000000000532.

Haploinsufficiency of A20 and other paediatric inflammatory disorders with mucosal involvement.

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**PURPOSE OF REVIEW:** This review aims at summarizing the current knowledge of A20 haploinsufficiency and other paediatric inflammatory disorders with mucosal involvement.

**RECENT FINDINGS:** A20 haploinsufficiency is a newly described autoinflammatory disease caused by loss-of-function mutations in TNFAIP3 that result in the activation of the nuclear factor (NF)-kB pathway. Patients may present with dominantly inherited, early-onset systemic inflammation and a Behçet-like disease, or a variety of autoinflammatory and autoimmune features. In Behçet disease, recent literature provides insights into genetic susceptibility and emerging treatment options; in addition, the first paediatric classification criteria were published. Recent advances in periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome (PFAPA) suggest that the disease has a complex underlying genetic mechanism and in some cases is inherited in an autosomal dominant pattern with reduced penetrance phenotype in many family members. Activation of the pyrin inflammasome through the RoA signalling pathway uncovers an interesting molecular connection between hyperimmunoglobulinemia D syndrome and familial Mediterranean fever. The description of new monogenic types of inflammatory bowel disease (IBD) may provide novel insights into disease pathogenesis. Finally, recent studies highlighted the role of gut microorganisms and dysbiosis in IBD.

**SUMMARY:** Monogenic diseases such as A20 haploinsufficiency may help to advance our understanding of disease pathogenesis and to develop targeted therapies for more common, multifactorial disorders with mucosal inflammation.

DOI: 10.1097/BOR.0000000000000532

PMID: 29916847

261. Clin Rheumatol. 2018 Jun 17. doi: 10.1007/s10067-018-4178-z. [Epub ahead of print]

Molecular genetic analysis for periodic fever syndromes: a supplemental role for

the diagnosis of adult-onset Still's disease.

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Adult-onset Still's disease (AOSD) represents a systemic autoinflammatory disease (SAID), and its diagnostic criteria are clinical without genetic testing. Given shared manifestations between AOSD and hereditary SAIDs, molecular analysis may help differentiate these diseases. A PubMed literature search was conducted using key words "adult-onset Still's disease," "autoinflammatory disease," and "genetic mutation" between 1970 and February 2018. Articles on genetic mutations in the genes MEFV, TNFRSF1A, mevalonate kinase, or NOD2 for hereditary SAIDs in AOSD/systemic onset juvenile idiopathic arthritis (SJIA) patients were reviewed and analyzed. Five case series studies consisting of a total of 162 of both adult and pediatric patients were included. All patients fulfilled the Yamaguchi criteria for AOSD or the diagnostic criteria for SJIA. The results showed that 31.4% (51/162) of patients were identified to carry at least one genetic variant for periodic fever syndromes. In addition, four patients with the diagnosis of SJIA in other reports were confirmed to have FMF or TRAPS with molecular testing. These data together suggest that some patients who satisfy the clinical diagnostic criteria for AOSD/SOJIA could well be diagnosed with other SAIDs; genetic testing, particularly for those with atypical presentation can be supplementary to the accurate disease diagnosis by excluding other autoinflammatory diseases. AOSD is a diagnosis of exclusion and shares common manifestations with other SAIDs. The currently employed clinical criteria for AOSD can cause misdiagnosis. An updated set of classification criteria to integrate the molecular genetic analysis to exclude other autoinflammatory diseases is warranted.

DOI: 10.1007/s10067-018-4178-z

PMID: 29909561

262. BMJ Case Rep. 2018 Jun 15;2018. pii: bcr-2017-223722. doi: 10.1136/bcr-2017-223722.

Transdermal rotigotine patch in Parkinson's disease with a history of intestinal operation.

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A 42-year-old Japanese man with a history of small intestine resection and familial Mediterranean fever was referred to our hospital for a second opinion on parkinsonism. At the age of 35, the patient attended a hospital due to impaired left-hand movement and resting tremor. He was previously diagnosed with multiple system atrophy based on the lack of effectiveness of levodopa treatment. With suspicion of malabsorption due to his history of ileostomy, a levodopa challenge test with levodopa intravenous infusion was conducted, and revealed a 65% improvement in Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale part III. Therefore, diagnosis of Parkinson's disease was made and a transdermal rotigotine patch was selected as a treatment. This treatment dose-dependently improved the patient's symptoms. The transdermal drug delivery should be considered when patients show dose failure due to malabsorption.

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DOI: 10.1136/bcr-2017-223722

PMCID: PMC6011449

PMID: 29909386 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: None declared.

## Use of Interleukin-1 Blockers in Pericardial and Cardiovascular Diseases.

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**PURPOSE OF REVIEW:** This review aims to summarize the role of the interleukin-1 (IL-1) blocking agents in cardiovascular diseases, briefly describing the pathogenetic rationale and the most relevant clinical studies.

**RECENT FINDINGS:** IL-1 is a pivotal cytokine of the innate immune system.

Anti-IL-1 agents are currently used for the treatment of several autoimmune and autoinflammatory conditions. Recently, the role of IL-1 has also emerged in cardiovascular diseases. Indeed, two recent randomized controlled trials have shown that the IL-1 receptor antagonist anakinra is effective for the treatment of idiopathic recurrent pericarditis and the IL-1 $\beta$  blocking agent canakinumab is effective in reducing myocardial infarction in people at risk. Interestingly, interfering with IL-1 has proved to be also effective in other cardiovascular manifestations, such as myocarditis, arrhythmias, and heart failure. Blocking the IL-1 pathway is a possible new therapeutic strategy, potentially leading to innovative therapies in many acute and chronic cardiovascular diseases.

264. Iran J Kidney Dis. 2018 May;12(3):150-155.

## Angiotensin Converting Enzyme Gene Insertion/Deletion Variant and Familial Mediterranean Fever-related Amyloidosis.

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**INTRODUCTION:** The most important complication of familial Mediterranean fever (FMF) is secondary amyloidosis, which can lead to kidney failure. Genetic variability in the genes of various components of the renin-angiotensin system may play a role in the pathogenesis of the kidney disorders. The aim of the present study was to investigate the association between angiotensin converting enzyme (ACE) gene I/D variant and risk of developing FMF-related amyloidosis in Turkish patients.

**MATERIALS AND METHODS:** A total of 240 individuals consisting of 40 patients with FMF-related amyloidosis, 100 FMF patients without amyloidosis, and 100 healthy controls were recruited. For all of the participants, ACE I/D variant was detected by the polymerase chain reaction using specific primers.

**RESULTS:** A significant difference was found between the patients with FMF-related amyloidosis and the control group as for genotype distribution of ACE I/D variant ( $P < .05$ ). The ACE D/D and I/D genotypes were more frequent in the patients with FMF-related amyloidosis while the I/I genotype was less frequent in the same patients. The FMF patients (with and without amyloidosis) had significantly higher percentages of the D/D and I/D genotypes than the healthy controls ( $P < .05$ ). Comparison between the subgroups of FMF patients, divided into those with and without amyloidosis, yielded a significant correlation according to ID+II versus DD genotypes ( $P < .03$ , odds ratio, 3.24; 95% confidence interval, 1.05 to 12.01). **Conclusions.** Based on these observations, the ACE I/D variant D/D genotypes implicate a possible risk in the FMF-related amyloidosis among Turkish population.

PMID: 29891744 [Indexed for MEDLINE]

265. Proc Natl Acad Sci U S A. 2018 Jun 26;115(26):6798-6803. doi: 10.1073/pnas.1802114115. Epub 2018 Jun 11.

SUMO2 and SUMO3 redundantly prevent a noncanonical type I interferon response.

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Detection of nucleic acids by innate immune sensors triggers the production of type I interferons (IFNs). While IFNs are essential for host defense against viral infection, dysregulated production of IFNs underlies numerous autoinflammatory diseases. We have found that the loss of sumoylation results in a potent, spontaneous IFN response. Vertebrates possess three small ubiquitin-like modifiers (SUMOs) that can be conjugated onto target proteins and alter protein function in diverse but still poorly characterized ways. We demonstrate that regulation of IFN by sumoylation is redundantly mediated by both SUMO2 and SUMO3, but not SUMO1, revealing a previously unknown function of SUMO2/3. Remarkably, this IFN response is independent of all known IFN-inducing pathways and does not require either of the canonical IFN-associated transcription factors IRF3 or IRF7. Taken together, our findings demonstrate that SUMO2 and SUMO3 are specific and essential negative regulators of a noncanonical mechanism of IFN induction.

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DOI: 10.1073/pnas.1802114115

PMCID: PMC6042150

PMID: 29891701 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare no conflict of interest.

266. Curr Opin Rheumatol. 2018 Sep;30(5):526-532. doi: 10.1097/BOR.0000000000000529.

Spondyloarthritis: new insights into clinical aspects, translational immunology and therapeutics.

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**PURPOSE OF REVIEW:** The spondyloarthropathies (SpA), which encompass related diseases that were originally viewed as autoimmune, are now known to have a strong innate immune or autoinflammatory initiation phase characterized by disease localization to tissue-specific sites based on the nuances and microanatomy and immunology of those sites. This review covers recent translational advances in the field of SpA.

**RECENT FINDINGS:** Imaging studies in SpA continue to add support for the pivotal role of enthesitis in disease initiation and expression. Although in its infancy, there is growing evidence for microbial intestinal dysbiosis in ankylosing spondylitis and psoriatic arthritis. The role of cytokines beyond tumour necrosis factor (TNF) continues to grow with support for the interleukin (IL)-23/17 axis being key to disease and emergent evidence for the importance of the IL-36 pathway. The treatment of inflammatory bowel disease (IBD) with vedolizumab an  $\alpha 4\beta 7$ -integrin blocker has been associated with arthritis flares and small molecules with Janus kinase inhibition appear to be as effective as the anti-TNFs. The disparate response of different domains in SpA points towards immunological heterogeneity even within what was considered a homogeneous disease.

**SUMMARY:** The clinical aspects and translational immunology and therapeutics of SpA continue to evolve and indicate the complexity of diagnosis and treatment of these conditions.

DOI: 10.1097/BOR.0000000000000529

PMID: 29889692

267. J Clin Invest. 2018 Jul 2;128(7):2760-2762. doi: 10.1172/JCI121526. Epub 2018 Jun 11.

JAK inhibitors in autoinflammation.

Hoffman HM, Broderick L.

Interferonopathies are a subset of autoinflammatory disorders with a prominent type I IFN gene signature. Treatment of these patients has been challenging, given the lack of response to common autoinflammatory therapeutics including IL-1 and TNF blockade. JAK inhibitors (Jak inhibitors) are a family of small-molecule inhibitors that target the JAK/STAT signaling pathway and have shown clinical efficacy, with FDA and European Medicines Agency (EMA) approval for arthritic and myeloproliferative syndromes. Sanchez and colleagues repurposed baricitinib to establish a significant role for JAK inhibition as a novel therapy for patients with interferonopathies, demonstrating the power of translational rare disease research with lifesaving effects.

DOI: 10.1172/JCI121526

PMCID: PMC6025991

PMID: 29889100

268. Hum Immunol. 2018 Aug;79(8):610-615. doi: 10.1016/j.humimm.2018.06.002. Epub 2018 Jun 7.

IL-1 $\beta$  induces expression of costimulatory molecules and cytokines but not immune feedback regulators in dendritic cells.

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Dendritic cells play an important role in the initiation of immune reactions. Due to their high capacity to prime T-cell responses, the activation of dendritic cells must be tightly controlled. Because Interleukin-1 $\beta$  (IL-1 $\beta$ ) is a key player in autoinflammatory diseases, we compared the ability of IL-1 $\beta$  to activate human dendritic cells and induce immune-regulatory molecules versus the effects induced by pathogen-derived stimuli. Upon activation with either IL-1 $\beta$  or microbial stimuli, monocyte-derived dendritic cells showed enhanced expression of costimulatory molecules, increased secretion of chemokines and cytokines, and the ability to activate T cells. In contrast, immune-feedback molecules, including PD-L1, IL-1RA, IL-10 and SOCS1, were exclusively upregulated in response to microbial stimuli, whereas IL-1 $\beta$  treatment had no inducing effect on them. Thus, the limited capacity of IL-1 $\beta$  to induce potential feedback inhibitors may support its key etiologic role in chronic inflammation and autoinflammatory responses.

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DOI: 10.1016/j.humimm.2018.06.002

PMID: 29886260 [Indexed for MEDLINE]

269. Autoimmun Rev. 2018 Aug;17(8):768-774. doi: 10.1016/j.autrev.2018.01.024. Epub 2018 Jun 6.

The use of interleukin 1 receptor antagonist (anakinra) in Kawasaki disease: A retrospective cases series.

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**OBJECTIVES:** To identify the clinical characteristics, reasons for use and response to treatment with anakinra in a series of patients with Kawasaki Disease (KD).

**STUDY DESIGN:** A retrospective chart review of patients treated with anakinra for KD diagnosed according to the AHA criteria. We compared clinical, biological and echocardiographic characteristics of KD before and after anakinra use. We analysed reasons for use of anakinra, and compared treatment regimens used in 7 European KD referral centres.

**RESULTS:** Eight boys and 3 girls with treatment-refractory KD, aged 4 months to 9 years old, received at least 2 different KD treatments prior to anakinra, which was given on mean at 25 days after disease onset (8 to 87 days). The main reasons for use of anakinra were clinical and biological inflammation, progression of coronary dilatations, and severe myocarditis with cardiac failure. Doses of anakinra ranged from 2 to 8 mg/kg and duration varied from 6 to 81 days. Efficacy of anakinra was judged in terms of fever resolution (100%), decrease of CRP (100%), and in terms of its effect on coronary artery dilatation Z scores, which decreased in 10/11 patients and increased in one who died suddenly of pericardial hemorrhage.

**CONCLUSION:** Anakinra used late in the disease course led to a rapid and sustained improvement in clinical and biological inflammation. Our retrospective analysis did show neither a striking nor a rapid decrease of coronary dilatations and we cannot determine if anakinra itself had an effect on coronary artery dimensions.

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DOI: 10.1016/j.autrev.2018.01.024

PMID: 29885546 [Indexed for MEDLINE]

270. Clin Exp Immunol. 2018 Jun;192(3):284-291. doi: 10.1111/cei.13125.

The United Kingdom Primary Immune Deficiency (UKPID) registry 2012 to 2017.

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Longhurst HJ(6), Slatter M(2)(3), Edgar DM(7), Thomas M(8), Worth A(1)(9), Huissoon A(10), Arkwright PD(4), Jolles S(11), Bourne H(12), Alachkar H(13), Savic S(14), Kumararatne DS(6), Patel S(15), Baxendale H(16), Noorani S(17), Yong PFK(18), Waruiru C(19), Pavaladurai V(20), Kelleher P(21), Herriot R(22), Bernatonienne J(23), Bhole M(24), Steele C(25), Hayman G(26), Richter A(27), Gompels M(28), Chopra C(29), Garcez T(4), Buckland M(1)(5)(9).

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This is the second report of the United Kingdom Primary Immunodeficiency (UKPID) registry. The registry will be a decade old in 2018 and, as of August 2017, had recruited 4758 patients encompassing 97% of immunology centres within the United Kingdom. This represents a doubling of recruitment into the registry since we reported on 2229 patients included in our first report of 2013. Minimum PID prevalence in the United Kingdom is currently 5.90/100 000 and an average incidence of PID between 1980 and 2000 of 7.6 cases per 100 000 UK live births. Data are presented on the frequency of diseases recorded, disease prevalence, diagnostic delay and treatment modality, including haematopoietic stem cell transplantation (HSCT) and gene therapy. The registry provides valuable information to clinicians, researchers, service commissioners and industry alike on PID within the United Kingdom, which may not otherwise be available without the existence of a well-established registry.

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DOI: 10.1111/cei.13125

PMCID: PMC5980391 [Available on 2019-06-01]

PMID: 29878323

271. Balkan J Med Genet. 2017 Dec 29;20(2):51-58. doi: 10.1515/bjmg-2017-0020. eCollection 2017 Dec.

Increased Frequency of MEFV Genes in Patients with Epigastric Pain Syndrome.

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Atypical clinical forms of familial Mediterranean fever (FMF) can be misdiagnosed as therapy-resistant epigastric pain syndrome (EPS) for they share many of the same clinical features, such as abdominal pain. Thus, we aimed to determine the frequency of FMF in patients who were followed with a diagnosis of therapy-resistant EPS. Seventy-five patients with therapy-resistant EPS and 20 controls were involved in the study. To detect the FMF in patients with therapy-resistant EPS, Tel-Hashomer criteria, family history of FMF were researched and recorded. We performed MEFV gene analysis on all patients. Forty-three patients with EPS (57.3%) had MEFV gene mutations and the carrier rate was 30.0%. The most common MEFV gene alteration was R202Q (55.8%), followed by E148Q (16.2%), R761H (16.2%), V726A (9.3%), M680I (9.3%) and M694V (4.6%). Rarely seen mutations in the Turkish population were also identified: K695R (2.3%), L110P (2.3%) and G304R (2.3%). Eight patients with EPS were diagnosed with FMF and started on colchicine therapy. Three patients with compound heterozygosities for three mutations, two patients with compound heterozygosities for two mutations (K695R/ V726A and R202Q/ R761H), one patient with homozygous R202Q, one patient with heterozygous R202Q mutation and one patient with non- R202Q heterozygous mutation (G304R/-) had clinical FMF symptoms and were started on colchicine therapy. Patients who have therapy-resistant EPS should also be questioned about FMF, especially in high risk populations.

DOI: 10.1515/bjmg-2017-0020

PMCID: PMC5972503

PMID: 29876233

272. Biomark Med. 2018 Jun;12(6):565-572. doi: 10.2217/bmm-2017-0344. Epub 2018 Jun 6.

Blood group 'A' may have a possible modifier effect on familial Mediterranean fever and blood group 'O' may be associated with colchicine resistance.

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**Aim/purpose:** Our aim was to investigate the association between blood groups and colchicine resistance in familial Mediterranean fever (FMF) patients.

**METHODS:** This is a single-center, cross-sectional study. Between January and December 2016, 385 FMF patients were assessed by the Adult and Pediatric Rheumatology outpatient clinics and 297 patients had blood groups (ABO and Rh) results. The patients were grouped into two groups: colchicine-responsive patients (Group CR) and colchicine-unresponsive patients (Group CUR).

**RESULTS:** Patients with blood group A had 1.5-fold higher FMF compared with non-A blood group (OR: 1.50 [95% CI: 1.11-1.87]), particularly having a Rh (+) blood group (OR: 1.47 [95% CI: 1.13-1.91]). Furthermore, patients with blood group A had a better response to colchicine treatment than non-A blood group; (OR: 2.21 [95% CI: 1.15-4.27]). Patients with blood group O were prominently associated with colchicine resistance.

**CONCLUSION:** ABO blood phenogroups may be used in combination with other risk factors to identify FMF patients and patients at high risk for colchicine resistance.

DOI: 10.2217/bmm-2017-0344

PMID: 29873519

273. J Allergy Clin Immunol Pract. 2018 Jul - Aug;6(4):1162-1170. doi: 10.1016/j.jaip.2018.05.006. Epub 2018 Jun 2.

Mimickers of Urticaria: Urticarial Vasculitis and Autoinflammatory Diseases.

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A wide differential diagnosis must be considered in a patient presenting with

urticarial plaques. Although acute and chronic urticaria are the commonest diagnoses, other differential diagnoses include polymorphous eruption of pregnancy, mast cell disorders, hypereosinophilic syndrome, urticarial vasculitis, pemphigoid, systemic lupus erythematosus, and autoinflammatory disease. This review will specifically address urticarial vasculitis and autoinflammatory syndromes. These entities represent contrasting examples of urticarial-like lesions resulting from either an adaptive immune complex-mediated mechanism (urticarial vasculitis) or an innate immune-mediated mechanism (autoinflammatory disorders), with differing therapeutic implications. In patients presenting with painful, persistent plaques that last more than 24 hours and resolve with bruising of the skin, consideration should be given to a diagnosis of urticarial vasculitis. A biopsy should be obtained to ascertain this diagnosis. In patients presenting with a persistent history of recurrent urticarial plaques associated with signs of systemic inflammation including fevers and elevated inflammatory markers (C-reactive protein [CRP]/serum amyloid A, leukocytosis, and negative connective tissue serologies), consideration should be given to autoinflammatory disorders: the 3 cryopyrin-associated periodic syndromes, Schnitzler syndrome, and familial cold autoinflammatory syndrome 2. Serum protein electrophoresis should be checked to rule out an underlying monoclonal gammopathy.

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DOI: 10.1016/j.jaip.2018.05.006

PMID: 29871797

274. J Control Release. 2018 Aug 28;284:103-111. doi: 10.1016/j.jconrel.2018.05.040. Epub 2018 Jun 2.

Ultrasound targeting of Q-starch/miR-197 complexes for topical treatment of psoriasis.

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Psoriasis is a common, worldwide autoinflammatory, incurable skin disease. miR-197 has therapeutic potential for psoriasis since it can down-regulate the expression of both IL-22RA1 and IL-17RA, subunits of the receptors of IL-22 and IL-17, respectively, which are key cytokines in the disease. Although miR-197 has the potential to treat the disease, several inherent physical barrier properties of the skin challenge miRNA's delivery to the target skin cells. In the present study, we evaluated a therapeutic approach that combines the use of ultrasound (US) as a means to enhance skin permeability with quaternized starch (Q-starch) as an miRNA delivery carrier. This resulted in decreased expression of the miR-197 target proteins and in a significant reduction in the psoriatic activity markers. Our results demonstrate the potential of combinations of US and Q-starch/miR-197 complexes for the topical skin treatment of psoriasis.

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DOI: 10.1016/j.jconrel.2018.05.040

PMID: 29870766

275. Biochem Biophys Res Commun. 2018 Sep 3;503(1):138-145. doi: 10.1016/j.bbrc.2018.05.199. Epub 2018 Jun 7.



The binding of TBK1 to STING requires exocytic membrane traffic from the ER.

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Stimulator of interferon genes (STING) is essential for the type I interferon and pro-inflammatory responses against DNA pathogens. In response to the presence of cytosolic DNA, STING translocates from the endoplasmic reticulum (ER) to the Golgi, and activates TANK-binding kinase 1 (TBK1), a cytosolic kinase that is essential for the activation of STING-dependent downstream signalling. The organelles where TBK1 binds to STING remain unknown. Here we show that TBK1 binds to STING at the Golgi, not at the ER. Treatment with brefeldin A, an agent to block ER-to-Golgi traffic, or knockdown of Sar1, a small GTPase that regulates coat protein complex II (COP-II)-mediated ER-to-Golgi traffic, inhibited the binding of TBK1 to STING. Endogenous TBK1 was recruited to the Golgi when STING was transported to the Golgi, as shown by immunofluorescence microscopy. STING variants that constitutively induce the type I interferon response were found in patients with autoinflammatory diseases. Even these disease-causative STING variants could not bind to TBK1 when the STING variants were trapped in the ER. These results demonstrate that the Golgi is an organelle at which STING recruits and activates TBK1 for triggering the STING-dependent type I interferon response.

276. Rheumatol Int. 2018 Aug;38(8):1345-1354. doi: 10.1007/s00296-018-4074-5. Epub 2018 Jun 4.

Novel insights into the role of inflammasomes in autoimmune and metabolic rheumatic diseases.

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Inflammasomes are large intracellular complexes that induce inflammation in response to exogenous and endogenous damage signals. They regulate production and release of the proinflammatory cytokines IL-1 $\beta$  and IL-18, playing a defensive role against infections. Inflammasomes have also been involved in the pathogenesis of a wide range of autoinflammatory conditions that are caused by dysregulation of the IL-1 pathway, such as cryopyrinopathies and hereditary periodic fever syndromes. On top of that, research in recent years suggests that defects in inflammasome regulation and signaling associate with a number of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis and others. In this review, we describe the inflammasome and mechanisms that trigger it, provide a brief review of autoinflammatory disorders and discuss the current understanding and emerging data from experimental and clinical studies for the role of the innate immune system and inflammasomes in the biology and pathogenesis of systemic autoimmune diseases.

DOI: 10.1007/s00296-018-4074-5  
PMID: 29869008 [Indexed for MEDLINE]

277. Front Immunol. 2018 May 18;9:1054. doi: 10.3389/fimmu.2018.01054. eCollection 2018.

Posttranslational Regulation of the NLR Family Pyrin Domain-Containing 3 Inflammasome.

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The NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome is a multi-protein complex that can be activated by a variety of pathogen-associated molecular patterns or damage-associated molecular patterns. Inappropriate NLRP3 inflammasome activation can induce autoinflammatory, autoimmune, or metabolic disorders. Therefore, NLRP3 is an attractive target against NLRP3 inflammasome activation, and specific targeting of NLRP3 might be an intriguing approach to the development of drugs for the treatment of NLRP3 inflammasome-related diseases. Although many studies with varied mechanistic approaches were reported in inhibition of NLRP3 inflammasome activation, mechanisms related to regulation of posttranslational modification (PTM) of NLRP3, as a focal point has not been thoroughly addressed. Recently, extensive investigations of PTMs of NLRP3 have led to partial understanding of the mechanisms involved in NLRP3 inflammasome activation. In this review, we focused on the role of PTMs regulating NLRP3 inflammasome activation.

DOI: 10.3389/fimmu.2018.01054  
PMCID: PMC5968104  
PMID: 29868015

## Detection of Inflammasome Activation and Pyroptotic Cell Death in Murine Bone Marrow-derived Macrophages.

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Inflammasomes are innate immune signaling platforms that are required for the successful control of many pathogenic organisms, but also promote inflammatory and autoinflammatory diseases. Inflammasomes are activated by cytosolic pattern recognition receptors, including members of the NOD-like receptor (NLR) family. These receptors oligomerize upon the detection of microbial or damage-associated stimuli. Subsequent recruitment of the adaptor protein ASC forms a microscopically visible inflammasome complex, which activates caspase-1 through proximity-induced auto-activation. Following the activation, caspase-1 cleaves pro-IL-1 $\beta$  and pro-IL-18, leading to the activation and secretion of these pro-inflammatory cytokines. Caspase-1 also mediates the inflammatory form of cell death termed pyroptosis, which features the loss of membrane integrity and cell lysis. Caspase-1 cleaves gasdermin D, releasing the N-terminal fragment which forms plasma membrane pores, leading to osmotic lysis. In vitro, the activation of caspase-1 can be determined by labeling bone marrow-derived macrophages with the caspase-1 activity probe FAM-YVAD-FMK and by labeling the cells with antibodies against the adaptor protein ASC. This technique allows the identification of inflammasome formation and caspase-1 activation in individual cells using fluorescence microscopy. Pyroptotic cell death can be detected by measuring the release of cytosolic lactate dehydrogenase into the medium. This procedure is simple, cost effective and performed in a 96-well plate format, allowing adaptation for screening. In this manuscript, we show that activation of the NLRP3 inflammasome by nigericin leads to the co-localization of the adaptor protein ASC and active caspase-1, leading to pyroptosis.

DOI: 10.3791/57463

PMCID: PMC6025848 [Available on 2019-05-21]

PMID: 29863661 [Indexed for MEDLINE]

279. Orv Hetil. 2018 Jun;159(23):898-907. doi: 10.1556/650.2018.31068.

[Autoinflammatory diseases].

[Article in Hungarian; Abstract available in Hungarian from the publisher]

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Autoinflammatory diseases are disorders of the innate immune system characterized by recurrent systematic inflammation and serious complications. Dysregulation of inflammasome and overproduction of interleukin-1 play a major role in the pathogenesis of autoinflammatory diseases. The diagnosis of these rare conditions rely on recognising the pattern of presentation and differential diagnosis. Manifestations may include fever, rash, serositis (pleuritis and peritonitis), arthritis, meningitis and uveitis. Secondary amyloidosis may complicate longstanding disease. Advances in our understanding of the molecular and pathophysiological basis of the autoinflammatory diseases have resulted in new treatment strategies. Early diagnosis and effective therapy are critical to prevent irreversible organ damage. The purpose of this review is to describe the major clinical, genetic, and therapeutic features of the most common autoinflammatory syndromes. Orv Hetil. 2018; 159(23): 898-907.

Publisher: Absztrakt: Az autoinflammációs szindrómák a veleszületett immunrendszert érintő, visszatérő szisztémás gyulladásos tünetekkel, súlyos szövődményekkel jellemezhető kórképek. A kórképek patomechanizmusában az inflammasoma kóros működése, fokozott interleukin-1-produkció áll. A ritka kórképek felismerése a visszatérő jellegű klinikai tünetek felismerésén és az egyéb kórképek kizárásán alapul. A láz mellett rash, serositis (pleuritis, peritonitis), arthritis, meningitis és uveitis jelentkezhethet. A hosszan fennálló gyulladás szekunder amyloidosis kialakulásához vezethet. A betegségek hátterében álló molekuláris és patofiziológiai okok fejlődő ismerete új terápiák bevezetését tette lehetővé. A betegség korai felismerése és hatásos kezelése révén az

irreverzibilis szervkárosodás megelőzhető. A közlemény a leggyakoribb autoinflammációs kórképek klinikai, genetikai jellemzőit és a terápiás lehetőségeket kívánja bemutatni. Orv Hetil. 2018; 159(23): 898–907.

DOI: 10.1556/650.2018.31068

PMID: 29860887 [Indexed for MEDLINE]

280. Orv Hetil. 2018 Jun;159(23):908-918. doi: 10.1556/650.2018.31064.

[Primary immunodeficiency and autoimmune diseases].

[Article in Hungarian; Abstract available in Hungarian from the publisher]

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Primary immunodeficiencies consist of a group of genetically heterogeneous immune disorders affecting distinct elements of the innate and adaptive immune system. Patients with primary immunodeficiency are more prone to develop not only recurrent infections, but non-infectious complications, like inflammatory or granulomatous conditions, lymphoproliferative and solid malignancies, autoinflammatory disorders, and a broad spectrum of autoimmune diseases. The concomitant appearance of primary immunodeficiency and autoimmunity appears to be rather paradoxical, therefore making the diagnosis of immunodeficiency patients with autoimmune complications challenging. Mutations of one or more genes playing a fundamental role in immunoregulation and/or immune tolerance network are thought to be responsible for primary immunodeficiencies. The diverse immunological abnormalities along with the compensatory and excessive sustained inflammatory response result in tissue damage and finally in manifestation of organ-, cell-specific or systemic autoimmune diseases. Several forms of primary immunodeficiency disorders are characterized by a variety of specific autoimmune phenomena. This overview addresses the spectrum of autoimmune diseases associated with primary immunodeficiencies, and explores the molecular and cellular mechanisms underlying abnormalities of the immune system. The case presented finally highlights that both the recognition of autoimmune diseases in association with immunodeficiencies and the diagnosis of immunodeficiency in those

phenotypes with predominant autoimmunity could be challenging. Orv Hetil. 2018; 159(23): 908-918.

Publisher: Absztrakt: A primer immunhiányos betegségek a természetes és az adaptív immunrendszer elemeit érintő, genetikailag heterogén immunológiai rendellenességek. A primer immunhiányban szenvedő betegek nemcsak visszatérő fertőzésekre, de noninfektív kórállapotokra, így gyulladásos vagy granulomatosus eltérésekre, lymphoproliferatív és szolid daganatos megbetegedésekre, autoinflammációs állapotokra, valamint a legkülönbébb autoimmun kórformákra is hajlamosabbak. Az elsődleges immunhiány és az autoimmunitás paradoxonnak tűnő együttes megjelenése valódi kihívást jelent az immunhiányos betegek autoimmun szövődményeinek felismerésében. A primer immunhiányos állapotok hátterében általában egy vagy több, az immunregulációban és/vagy az immuntolerancia kialakításában kulcsszerepet játszó gén mutációja áll. A szerteágazó immunológiai rendellenességek, a kompenzatorikus, túlzott mértékű krónikus gyulladásos válaszreakció és a következményes szövetkárosodás együttese végső soron szerv-, sejtspecifikus vagy szisztémás autoimmun betegségek kialakulásához vezet. Számos primer immunhiányos kórképet különböző, sajátos autoimmun manifesztáció jellemez. A jelen összefoglaló célja a primer immunhiányos állapotokban megjelenő autoimmun kórképek, valamint az immunrendszeri rendellenességek alapjául szolgáló molekuláris és celluláris mechanizmusok áttekintése. A dolgozat végén ismertetett eset rávilágít arra, hogy immunhiányos állapotokban az autoimmun betegségek felismerése, illetve a dominálón autoimmun kórkép formájában induló fenotípusoknál az immunhiány kórismézése egyaránt kihívást jelenthet. Orv Hetil. 2018; 159(23): 908–918.

DOI: 10.1556/650.2018.31064

PMID: 29860882 [Indexed for MEDLINE]

281. Int J Pediatr Otorhinolaryngol. 2018 Jul;110:100-104. doi: 10.1016/j.ijporl.2018.05.005. Epub 2018 May 8.

Tonsillar antimicrobial peptide (AMP) expression profiles of periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) patients.

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**INTRODUCTION:** PFAPA (periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis) is the most frequent non-infectious cause of high fever observed among the European child population. While its cause is still not yet fully identified, PFAPA patients were previously shown to have altered tonsillar microbiome composition. Our study hypothesized that this is associated with a change in antimicrobial peptide (AMP) expression levels, as in the case of Crohn's disease which is another autoinflammatory disorder.

**METHODS AND MATERIALS:** The tonsil specimens were isolated from seven patients with PFAPA syndrome, and six patients with group A beta-hemolytic streptococcal (GABHS) recurrent tonsillitis. Tonsillar expression levels of human beta-defensin 1-2, cathelicidin, ribonuclease-7, and liver expressed antimicrobial peptide-1 were monitored by immunohistochemistry (IHC). Expression levels were scored using semi-quantitative analysis method and were statistically analyzed by Two-Way Repeated Measures Analysis of Variance test.

**RESULTS:** Our results showed no significant difference in AMP expression levels between PFAPA and GABHS patients. Immunolocalization of human beta-defensin 1 was different between the two groups; expressed at higher levels on tonsil surface epithelium (SE) than lymphoid interior (LI) in PFAPA patient group, while this was not evident in GABHS patients group.

**CONCLUSIONS:** Our results suggest that, PFAPA patients may be associated with altered AMP expression as in other autoinflammatory diseases. Future studies with subjects without any inflammatory condition are required for more precise conclusions.

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DOI: 10.1016/j.ijporl.2018.05.005



PMID: 29859567 [Indexed for MEDLINE]

282. Ann Rheum Dis. 2018 Jun 1. pii: annrheumdis-2018-213745. doi: 10.1136/annrheumdis-2018-213745. [Epub ahead of print]

Comment on: 'Aberrant tRNA processing causes an autoinflammatory syndrome responsive to TNF inhibitors' by Giannelou et al: mutations in TRNT1 result in a constitutive activation of type I interferon signalling.

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DOI: 10.1136/annrheumdis-2018-213745

PMID: 29858171

Conflict of interest statement: Competing interests: None declared.

283. Rheumatol Int. 2018 May 31. doi: 10.1007/s00296-018-4070-9. [Epub ahead of print]

Stress proteins in the pathogenesis of spondyloarthritis.

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Spondyloarthritis is an autoinflammatory rheumatic disease in which arthritis and osteoproliferation lead the patients who suffer from it to chronic disability. This disease is associated with the expression of class I MHC molecule HLA-B27, which tends to be misfolded in the endoplasmic reticulum and, therefore, expressed in aberrant forms. This phenomena lead to endoplasmic reticulum stress, which in time, evokes a whole response to cellular injury. Under these conditions, the molecules involved in restoring cell homeostasis play a key role. Such is the case of the "heat-shock proteins", which usually regulate protein folding, but also have important immunomodulatory functions, as well as some roles in tissue modeling. In this review, we attempt to summarize the involvement of cell stress and heat-shock proteins in the homeostatic disturbances and pathological conditions associated with this disease.

DOI: 10.1007/s00296-018-4070-9

PMID: 29855675

284. Case Rep Rheumatol. 2018 May 2;2018:6580835. doi: 10.1155/2018/6580835.

eCollection 2018.

## An Underlooked Cause of Periodic Fever (PFAPA) in an Adult Patient with No Response to Tonsillectomy.

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Periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA) is an autoinflammatory disease manifested as recurrent febrile episodes associated with one of the following cardinal features: aphthous ulceration, pharyngitis, and cervical adenitis. It was initially described in children and thought to be a disease of pediatric age group. Few adult cases were also reported in the literature. We describe the case of a 39-year-old female affected by PFAPA who presented with a history of febrile episodes associated with aphthous ulceration, stomatitis, and tonsillitis for 4 years. The febrile episodes occurred at a regular interval of 4 weeks and resolved within 5 days. The patient underwent tonsillectomy without any significant improvement. The patient responded only to a single high dose of steroid during the attack. Although PFAPA was initially thought to be a disease of pediatric age group, it should be considered in patients with recurrent febrile illness in all age groups.

DOI: 10.1155/2018/6580835

PMCID: PMC5954889

PMID: 29854539

285. Case Rep Rheumatol. 2018 Apr 11;2018:5416907. doi: 10.1155/2018/5416907. eCollection 2018.

## Increasing the Interval of Canakinumab Administration Effectively Supports the Remission of Schnitzler's Syndrome.

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Schnitzler's syndrome (SchS) is a rare, disabling, autoinflammatory disorder characterized by recurrent urticarial rash and monoclonal IgM gammopathy. Interleukin-1 beta (IL-1 $\beta$ ) plays an important role in the pathophysiology of SchS. Only anecdotal reports demonstrate the efficiency and safety of human monoclonal anti-human IL-1 $\beta$  antibody (canakinumab) use in SchS therapy. However, there are no generally accepted recommendations concerning the scheme (or frequency) of canakinumab use for this disease. Here, we report the effective long-term treatment of SchS in a 44-year-old male with a standard canakinumab dose (150 mg) but with an increased 4-month injection interval.

DOI: 10.1155/2018/5416907

PMCID: PMC5925130

PMID: 29850358

286. Arthritis Res Ther. 2018 May 30;20(1):98. doi: 10.1186/s13075-018-1603-2.

Transcription factor motif enrichment in whole transcriptome analysis identifies STAT4 and BCL6 as the most prominent binding motif in systemic juvenile idiopathic arthritis.

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**BACKGROUND:** The term systemic juvenile idiopathic arthritis (sJIA) describes an autoinflammatory condition characterized by arthritis and severe systemic inflammation, which in later stages can transform into interleukin (IL)-17-driven

autoimmune arthritis. IL-1 antagonists have been used with good efficacy in the early stages of sJIA.

**METHODS:** A whole transcriptome analysis of peripheral blood RNA samples was performed in six patients with sJIA and active systemic disease, before initiating treatment with the IL-1 $\beta$  receptor antagonist anakinra, and after induction of inactive disease, compared with a single-sample control cohort of 21 patients in several clinical stages of sJIA activity. Whole transcriptomes were compared longitudinally and interindividually including gene ontology and motif enrichment analysis of differentially expressed genes.

**RESULTS:** There were 741 transcripts were identified using a threshold with a p value <0.01 and a fold change > 2. HLADRB1 and CD74 were identified as the most strongly upregulated genes in inactive compared to active disease; CD177 expression was significantly enhanced in active disease compared to inactive disease. Motif enrichment analysis revealed STAT4, BCL6, and STAT3 as the most prominent transcription factors that were present during active disease. In addition, strong upregulation of the major histocompatibility complex II (MHCII) ligand CD74 was found in both active and inactive sJIA compared to healthy controls.

**CONCLUSION:** Using transcription factor motif enrichment, this study identifies novel putative pathways in sJIA (STAT4, BCL6) implicating B cell activation at an earlier stage than predicted in refractory disease. The implication of BCL-6 dependent pathways argues for occurrence of autoimmunity early within the process of sJIA chronification. Transcriptional regulation of HLA-DRB1, a recently described independent genetic risk factor, in combination with its cooperating partner CD74 in patients where sJIA is confirmed, supports pathogenic involvement in alterations in antigen presentation during sJIA.

DOI: 10.1186/s13075-018-1603-2

PMCID: PMC5977738

PMID: 29848367

287. Curr Rheumatol Rep. 2018 May 30;20(7):39. doi: 10.1007/s11926-018-0749-x.

An Update on Autoinflammatory Diseases: Relopathies.

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**PURPOSE OF REVIEW:** The nuclear factor  $\kappa$ B (NF- $\kappa$ B) pathway is tightly regulated through multiple posttranslational mechanisms including ubiquitination. Mutations in these regulatory pathways can cause disease and are the focus of this review.

**RECENT FINDINGS:** The linear ubiquitin chain assembly complex (LUBAC) is a trimer made up of HOIL-1L, SHARPIN, and the catalytic subunit HOIP. Loss of function mutations in HOIL-1L and HOIP result in largely overlapping phenotypes, characterized by multi-organ autoinflammation, immunodeficiency, and amylopectinosis. Interestingly, patient fibroblasts exhibited diminished IL-1 $\beta$ - and TNF-induced NF- $\kappa$ B activation, yet monocytes were hyper-responsive to IL-1 $\beta$ , hinting at cell type or target specific roles of LUBAC-mediated ubiquitination. Ubiquitin-driven signaling is counterbalanced by deubiquitinase enzymes (DUBs), such as OTULIN and A20. Hypomorphic mutations in OTULIN result in elevated NF- $\kappa$ B signaling causing an autoinflammatory syndrome. Similarly, patients with high-penetrance heterozygous mutations in the gene encoding A20 (haploinsufficiency of A20 (HA20)) display excessive ubiquitination and increased activity of NF- $\kappa$ B and of NLRP3 inflammasome activation. HA20 patients present with Behçet-like characteristics or an autoimmune lymphoproliferative syndrome (ALPS)-like phenotype, indicating diverse protein functions. This review summarizes recent discoveries in the field of NF- $\kappa$ B-related autoinflammatory diseases (relopathies) within the past 3 years and points to several questions that still remain unanswered.

DOI: 10.1007/s11926-018-0749-x

PMID: 29846841

## An Update on Autoinflammatory Diseases: Inflammasomopathies.

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**PURPOSE OF REVIEW:** Autoinflammatory diseases are driven by abnormal innate immune activation. In the case of inflammasomopathies, these are all attributable to activation of an inflammasome complex, nucleated by an innate immune sensor such as NLRP3. This review will focus on recent advances that have helped to elucidate the role of three other sensors (NLRP1, NLRC4 and pyrin) which can also cause inflammasomopathies.

**RECENT FINDINGS:** Mutations in pyrin (S242R or E244K) destroy an inhibitory 14-3-3 binding site and result in the newly characterised disease pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND). Moreover, a separate autoinflammatory disease driven by mevalonate kinase deficiency leads to defective RhoGTPase prenylation and subsequent loss of pyrin S242R phosphorylation, suggesting a shared mechanism of disease. Other inflammasomes such as NLRP1 and NLRC4 have had novel mutations described recently, which inform about the specific domains required for activation and autoinhibition. This review covers recent advances in the study of inflammasomopathies, focussing on gene discoveries that elucidate new pathogenic mechanisms.

DOI: 10.1007/s11926-018-0750-4

PMID: 29846819

# An Update on Autoinflammatory Diseases: Interferonopathies.

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**PURPOSE OF REVIEW:** Type I interferons (IFN $\alpha\beta$ ) induce the expression of hundreds of genes; thus, it is unsurprising that the initiation, transmission, and resolution of the IFN $\alpha\beta$ -mediated immune response is tightly controlled. Mutations that alter nucleic acid processing and recognition, ablate IFN $\alpha\beta$ -specific negative feedback mechanisms, or result in dysfunction of the proteasome system can all induce pathogenic IFN $\alpha\beta$  signalling and are the focus of this review.

**RECENT FINDINGS:** Recent advances have delineated the precise cytoplasmic mechanisms that facilitate self-DNA to be recognised by cGAS and self-RNA to be recognised by RIG-I or MDA-5. This helps clarify interferonopathies associated with mutations in genes which code for DNase-II and ADAR1, among others. Similarly, loss of function mutations in Pol  $\alpha$ , which lowers the presence of antagonistic ligands in the cytosol, or gain of function mutations in RIG-I and MDA-5, result in increased propensity for receptor activation and therefore IFN $\alpha\beta$  induction. As the aetiology of monogenic autoinflammatory diseases are uncovered, novel and sometimes unsuspected molecular interactions and signalling pathways are being defined. This review covers developments that have come to light over the past 3 years, with reference to the study of interferonopathies.

DOI: 10.1007/s11926-018-0748-y

PMID: 29846818



[Periodic fever syndromes].

[Article in Danish]

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Periodic fever syndromes (PFS) are characterised by recurrent fever and excessive systemic inflammation. These rare and hereditary syndromes include familial Mediterranean fever, tumour necrosis factor receptor-1 associated periodic syndrome, mevalonate kinase deficiency and cryopyrin-associated periodic syndrome. Each PFS has distinct clinical and genetic features. Availability of improved genetic methods has improved the understanding of the syndromes and diagnostic testing. The main complication is systemic amyloidosis. Targeted biological therapy such as interleukin-1 inhibitors is emerging as an effective treatment.

PMID: 29808817

291. Case Rep Rheumatol. 2018 Apr 1;2018:9670801. doi: 10.1155/2018/9670801. eCollection 2018.

A Case of Familial Mediterranean Fever with Extensive Lymphadenopathy and Complex Heterozygous Genotype Presenting in the Fourth Decade.

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Familial Mediterranean fever (FMF) is an inherited disease caused by loss of function mutations in the MEFV gene encoding pyrin, a negative regulator of interleukin-1. The disease is characterized by recurrent fever and self-limited attacks of joint, chest, and abdominal pain but lymphadenopathy is an infrequent manifestation. While mesenteric lymphadenopathy has been described in several cases in the literature; hilar, paratracheal, axillary, pelvic, and retroperitoneal lymphadenopathy are extremely rare and have been reported separately in very few individuals. In this report, we present a patient with late-onset FMF with extensive lymphadenopathy in all of the aforementioned anatomic regions. Genetic analysis identified three heterozygous pyrin mutations in a patient with no affected family members. Genetic investigation of the patient's mother identified a novel carrier haplotype E148Q/P369S. The proband also inherited the previously described and rare A744S mutation previously not thought to be a disease-defining lesion. This unique compound heterozygous genotype resulted in a novel genotype-phenotype association producing an atypical clinical presentation of FMF that fits within the pattern of several case reports of late-onset disease with respect to clinical course and therapeutic response.

DOI: 10.1155/2018/9670801

PMCID: PMC5901998

PMID: 29808155

292. Am J Hum Genet. 2018 Jun 7;102(6):1126-1142. doi: 10.1016/j.ajhg.2018.04.010. Epub 2018 May 24.

Heterozygous Truncating Variants in POMP Escape Nonsense-Mediated Decay and Cause a Unique Immune Dysregulatory Syndrome.

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The proteasome processes proteins to facilitate immune recognition and host defense. When inherently defective, it can lead to aberrant immunity resulting in a dysregulated response that can cause autoimmunity and/or autoinflammation. Biallelic or digenic loss-of-function variants in some of the proteasome subunits have been described as causing a primary immunodeficiency disease that manifests as a severe dysregulatory syndrome: chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE). Proteasome maturation protein (POMP) is a chaperone for proteasome assembly and is critical for the incorporation of catalytic subunits into the proteasome. Here, we characterize and describe POMP-related autoinflammation and immune dysregulation disease (PRAID) discovered in two unrelated individuals with a unique constellation of early-onset combined immunodeficiency, inflammatory neutrophilic dermatosis, and autoimmunity. We also begin to delineate a complex genetic mechanism whereby de novo heterozygous frameshift variants in the penultimate exon of POMP escape nonsense-mediated mRNA decay (NMD) and result in a truncated protein that perturbs proteasome assembly by a dominant-negative mechanism. To our knowledge, this mechanism has not been reported in any primary immunodeficiencies, autoinflammatory syndromes, or autoimmune diseases. Here, we define a unique hypo- and hyper-immune phenotype and report an immune dysregulation syndrome caused by frameshift mutations that escape NMD.

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DOI: 10.1016/j.ajhg.2018.04.010

PMCID: PMC5992134

PMID: 29805043 [Indexed for MEDLINE]

293. J Allergy Clin Immunol. 2018 May 23. pii: S0091-6749(18)30758-9. doi: 10.1016/j.jaci.2018.04.034. [Epub ahead of print]

Severe combined immunodeficiency in stimulator of interferon genes (STING) V154M/wild-type mice.

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**BACKGROUND:** Autosomal dominant gain-of-function mutations in human stimulator of interferon genes (STING) lead to a severe autoinflammatory disease called STING-associated vasculopathy with onset in infancy that is associated with enhanced expression of interferon-stimulated gene transcripts.

**OBJECTIVE:** The goal of this study was to analyze the phenotype of a new mouse model of STING hyperactivation and the role of type I interferons in this system.

**METHODS:** We generated a knock-in model carrying an amino acid substitution (V154M) in mouse STING, corresponding to a recurrent mutation seen in human patients with STING-associated vasculopathy with onset in infancy. Hematopoietic development and tissue histology were analyzed. Lymphocyte activation and proliferation were assessed in vitro. STING V154M/wild-type (WT) mice were crossed to IFN- $\alpha/\beta$  receptor (IFNAR) knockout mice to evaluate the type I interferon dependence of the mutant Sting phenotype recorded.

**RESULTS:** In STING V154M/WT mice we detected variable expression of inflammatory infiltrates in the lungs and kidneys. These mice showed a marked decrease in survival and developed a severe combined immunodeficiency disease (SCID) affecting B, T, and natural killer cells, with an almost complete lack of antibodies and a significant expansion of monocytes and granulocytes. The blockade in B- and T-cell development was present from early immature stages in bone marrow and thymus. In addition, in vitro experiments revealed an intrinsic proliferative defect of mature T cells. Although the V154M/WT mutant demonstrated

increased expression of interferon-stimulated genes, the SCID phenotype was not reversed in STING V154M/WT IFNAR knockout mice. However, the antiproliferative defect in T cells was rescued partially by IFNAR deficiency.

CONCLUSIONS: STING gain-of-function mice developed an interferon-independent SCID phenotype with a T-cell, B-cell, and natural killer cell developmental defect and hypogammaglobulinemia that is associated with signs of inflammation in lungs and kidneys. Only the intrinsic proliferative defect of T cells was partially interferon dependent.

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DOI: 10.1016/j.jaci.2018.04.034

PMID: 29800647

294. J Exp Med. 2018 Jun 4;215(6):1519-1529. doi: 10.1084/jem.20172060. Epub 2018 May 23.

GSDMD is critical for autoinflammatory pathology in a mouse model of Familial Mediterranean Fever.

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Pyroptosis is an inflammasome-induced lytic cell death mode, the physiological role of which in chronic inflammatory diseases is unknown. Familial Mediterranean Fever (FMF) is the most common monogenic autoinflammatory disease worldwide, affecting an estimated 150,000 patients. The disease is caused by missense mutations in *Mefv* that activate the Pyrin inflammasome, but the pathophysiologic mechanisms driving autoinflammation in FMF are incompletely understood. Here, we show that *Clostridium difficile* infection of FMF knock-in macrophages that express a chimeric FMF-associated *Mefv*V726A Pyrin elicited pyroptosis and gasdermin D (GSDMD)-mediated interleukin (IL)-1 $\beta$  secretion. Importantly, in vivo GSDMD deletion abolished spontaneous autoinflammatory disease. GSDMD-deficient FMF knock-in mice were fully protected from the runted growth, anemia, systemic inflammatory cytokine production, neutrophilia, and tissue damage that characterize this autoinflammatory disease model. Overall, this work identifies pyroptosis as a critical mechanism of IL-1 $\beta$ -dependent autoinflammation in FMF and highlights GSDMD inhibition as a potential antiinflammatory strategy in inflammasome-driven diseases.

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DOI: 10.1084/jem.20172060

PMCID: PMC5987922

PMID: 29793924

295. Adv Clin Exp Med. 2018 Jun;27(6):721-725. doi: 10.17219/acem/78020.

The expression of selected molecular markers of immune tolerance in psoriatic patients.

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**BACKGROUND:** Psoriasis is a chronic autoinflammatory disease whose underlying molecular mechanisms remain unclear. The disease is mediated by the cells and molecules of both the innate and adaptive immune systems. Some T cell surface molecules, including neuropilin-1 (NRP1), programmed death 1 (PD-1) and the human leukocyte antigen G (HLA-G), are known to play a role in the maintenance of immune tolerance.

**OBJECTIVES:** The aim of this study was to investigate HLA-G, NRP1 and programmed cell death gene (PDCD1) mRNA expression in psoriatic patients.

**MATERIAL AND METHODS:** The study included 72 psoriatic patients and 35 healthy individuals. Twentyone patients (29.17%) suffered from concomitant psoriatic arthritis. The mRNA expression of HLA-G, NRP1, and PDCD1 were determined using quantitative real-time reverse transcription polymerase chain reaction (qRT-PCR). The severity of skin lesions was assessed by means of the Psoriasis Area and Severity Index (PASI), Body Surface Area (BSA), the Patient Global Assessment (PGA), and the Dermatology Life Quality Index (DLQI).

**RESULTS:** The median value of the PASI was 11.5, and of BSA was 15.8%. The expressions of NRP1 and PDCD1, but not HLA-G, were significantly lower in psoriatic patients in comparison with the control group. The expression of HLA-G, NRP1 and PDCD1 were not significantly different in the psoriatic arthritis and psoriasis vulgaris patients.

**CONCLUSIONS:** The results of this study suggest that the molecular markers of immune tolerance, i.e., HLA-G, NRP1, and PD-1, may be involved in the immune response in psoriatic patients.

DOI: 10.17219/acem/78020

PMID: 29790686 [Indexed for MEDLINE]

296. Inflamm Bowel Dis. 2018 Nov 29;24(12):2613-2620. doi: 10.1093/ibd/izy165.

Infantile Onset Intractable Inflammatory Bowel Disease Due to Novel Heterozygous Mutations in TNFAIP3 (A20).

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**Background:** Mutations in tumor necrosis factor alpha-induced protein 3 (TNFAIP3), a key player in the negative feedback regulation of nuclear factor- $\kappa$ B signaling, have recently been recognized as leading to early onset autoinflammatory and autoimmune syndrome. Here, we have reported the phenotypes of 3 infantile onset intractable inflammatory bowel disease (IBD) patients with TNFAIP3 mutations and reviewed previously reported cases to establish phenotypic features associated with TNFAIP3 monogenicity.

**Methods:** From January 1, 2015, to December 31, 2017, we recruited 58 infantile-onset IBD patients. Targeted sequencing and whole-exome sequencing were performed. Sanger sequencing confirmed the variants and determined the parental origin. We followed all the patients with TNFAIP3 mutations in our cohort and analyzed their clinical data.

**Results:** Genetic screening in all 58 patients with infantile-onset IBD revealed 44 (75.9%) cases of monogenic disorders, and 3 de novo TNFAIP3 mutations were identified, including 1 nonsense and 2 frame shift mutations. All the mutations resulted in premature stop codon. All 3 patients had multiple systemic involvements, with predominant gastrointestinal diseases.

**Conclusions:** Most infantile-onset IBD was associated with monogenetic mutation, and in addition to the 50 reported genes, other rare genetic variants need to be determined. TNFAIP3 may be an important candidate gene. The treatment of TNFAIP3-associated infantile-onset-IBD was challenging.

10.1093/ibd/izy165\_video1izy165.video15789607089001.

DOI: 10.1093/ibd/izy165

PMID: 29788367

297. PLoS One. 2018 May 22;13(5):e0197829. doi: 10.1371/journal.pone.0197829. eCollection 2018.

Analysis of microRNAs in familial Mediterranean fever.

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**OBJECTIVES:** Although Familial Mediterranean fever (FMF) is categorized as autosomal recessive, frequent exceptions to this model exist and therefore we aimed to search epigenetic modifications in this disease.

**METHODS:** Ten M694V homozygous FMF patients (the most severe phenotype) were recruited for this study. Patients with inflammatory flare were excluded. Total RNA was extracted from peripheral blood, and microRNA expression profiled using NanoString nCounter technology. These patients were compared to 10 healthy age- and sex-matched controls.

**RESULTS:** Seven hundred eighty-eight mature human miRNAs were probed, 103 of which had expression levels above the negative control probes. Seven miRNAs showed significant differences in expression in samples from FMF patients compared to healthy controls: four miRNAs were upregulated (miR-144-3p, miR-21-5p, miR-4454, and miR-451a), and three were downregulated (miR-107, let-7d-5p, and miR-148b-3p).

**CONCLUSION:** In this pilot study, we identified epigenetic modifications in clinically quiescent FMF patients. More studies are required for exploration of their contribution to FMF pathogenesis and their potential role as clinical biomarkers.

DOI: 10.1371/journal.pone.0197829

PMCID: PMC5963758

PMID: 29787577 [Indexed for MEDLINE]

**Conflict of interest statement:** The study was funded by a commercial source: Novartis Inc. The corresponding author hereby declares on behalf of all authors that there are no financial, non-financial professional or personal competing interests between this funder to any of the authors in relationship to this work and manuscript. (Competing interest is defined as anything that interferes with, or could reasonably be perceived as interfering with, the full and objective presentation, peer review, editorial decision making, or publication of research or non-research articles submitted to one of the journals). This does not alter our adherence to PLOS ONE policies on sharing data and materials (as detailed online in the guide for authors

<http://journals.plos.org/plosone/s/competing-interests>).

298. Intern Med. 2018 Oct 1;57(19):2901-2904. doi: 10.2169/internalmedicine.0431-17. Epub 2018 May 18.

Familial Mediterranean Fever Mutations in a Patient with Periodic Episodes of Systemic Pain Deriving from Cancer Bone Metastases.

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Familial Mediterranean fever (FMF), the most common autoinflammatory disorder, is characterized by recurrent febrile attacks and polyserositis. FMF is caused by mutations in MEFV, which encodes pyrin. In this report, we present an atypical FMF case with E148Q/L110P mutations in MEFV. The patient experienced periodic episodes of systemic pain originating from prostate cancer bone metastases. The pain attacks were prevented by continuous prophylactic therapy with colchicine. In this case, the presence of atypical FMF may have modulated the clinical manifestations of cancer bone metastases. To our knowledge, this is the first report to demonstrate the potential modulatory effect of MEFV mutations on cancer manifestations.

DOI: 10.2169/internalmedicine.0431-17

PMCID: PMC6207823

PMID: 29780113 [Indexed for MEDLINE]

299. J Allergy Clin Immunol. 2018 Dec;142(6):1956-1967.e6. doi: 10.1016/j.jaci.2018.04.033. Epub 2018 May 17.

Autoinflammatory mutation in NLRC4 reveals a leucine-rich repeat (LRR)-LRR oligomerization interface.

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**BACKGROUND:** Monogenic autoinflammatory disorders are characterized by dysregulation of the innate immune system, for example by gain-of-function mutations in inflammasome-forming proteins, such as NOD-like receptor family CARD-containing 4 protein (NLRC4).

**OBJECTIVE:** Here we investigate the mechanism by which a novel mutation in the

leucine-rich repeat (LRR) domain of NLRC4 (c.G1965C, p.W655C) contributes to autoinflammatory disease.

**METHODS:** We studied 2 unrelated patients with early-onset macrophage activation syndrome harboring the same de novo mutation in NLRC4. In vitro inflammasome complex formation was quantified by using flow cytometric analysis of apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) specks. Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas9 techniques and lentiviral transduction were used to generate THP-1 cells with either wild-type or mutant NLRC4 cDNA. Cell death and release of IL-1 $\beta$ /IL-18 were quantified by using flow cytometry and ELISA, respectively.

**RESULTS:** The p.W655C NLRC4 mutation caused increased ASC speck formation, caspase-1-dependent cell death, and IL-1 $\beta$ /IL-18 production. ASC contributed to p.W655C NLRC4-mediated cytokine release but not cell death. Mutation of p.W655 activated the NLRC4 inflammasome complex by engaging with 2 interfaces on the opposing LRR domain of the oligomer. One key set of residues (p.D1010, p.D1011, p.L1012, and p.I1015) participated in LRR-LRR oligomerization when triggered by mutant NLRC4 or type 3 secretion system effector (PrgI) stimulation of the NLRC4 inflammasome complex.

**CONCLUSION:** This is the first report of a mutation in the LRR domain of NLRC4 causing autoinflammatory disease. c.G1965C/p.W655C NLRC4 increased inflammasome activation in vitro. Data generated from various NLRC4 mutations provides evidence that the LRR-LRR interface has an important and previously unrecognized role in oligomerization of the NLRC4 inflammasome complex.

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DOI: 10.1016/j.jaci.2018.04.033

PMCID: PMC6281029

PMID: 29778503

300. Rev Esp Cir Ortop Traumatol. 2018 May 15. pii: S1888-4415(18)30071-7. doi: 10.1016/j.recot.2018.03.008. [Epub ahead of print]

Chronic recurrent multifocal osteomyelitis in pediatrics: A diagnostic challenge.

[Article in English, Spanish]

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Chronic recurrent multifocal osteomyelitis (CRMO) is an autoinflammatory disease that presents with aseptic bone inflammation and can be accompanied by multisystemic symptoms. We present the case of a 14-year-old male with a 2-week history of pain located at the tibial metaphysis and fever. X-ray revealed a lytic lesion in the tibial metaphysis. MRI revealed an intramedullary bone lesion with perilesional bone oedema. CT-guided biopsy discounted malignancy and microbiological cultures were negative. The patient's symptoms and fever worsened after the biopsy; therefore antibiotherapy was commenced for a suspected superinfection. A body MRI was performed given the persistence of the fever, which found a second active lesion in the spine that was diagnosed as CRMO and progressed well with anti-inflammatories. CRMO is an entity that is difficult to diagnose. Differential diagnosis is extensive with infectious diseases, tumours and other autoinflammatory diseases. Prompt diagnosis and appropriate treatment are crucial to prevent sequelae.

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DOI: 10.1016/j.recot.2018.03.008

PMID: 29776891

301. Amyloid. 2018 Jun;25(2):115-119. doi: 10.1080/13506129.2018.1474733. Epub 2018 May 18.

Profile of renal AA amyloidosis in older and younger individuals: a single-centre experience.

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**OBJECTIVE:** In epidemiological studies of amyloid A (AA) amyloidosis from Turkey, the most frequently cause was familial Mediterranean fever (FMF) and it occurs generally in young age population. However, there are no sufficient data regarding aetiology, clinical presentation and prognosis of renal AA amyloidosis in advanced age patients. In this study, we aimed to investigate demographic, clinical presentation, aetiology and outcomes of adults aged 60 years or older patients with biopsy-proven renal AA amyloidosis.

**METHODS:** This is a retrospective study involving 53 patients who were diagnosed with AA amyloidosis by kidney biopsy from 2006 to 2016. In all patients, kidney biopsies were performed due to asymptomatic proteinuria, nephrotic syndrome and/or renal insufficiency. The patients were separated into two groups on the basis of age (group I:  $\geq 60$  years and group II:  $< 60$  years). Outcomes of patients in terms of the requirement of renal replacement therapy and mortality were recorded.

**RESULTS:** In patients with group I, the causes of AA amyloidosis were as follows: FMF 16 (50%), bronchiectasis 7 (23%), chronic osteomyelitis 2 (6%), inflammatory bowel disease 2 (6%), rheumatoid arthritis 2 (6%), ankylosing spondylitis 1 (3%) and unknown aetiology 2 (6%). The underlying disorders of AA amyloidosis in group II patients were as follows: FMF 17 (81%), Behcet's disease 1 (5%) and unknown aetiology 3 (14%). No statistically significant differences were detected between two groups with regard to systolic and diastolic blood pressures, albumin, proteinuria and lipids. The combination of chronic kidney disease and nephrotic syndrome was the most common clinical presentation in group I (73%) and group II (43%) ( $p = .05$ ). Compared to the group II, estimated glomerular filtration rate was significantly lower in group I at the time of kidney biopsy ( $p = .003$ ). At 12-month follow-up, 61% of the group I and 33% of the group II developed end-stage kidney disease requiring dialysis, while 11% of the group I died.

**CONCLUSION:** Our results indicated that renal AA amyloidosis is a rare disease in advanced age patients. At baseline and follow-up period, advanced age patients had worse kidney disease and outcomes.

DOI: 10.1080/13506129.2018.1474733

PMID: 29775082



302. Best Pract Res Clin Rheumatol. 2017 Aug;31(4):596-609. doi: 10.1016/j.berh.2017.12.001. Epub 2018 Jan 11.

Periodic fever syndromes.

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Periodic fever syndromes are autoinflammatory diseases. The majority present in infancy or childhood and are characterised by recurrent episodes of fever and systemic inflammation that occur in the absence of autoantibody production or identifiable infection. The best recognised disorders include CAPS, FMF, TRAPS and MKD. Understanding the molecular pathogenesis of these disorders provides unique insights into the regulation of innate immunity. Diagnosis relies on clinical acumen and is supported by genetic testing. With the exception of FMF, which is prevalent in populations originating from the Mediterranean, these syndromes are rare and easily overlooked in the investigation of recurrent fevers. Disease severity varies from mild to life threatening, and one of the most feared complications is AA amyloidosis. Effective therapies are available for many of the syndromes, including colchicine, IL-1 blockade and anti-TNF therapies, and there is an increasing interest in blocking interferon pathways.

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DOI: 10.1016/j.berh.2017.12.001

PMID: 29773275 [Indexed for MEDLINE]

303. Best Pract Res Clin Rheumatol. 2017 Aug;31(4):505-516. doi: 10.1016/j.berh.2018.02.002. Epub 2018 Mar 21.

Systemic juvenile idiopathic arthritis: New insights into pathogenesis and cytokine directed therapies.

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Systemic juvenile idiopathic arthritis (sJIA) is considered as a polygenic autoinflammatory disease. The prominent systemic clinical features, the marked elevation of inflammatory markers, and the absence of autoantibodies make this disease very different from the other juvenile idiopathic arthritis (JIA) forms. Innate immune mechanisms appear to play a central role: the overproduction of inflammatory cytokines of innate immunity is a typical feature of sJIA. Increased understanding of the role of these cytokines has been translated into therapeutic approaches. Indeed, remarkable results have been observed with interleukin-1 (IL-1) and interleukin-6 (IL-6) inhibitors both in clinical trials and in real life. Other inhibitors of these cytokines will be available in the near future, thereby increasing the therapeutic armamentarium. A better understanding of the pathophysiology of sJIA is still needed to identify IL-1 or IL-6 responders, define a potential window of opportunity for early cytokine blockade, and identify a targeted treatment for macrophage activation syndrome. Additional therapeutic targets are needed for a small proportion of patients who do not respond to either IL-1 or IL-6 inhibition.

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DOI: 10.1016/j.berh.2018.02.002

PMID: 29773270 [Indexed for MEDLINE]

304. J Med Case Rep. 2018 May 18;12(1):130. doi: 10.1186/s13256-018-1691-2.

Long-term familial Mediterranean fever remission on successful hepatitis C virus treatment in a patient not responding to colchicine: a case report.

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**BACKGROUND:** Familial Mediterranean fever is an autosomal recessive disorder characterized by periodic febrile attacks of aseptic serositis and/or arthritis.

The main treatment is colchicine which prevents attacks in the majority of patients except for a group of colchicine-resistant cases. Chronic hepatitis C is a viral infection causing chronic inflammation of liver tissue (hepatitis) which ultimately progresses to fibrosis and liver cirrhosis with a high chance of hepatocellular carcinoma. However, we found no data in the literature concerning the impact of hepatitis C on the course of attacks of familial Mediterranean fever.

**CASE PRESENTATION:** We report a case of a 21-year-old white woman with familial Mediterranean fever who had not been responding to a high dose of colchicine (2 mg/day). She presented to our clinic with a finding of chronic hepatitis C genotype 3 infection. After successful antiviral therapy with peginterferon and ribavirin, she became attack-free for 2 years and went on to a lower dose of colchicine.

**CONCLUSIONS:** This unusual case illustrates complete resolution of attacks of autoinflammatory disease after drug-induced clearance of chronic hepatitis C infection. Coexisting infections should be viewed as potentially altering the course of autoinflammatory disorders, and any attempt to cure the infections should be made in order to gain an added value of benefiting the chronic disease. This case highlights the interrelation of external pathogen-related and genetically inherited alterations in immunity and the importance of considering the whole spectrum of possible causative factors rather than implementing separate guidelines in order to achieve best quality of medical care in any given patient.

DOI: 10.1186/s13256-018-1691-2

PMCID: PMC5958404

PMID: 29773081 [Indexed for MEDLINE]

305. Clin Rheumatol. 2018 May 17. doi: 10.1007/s10067-018-4119-x. [Epub ahead of print]

Safety profile of the interleukin-1 inhibitors anakinra and canakinumab in real-life clinical practice: a nationwide multicenter retrospective observational study.

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A few studies have reported the safety profile of interleukin (IL)-1 blockers from real life. The aim of this study is to describe anakinra (ANA) and canakinumab (CAN) safety profile in children and adults, based on data from a real-life setting. Demographic, clinical, and therapeutic data from patients treated with ANA and CAN were retrospectively collected and analyzed. Four hundred and seventy five patients were enrolled; ANA and CAN were prescribed in 421 and 105 treatment courses, respectively. During a mean follow-up of  $24.39 \pm 27.04$  months, 89 adverse events (AE) were recorded; 13 (14.61%) were classified as serious AE (sAE). The overall estimated rate of AE and sAE was 8.4 per 100 patients/year. Safety concerns were more frequent among patients aged  $\geq 65$  years compared with patients  $< 16$  years ( $p = 0.002$ ). No differences were detected in the frequency of safety concerns between monotherapy and combination therapy with immunosuppressants ( $p = 0.055$ ), but a significant difference was observed when injection site reactions were excluded from AE ( $p = 0.01$ ). No differences were identified in relation to gender ( $p = 0.462$ ), different lines of biologic therapy ( $p = 0.775$ ), and different dosages ( $p = 0.70$  ANA;  $p = 0.39$  CAN). The overall drug retention rate was significantly different according to the occurrence of safety concerns ( $p$  value  $< 0.0001$ ); distinguishing between ANA and CAN, significance was maintained only for ANA ( $p < 0.0001$  ANA;  $p > 0.05$  CAN). Treatment duration was the only variable associated with onset of AE (OR = 0.399 [C.I. 0.250-0.638],  $p = 0.0001$ ). ANA and CAN have shown an excellent safety profile; the risk for AE and sAE tends to decrease over time from the start of IL-1 inhibition.

DOI: 10.1007/s10067-018-4119-x

PMID: 29770930

306. N Engl J Med. 2018 May 17;378(20):1908-1919. doi: 10.1056/NEJMoa1706314.

Canakinumab for the Treatment of Autoinflammatory Recurrent Fever Syndromes.

De Benedetti F(1), Gattorno M(1), Anton J(1), Ben-Chetrit E(1), Frenkel J(1), Hoffman HM(1), Koné-Paut I(1), Lachmann HJ(1), Ozen S(1), Simon A(1), Zeff A(1), Calvo Penades I(1), Moutschen M(1), Quartier P(1), Kasapcopur O(1), Shcherbina A(1), Hofer M(1), Hashkes PJ(1), Van der Hilst J(1), Hara R(1), Bujan-Rivas S(1), Constantin T(1), Gul A(1), Livneh A(1), Brogan P(1), Cattalini M(1), Obici L(1), Lheritier K(1), Speziale A(1), Junge G(1).

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**BACKGROUND:** Familial Mediterranean fever, mevalonate kinase deficiency (also known as the hyperimmunoglobulinemia D syndrome), and the tumor necrosis factor receptor-associated periodic syndrome (TRAPS) are monogenic autoinflammatory diseases characterized by recurrent fever flares.

**METHODS:** We randomly assigned patients with genetically confirmed colchicine-resistant familial Mediterranean fever, mevalonate kinase deficiency, or TRAPS at the time of a flare to receive 150 mg of canakinumab subcutaneously or placebo every 4 weeks. Patients who did not have a resolution of their flare received an add-on injection of 150 mg of canakinumab. The primary outcome was complete response (resolution of flare and no flare until week 16). In the subsequent phase up to week 40, patients who had a complete response underwent a second randomization to receive canakinumab or placebo every 8 weeks. Patients who underwent a second randomization and had a subsequent flare and all other patients received open-label canakinumab.

**RESULTS:** At week 16, significantly more patients receiving canakinumab had a complete response than those receiving placebo: 61% vs. 6% of patients with colchicine-resistant familial Mediterranean fever ( $P<0.001$ ), 35% versus 6% of those with mevalonate kinase deficiency ( $P=0.003$ ), and 45% versus 8% of those with TRAPS ( $P=0.006$ ). The inclusion of patients whose dose was increased to 300 mg every 4 weeks yielded a complete response in 71% of those with colchicine-resistant familial Mediterranean fever, 57% of those with mevalonate kinase deficiency, and 73% of those with TRAPS. After week 16, an extended dosing regimen (every 8 weeks) maintained disease control in 46% of patients with colchicine-resistant familial Mediterranean fever, 23% of those with mevalonate kinase deficiency, and 53% of those with TRAPS. Among patients who received canakinumab, the most frequently reported adverse events were infections (173.3, 313.5, and 148.0 per 100 patient-years among patients with colchicine-resistant familial Mediterranean fever, those with mevalonate kinase deficiency, and those with TRAPS, respectively), with a few being serious infections (6.6, 13.7, and 0.0 per 100 patient-years).

**CONCLUSIONS:** In this trial, canakinumab was effective in controlling and preventing flares in patients with colchicine-resistant familial Mediterranean



fever, mevalonate kinase deficiency, and TRAPS. (Funded by Novartis; CLUSTER ClinicalTrials.gov number, NCT02059291 ).

DOI: 10.1056/NEJMoa1706314

PMID: 29768139 [Indexed for MEDLINE]

307. Clin Rheumatol. 2018 May 16. doi: 10.1007/s10067-018-4145-8. [Epub ahead of print]

Resolution of femoral metaphyseal dysplasia in CINCA syndrome after long-term treatment with interleukin-1 blockade.

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Chronic infantile neurological cutaneous articular (CINCA) syndrome is a rare autoinflammatory disorder driven by uncontrolled hypersecretion of interleukin (IL)-1, which can be clinically depicted by striking cutaneous, neurologic, and skeletal features. Little is known about the exact pathogenesis of CINCA bone disease, which mainly involves the knees. We report a 20-year-old CINCA patient, who was consecutively treated firstly with anakinra, started at 7 years, then with full dose canakinumab, started at 17 years, focusing on the typical bone abnormalities of the syndrome: the comparison of radiographs of knees performed at 7 and 20 years has shown the disappearance of a typical metaphyseal dysplasia occurring in the femurs of this CINCA patient, regularly treated with IL-1 blockade for a period of 13 years. A review of the medical literature reveals poor information on the skeletal response of CINCA syndrome to IL-1-inhibiting therapies. This contribution confirms the protean striking effects of IL-1 blockade in this peculiar autoinflammatory disorder, showing for the first time

the reversal of the characteristic CINCA metaphyseal dysplasia over long-term treatment.

DOI: 10.1007/s10067-018-4145-8

PMID: 29766377

308. Clin Rheumatol. 2018 May 15. doi: 10.1007/s10067-018-4133-z. [Epub ahead of print]

Efficacy of adalimumab and infliximab in recalcitrant retinal vasculitis inadequately responsive to other immunomodulatory therapies.

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The primary aim of the study was to evaluate the efficacy of tumor necrosis factor (TNF)- $\alpha$  blockers adalimumab (ADA) and infliximab (IFX) in refractory sight-threatening retinal vasculitis (RV) during a 12-month follow-up period. Secondary aims were to evaluate (i) any impact of concomitant conventional disease-modifying anti-rheumatic drugs (cDMARDs) and different lines of biologic therapy; (ii) any difference in terms of efficacy between ADA and IFX; (iii) consequences of biotherapies on the best-corrected visual acuity (BCVA); (iv) corticosteroid-sparing effect; and (v) ocular complications during anti-TNF- $\alpha$  treatment. Demographic, clinical, and therapeutic data were retrospectively collected from the medical records and statistically analyzed. Forty-eight patients (82 eyes) were recruited, 22 (45.8%) of which received IFX and 26 (54.2%) ADA. The percentages of patients achieving RV remission within 3 and 12 months were 54 and 86%, respectively. A significant decrease in RV detection was identified from baseline to 3-month ( $p < 0.0001$ ) and 12-month ( $p < 0.0001$ ) assessments and between 3-month and 12-month visits ( $p = 0.004$ ). No differences were identified in terms of RV resolution between (i) patients undergoing monotherapy and those co-administered with cDMARDs at 3-month ( $p = 0.560$ ) and 12-month ( $p = 0.611$ ) follow-up; (ii) biologic-naïve patients and those already exposed to other biologics at 3-month ( $p = 0.497$ ) and 12-month ( $p > 0.99$ ) visits; and (iii) patients treated with ADA and those treated with IFX ( $p = 0.357$ ). During the study period, a statistically significant corticosteroid-sparing effect was observed ( $p = 0.0002$ ), while BCVA values did not significantly change ( $p = 0.950$ ). Anti-TNF- $\alpha$  monoclonal antibodies have proved excellent results in patients with recalcitrant sight-threatening RV.

DOI: 10.1007/s10067-018-4133-z

PMID: 29766375

309. Cell Biol Int. 2018 Aug;42(8):1079-1084. doi: 10.1002/cbin.10988. Epub 2018 Jun 19.

Colchicine, a microtubule-disassembling drug, in the therapy of cardiovascular diseases.

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*Colchicum autumnale*, from which colchicine has been isolated more than 100 years ago, has been used as a treatment for pain and swelling for thousands of years. It is one of the few drugs known from that time period whose use has survived to modernity. Over the past decades, advances in the knowledge of (i) cytoskeletal microtubules (MT), and (ii) anti-inflammatory and anti-fibrotic effects of colchicine, a classical MT-disassembling (tubulin-targeting) agent, have led to potential new uses for this very old drug extended beyond acute gouty arthritis and familial Mediterranean fever. Here, in brief, I present the Bulgarian contribution to possible potential of colchicine in the therapy of cardiovascular diseases that has emerged in the early 1970s in the Laboratory of Electron Microscopy, Medical Institute, Varna, Bulgaria, studying the secretory function of vascular smooth muscle cells. From this time onward, low-dose colchicine (0.5-1.0 mg/daily) was increasingly administered orally for therapy of cardiovascular diseases such as acute coronary syndromes, postoperative atrial fibrillation (in cardiac surgery), pericarditis, cardiac hypertrophy-associated heart failure, restenosis after angioplasty, and systemic necrotizing vasculitis. Thus, colchicine might be a new tool in the present therapeutic armamentarium for cardiovascular diseases. It is simply an example of MT-disassembling drugs. Further studies will definitely be required before gaining real confidence in this kind of antitubulin pharmacology and therapy. This may lead to developing new and more specific antitubulins for cardiovascular diseases.

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DOI: 10.1002/cbin.10988

PMID: 29762881 [Indexed for MEDLINE]

310. J Periodontol. 2018 Sep;89(9):1112-1120. doi: 10.1002/JPER.17-0638. Epub 2018 Aug 13.

The evaluation of salivary oxidative stress in patients with familial Mediterranean fever and chronic periodontitis.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is an inherent autoinflammatory disease and have a high prevalence in Mediterranean countries. The aim of this study was to evaluate salivary levels of oxidative stress parameters in patients with FMF and chronic periodontitis.

**METHODS:** The study population consists of 81 patients with FMF and 85 systemically healthy controls. The test and control groups were classified as chronic periodontitis and periodontally healthy [FMF-periodontitis (n = 37); FMF-periodontally healthy (n = 44); systemically healthy-periodontitis (n = 37); systemically and periodontally healthy (n = 48)]. Total salivary samples were collected. Clinical periodontal parameters including plaque index, gingival index (GI), probing depth (PD), the percentage of bleeding on probing (BOP%), and clinical attachment level (CAL), were measured. Salivary total antioxidant status (TAS), total oxidant status (TOS), 8-hydroxydeoxyguanosine (8-OHdG), malondialdehyde (MDA), and oxidative stress index (OSI) were evaluated.

**RESULTS:** The FMF-periodontitis group had significantly higher levels of 8-OHdG, MDA, and OSI than that of the FMF-periodontally healthy group. In the FMF-periodontitis group, PD, 8-OHdG, MDA, and OSI levels were significantly higher than in the systemically healthy-periodontitis group ( $P = 0.035$ ,  $P = 0.000$ ,  $P = 0.000$ , and  $P = 0.000$ , respectively). 8-OHdG values were significantly correlated with BOP% and GI, and TOS values were significantly correlated with PD and CAL in the FMF-periodontitis group.

**CONCLUSIONS:** In the presence of FMF and chronic periodontitis, there were increased salivary levels of oxidative stress. Thus, oxidative stress could be an important inflammatory mechanism in the FMF and chronic periodontitis. Further studies need to clarify the oxidative mechanisms of FMF and chronic periodontitis.

311. Arch Argent Pediatr. 2018 Jun 1;116(3):e385-e391. doi: 10.5546/aap.2018.eng.e385.

MEFV gene mutations and clinical course in pediatric patients with Henoch-Schönlein purpura.

[Article in English, Spanish; Abstract available in Spanish from the publisher]

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**OBJECTIVE:** To determine the frequency of the MEFV gene mutations in pediatric patients diagnosed with HSP and to assess the effect of the MEFV gene mutations on their prognosis. **Material and Methods.** Ccross-sectional study; pediatric patients between 2-11 years diagnosed with HSP were included. These cases were investigated for 6 MEFV gene mutations (M694V, M680I, A744S, R202Q, K695R, E148Q).

**RESULTS:** Eighty cases were included in the study of which 55% were male (n= 44). The mean age was  $6.44 \pm 2.52$  years. Disease recurrence occurred in 9 patients, invagination in 5 patients and convulsion in 1 patient during follow-up.

Approximately half of the patients received steroids. The MEFV gene mutations was not detected in 44 (55%) of the patients. There was a heterozygous mutation in 19 (22%). E148Q was found in 8 patients, M694V in 5 patients, A744S in 4 patients, and the R202Q heterozygous mutation in 2 patients. The M608I homozygous mutation was detected in 1 patient and the M694V homozygous mutation in 1 patient. The compound heterozygous MEFV gene mutations was found in 15 patients. The presence of the MEFV gene mutations was not correlated with the frequency of renal and

gastrointestinal involvement and prognosis, the development of complications and the use of steroids.

CONCLUSION: The presence of the MEFV gene mutations does not correlate with the clinical course and complication in Turkish pediatric patients with HSP.

Publisher: **Objetivo.** Determinar la frecuencia de mutaciones del gen MEFV en niños con diagnóstico de púrpura de Schönlein-Henoch y evaluar el efecto que tienen en el pronóstico. **Materiales y métodos.** Estudio transversal que incluyeron pacientes pediátricos de entre 2 y 11 años, con diagnóstico de púrpura de Schönlein-Henoch. Se estudiaron para detectar 6 mutaciones en el gen MEFV (M694V, M680I, A744S, R202Q, K695R y E148Q). **Resultados.** Se incluyeron ochenta pacientes, de los cuales el 55% eran de sexo masculino (n= 44). La media de edad fue 6,44 ± 2,52 años. Durante el seguimiento, 9 pacientes presentaron recurrencia de la enfermedad, 5 sufrieron invaginación intestinal y 1 paciente tuvo convulsiones. Aproximadamente la mitad de los pacientes recibió corticoides. En 44 pacientes (55%) no se detectaron mutaciones en el gen MEFV. En 19 pacientes (22%) hubo una mutación heterocigota. Se encontró E148Q en 8 pacientes, M694V en 5 pacientes, A744S en 4 pacientes y la mutación heterocigota R202Q en 2 pacientes. En 1 paciente se detectó la mutación heterocigota M608I y en otro paciente se encontró la mutación homocigota M694V. En 15 pacientes se encontraron mutaciones heterocigotas compuestas en el gen MEFV. Las mutaciones en el gen MEFV no se correlacionaban con la frecuencia de compromiso renal y gastrointestinal ni con el pronóstico, desarrollo de complicaciones y uso de corticoides. **Conclusiones.** Las mutaciones en el gen MEFV no se correlacionan con la evolución clínica ni con las complicaciones en pacientes pediátricos con púrpura de Schönlein-Henoch en Turquía.

Sociedad Argentina de Pediatría.

DOI: 10.5546/aap.2018.eng.e385

PMID: 29756710

312. J Allergy Clin Immunol. 2018 Nov;142(5):1589-1604.e11. doi: 10.1016/j.jaci.2018.04.023. Epub 2018 May 8.

Mutations affecting the actin regulator WD repeat-containing protein 1 lead to aberrant lymphoid immunity.

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**BACKGROUND:** The actin-interacting protein WD repeat-containing protein 1 (WDR1) promotes cofilin-dependent actin filament turnover. Biallelic WDR1 mutations have been identified recently in an immunodeficiency/autoinflammatory syndrome with aberrant morphology and function of myeloid cells.

**OBJECTIVE:** Given the pleiotropic expression of WDR1, here we investigated to what extent it might control the lymphoid arm of the immune system in human subjects.

**METHODS:** Histologic and detailed immunologic analyses were performed to elucidate the role of WDR1 in the development and function of B and T lymphocytes.

**RESULTS:** Here we identified novel homozygous and compound heterozygous WDR1 missense mutations in 6 patients belonging to 3 kindreds who presented with respiratory tract infections, skin ulceration, and stomatitis. In addition to defective adhesion and motility of neutrophils and monocytes, WDR1 deficiency was associated with aberrant T-cell activation and B-cell development. T lymphocytes appeared to develop normally in the patients, except for the follicular helper T-cell subset. However, peripheral T cells from the patients accumulated atypical actin structures at the immunologic synapse and displayed reduced calcium flux and mildly impaired proliferation on T-cell receptor stimulation. WDR1 deficiency was associated with even more severe abnormalities of the B-cell compartment, including peripheral B-cell lymphopenia, paucity of B-cell progenitors in the bone marrow, lack of switched memory B cells, reduced clonal diversity, abnormal B-cell spreading, and increased apoptosis on B-cell receptor/Toll-like receptor stimulation.

**CONCLUSION:** Our study identifies a novel role for WDR1 in adaptive immunity, highlighting WDR1 as a central regulator of actin turnover during formation of the B-cell and T-cell immunologic synapses.

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DOI: 10.1016/j.jaci.2018.04.023

PMID: 29751004

313. J Pediatric Infect Dis Soc. 2018 May 9;7(suppl\_1):S2-S5. doi: 10.1093/jpids/piy008.

Chronic Granulomatous Disease: Epidemiology, Pathophysiology, and Genetic Basis of Disease.

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Chronic Granulomatous Disease is one of the classic primary immunodeficiencies of childhood. While the incidence and severity of bacterial and fungal infections have been greatly reduced in this patient population, much remains to be learned about the pathophysiology of the disease, particularly for autoinflammatory manifestations. In this review, we examine the epidemiology, pathophysiology, and genetic basis for CGD.

DOI: 10.1093/jpids/piy008

PMCID: PMC5946813

PMID: 29746675 [Indexed for MEDLINE]

314. Clin Exp Rheumatol. 2018 Jan-Feb;36 Suppl 110(1):54-60. Epub 2018 May 3.

Renal involvement in autoinflammatory diseases and inflammasome-mediated chronic kidney damage.

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Unprovoked activation of innate immune pathways and increased secretion of interleukin (IL)-1 $\beta$  and IL-18 are responsible for the protean clinical manifestations and the marked inflammatory response that characterise most hereditary autoinflammatory disorders. The kidney is a major target organ of this inflammatory process. The deposition of the acute-phase reactant serum amyloid A (SAA) as amyloid causes progressive glomerular and vascular damage and leads to organ failure. In this review we focus on the potential impact of hereditary autoinflammatory diseases on renal function, provide red flags that may guide the clinical suspicion of amyloid kidney damage and discuss the relevance of close renal monitoring for early diagnosis and prompt treatment. Moreover, NLRP3 inflammasome activation is increasingly recognised to play a key causative role in the pathogenesis of several chronic kidney diseases in which activation of caspase-1 and the proteolytic cleavage of IL-1 $\beta$  and IL-18 into their biologically active forms mediate glomerular and tubulointerstitial damage. Although much of the knowledge about the role of the inflammasome in kidney injury has been mostly gathered in experimental models, inhibition of IL-1 is also becoming an attractive potential therapeutic target in a variety of chronic renal disorders with a substantial inflammatory component.

PMID: 29742060 [Indexed for MEDLINE]

315. Clin Exp Rheumatol. 2018 Jan-Feb;36 Suppl 110(1):39-43. Epub 2018 May 3.

Autoinflammatory diseases as a cause of acute abdominal pain in the emergency department.

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Autoinflammatory diseases (AIDs) usually present with acute abdominal pain and fever, both of which are also the main causes of referral in the emergency department. As some patients with acute abdominal pain may be discharged from the emergency department without a definitive diagnosis, it is not surprising that, due to their rarity, most cases of AID remain undiagnosed or are misdiagnosed as acute appendicitis. Indeed, the diagnosis of familial Mediterranean fever and autoinflammatory syndromes requires a high index of suspicion and careful assessment of clinical history. Age of onset and clinical features, in particular the self-limiting acute attacks, together with prodromal symptoms and trigger factors, are useful to suspect these disorders. In addition, discrepancies in laboratory tests that show an increase in acute phase reactants as well as diagnostic imaging, which usually fails to show specific abdominal disorders, may help in the identification of patients who require genetic testing to confirm a diagnosis of AID.

PMID: 29742059 [Indexed for MEDLINE]

316. Clin Exp Rheumatol. 2018 Jan-Feb;36 Suppl 110(1):61-67. Epub 2018 May 3.

Neurological manifestations in autoinflammatory diseases.

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Autoinflammatory diseases (AIDs) are a distinct group of diseases characterised by a dysregulation of the innate immune response leading to systemic inflammation. The clinical spectrum of these conditions is extremely variable and

possibly every system and tissue can be involved, including the central nervous system (CNS). Indeed, neurological manifestations may dominate the clinical picture from disease onset in some rare conditions. However, the involvement of the CNS in AIDs is not a disease in itself, but represents a rare complication which is consequent to a systemic or local immune response, mainly involving cells of the innate immunity. This review will describe neurological manifestations associated with AIDs, including: chronic aseptic meningitis and brain atrophy, sensori-neural hearing loss, early-onset haemorrhagic and ischaemic strokes, mental retardation, cerebellitis, and ataxia, and severe encephalopathy with brain calcifications.

PMID: 29742058 [Indexed for MEDLINE]

317. Clin Exp Rheumatol. 2018 Jan-Feb;36 Suppl 110(1):44-53. Epub 2018 May 3.

The eye involvement in monogenic autoinflammatory diseases: literature review and update.

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Monogenic autoinflammatory diseases (AIDs) are rare entities characterised by improper activation of the innate immune system. This in turn determines recurrent episodes of systemic inflammation characterised by fever, which is variously combined with a wide range of inflammatory manifestations involving the skin, joints, serous membranes, gastrointestinal tract, and central nervous system. As shown by research efforts conducted during the last decade, the eye is not exempt from the systemic inflammatory process and may be involved in almost all of the most frequent AIDs, with several distinct peculiarities. Ocular affections may severely impact patients' quality of life due to orbital pain, impairment of visual acuity, and/ or long-term, sight-threatening complications. Consequently, in the context of a multidisciplinary team, ophthalmologists should be aware of ocular manifestations related to these disorders as they may have a dominant diagnostic weight in patients with a challenging presentation as well as a salient role in therapeutic choice in sight-threatening situations. This review describes a variety of aspects of ophthalmologic involvement in AIDs, looking at both well-recognised eye manifestations as well as rarely reported ocular presentations, with a particular focus on the recent literature.

PMID: 29742057 [Indexed for MEDLINE]

318. Clin Exp Rheumatol. 2018 Jan-Feb;36 Suppl 110(1):32-38. Epub 2018 May 3.

A dermatologic perspective on autoinflammatory diseases.

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Autoinflammatory diseases (AIDs) encompass a heterogeneous group of disorders pathogenetically related to an abnormal activation of the innate immunity and

clinically characterised by aseptic inflammation in the affected organs in the absence of high titer of circulating autoantibodies or autoreactive T cells. In classic monogenic AIDs, the skin is frequently involved with a wide range of cutaneous lesions. Monogenic AIDs result from different mutations in a single gene, which regulates the innate immunity. These mutations cause an uncontrolled activation of the inflammasome, leading to an overexpression of interleukin (IL)-1 $\beta$ . IL-1 $\beta$  is the pivotal cytokine which is responsible for the exaggerated production of cytokines and chemokines that induce the recruitment of neutrophils, key cells in autoinflammation. Paradigmatic autoinflammatory forms are the cryopyrin-associated periodic syndromes (CAPS), whose skin involvement consists of urticarial lesions. Similar IL-1 $\beta$ -mediated autoinflammatory pathomechanisms also occur in deficiency of IL-1 receptor antagonist (DIRA) and deficiency of IL-36 receptor antagonist (DITRA), whose cutaneous appearance is characterised by pustular lesions, as well as in pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome. Pyoderma gangrenosum, which is the cutaneous hallmark of the PAPA syndrome, is a prototypic neutrophil-mediated skin disease, manifesting as single or multiple ulcers with undermined, raised erythematous to violaceous borders. This review is focused on the CAPS, DIRA/DITRA and PAPA syndromes with emphasis on their cutaneous manifestations, as well as their histology and pathophysiology.

PMID: 29742056 [Indexed for MEDLINE]

319. Clin Exp Rheumatol. 2018 Jan-Feb;36 Suppl 110(1):25-31. Epub 2018 May 3.

Musculoskeletal manifestations in hereditary periodic fever syndromes.

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Monogenic autoinflammatory diseases (AIDs) are a group of inflammatory disorders induced by deregulation of the innate immune system and characterised by inflammatory bouts with fever as well as a large spectrum of other possible manifestations involving most organs and tissues. In this context, musculoskeletal manifestations represent a frequent finding in the clinical picture of patients with AIDs and may range from less severe affections including myalgia and arthralgia to severe arthritis, muscle fasciitis, bone erosions, and joint deformities. Therefore, as diagnostic suspicions originates from a careful and detailed clinical evaluation, physicians dealing with mono- genic AIDs should bear in mind their possible muscle and joint manifestations, some of which are typical and very useful for diagnostic purposes. Indeed, their prompt recognition may reduce the diagnostic delay thus allowing an early and appropriate therapeutic management. For these reasons, the present review is aimed at providing a wide overview on the different patterns of joint and muscle affections in the four main monogenic AIDs.

PMID: 29742055 [Indexed for MEDLINE]

320. Clin Exp Rheumatol. 2018 Jan-Feb;36 Suppl 110(1):10-24. Epub 2018 May 3.

Overview of fever of unknown origin in adult and paediatric patients.

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Fever of unknown origin (FUO) can be caused by a wide group of diseases, and can include both benign and serious conditions. Since the first definition of FUO in the early 1960's, several updates to the definition, diagnostic and therapeutic approaches have been proposed. This review outlines a case report of an elderly Italian male patient with high fever and migrating arthralgia who underwent many procedures and treatments before a final diagnosis of Adult-onset Still's disease was achieved. This case report highlights the difficulties in diagnosing certain causes of FUO that requires a very high index of suspicion. The main causes of FUO in paediatric and adult patients will be reviewed here, underlying the fact that a physician should also consider the possibility that a patient with FUO may have a monogenic autoinflammatory disease (AID). The identification of AIDs requires a careful evaluation of both history and clinical details that may reveal important clues to identify the correct aetiology. We also provide a comprehensive account of specific signs and symptoms that could suggest possible diagnoses and guide the work-up of FUO and non-genetic periodic fevers in children.

PMID: 29742054 [Indexed for MEDLINE]

321. Clin Exp Rheumatol. 2018 Jan-Feb;36 Suppl 110(1):3-9. Epub 2018 May 3.

Updated overview of molecular pathways involved in the most common monogenic autoinflammatory diseases.

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An apparently unprovoked recurrent inflammation is the quintessential hallmark of autoinflammatory diseases (AIDs), a large and heterogeneous group of disorders in which there is poor regulation of the innate immune system with no clearly demonstrated autoimmune machinery involvement. Innate immunity pathways are diverse and our understanding of their molecular composition and function is continuously expanding. The impaired immune responses we observe in monogenic AIDs, mostly in the hereditary periodic fever syndromes, is officiated by target molecules of microbial origin (pathogen-associated molecular patterns) and also host molecules (danger-associated molecular patterns). Further crucial components of innate immune mechanisms that contribute differently in the deregulated inflammatory patterns of different AIDs include Toll-like receptors, Nod-like receptors, scaffolding proteins (such as the caspase recruitment domain of proteins), cytosolic DNA-sensing molecules, inflammatory multi-protein complexes (referred to as inflammasomes), complement system, and others. In recent years, the knowledge of protean molecular pathways responsible for the most common monogenic AIDs has expanded, in parallel with very recent extraordinary technological advances, allowing the identification and characterisation of some unknown aspects of the innate immunity. This review will list and describe the most common monogenic febrile syndromes belonging to AIDs and will focus on current insights dealing with their pathologic processes.

PMID: 29742053 [Indexed for MEDLINE]

322. J Clin Med. 2018 May 7;7(5). pii: E105. doi: 10.3390/jcm7050105.

The Frequency of MEFV Gene Mutations and Genotypes in Sanliurfa Province, South-Eastern Region of Turkey, after the Syrian Civil War by Using Next Generation Sequencing and Report of a Novel Exon 4 Mutation (I423T).

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**BACKGROUND:** Familial Mediterranean Fever (FMF) is a genetic disorder characterized by recurrent episodes of fever and abdominal pain. Mutations in the Mediterranean fever (MEFV) gene are localized on the p arm of chromosome 16. Over 333 MEFV sequence variants have been identified so far in FMF patients, which occur mostly in the 2nd and 10th exons of the gene.

**METHODS:** In this study, 296 unrelated patients with clinical suspicion of FMF, which were admitted during January–December 2017, were retrospectively reviewed to identify the frequency of MEFV gene mutations by using next generation sequencing.

**RESULTS:** Eighteen different mutations, 45 different genotypes and a novel exon 4 (I423T) mutation were identified in this study. This mutation is the fourth mutation identified in exon 4. The most frequent mutation was R202Q, followed by M694V, E148Q, M680I, R761H, V726A and R354W.

**CONCLUSIONS:** One of the most important aims of this study is to investigate the MEFV mutation type and genotype of migrants coming to Sanliurfa after the civil war of Syria. This study also examines the effect of the condition on the region's gene pool and the distribution of different types of mutations. Our results indicated that MEFV mutations are highly heterogeneous in our patient population, which is consistent with the findings of other studies in our region. Previously used methods, such as Restriction Fragment Length Polymorphism (RFLP), do not define uncommon or especially novel mutations. Therefore, Next Generation Sequencing (NGS) analysis of the MEFV gene could be useful for finding novel mutations, except for those located on exon 2 and 10.

DOI: 10.3390/jcm7050105

PMCID: PMC5977144

PMID: 29735907

323. Gerodontology. 2018 Jun;35(2):139-142. doi: 10.1111/ger.12320.

Adult-onset Still's disease initially thought to be an odontogenic infection: A case report.

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**OBJECTIVE:** To present a case of Adult-onset Still's disease (AOSD) initially suspected to be odontogenic inflammation.

**BACKGROUND:** Adult-onset Still's disease is a rare, complex autoinflammatory disease and a known cause of fever of unknown origin.

**MATERIALS AND METHODS:** The patient had both a fever and dental pain. Following meticulous examination, the patient was diagnosed with AOSD.

**CONCLUSION:** Clinicians should keep in mind that a patient such as AOSD may visit their clinics.

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DOI: 10.1111/ger.12320

PMID: 29733534 [Indexed for MEDLINE]

324. Rheumatol Int. 2018 Jul;38(7):1179-1190. doi: 10.1007/s00296-018-4039-8. Epub 2018 May 7.

Coronary flow reserve in systemic rheumatic diseases: a systematic review and meta-analysis.

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Coronary flow reserve (CFR), a measure of both obstructive coronary artery disease and microvascular dysfunction, has been evaluated in systemic rheumatic diseases (RDs), but a comprehensive critical appraisal of the available evidence is lacking. The objective of this study is to conduct a systematic review and meta-analysis of studies with small sample size investigating the associations between the presence of RDs and CFR to increase statistical power and accuracy. PubMed, Web of Science, Scopus, and Google Scholar, from inception to March 2018, were searched for studies reporting on CFR in RDs in comparison to healthy subjects. Standardized mean differences (SMD) with 95% confidence intervals (CI) were calculated. Meta-regressions and sensitivity analyses assessed study heterogeneity by type of RDs, age, traditional cardiovascular risk factors, systemic inflammation, and methodology used to evaluate CFR. Twenty-one studies (709 RDs patients and 650 healthy controls) were included in the meta-analysis. Pooled results showed that CFR values were significantly lower in patients with RDs than in healthy controls (SMD = - 1.51, 95% CI - 1.91, - 1.11;  $p < 0.001$ ;  $I^2 = 90.1\%$ ,  $p < 0.001$ ). The between-group differences in CFR were not associated with inflammatory burden, age, lipids, body mass index, blood pressure, or assessment methods. Patients with prevalent autoimmune features (e.g., systemic lupus erythematosus) showed a significantly lower CFR when compared to patients with mixed autoimmune and autoinflammatory features (e.g., psoriatic arthritis). This meta-analysis showed a significant impairment in CFR in patients with RDs with respect to the general population. Differences in pathogenetic mechanisms may influence the severity of CFR impairment in RDs.

DOI: 10.1007/s00296-018-4039-8

PMID: 29732488 [Indexed for MEDLINE]

325. Clin Calcium. 2018;28(5):678-685. doi: CliCa1805678685.

[Diagnosis and treatment of rheumatoid arthritis:toward the best practice. Best practice with JAK inhibitors.]

[Article in Japanese]

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Janus kinase(JAK)inhibitor is a new orally available disease modifying anti-rheumatic drug that has shown anti-rheumatic effect resembling biologics. Clinical trials for autoinflammatory and autoimmune diseases are under investigation. Administration route is convenient compared to biologics and possess high anti-rheumatic effect, however specific side effects considered as a class-effect exists. I would like to offer the best conceivable practice with JAK inhibitors based on evidence from clinical trials and real world experiences.

DOI: CliCa1805678685

PMID: 29731464

326. Stem Cell Reports. 2018 Jun 5;10(6):1835-1850. doi: 10.1016/j.stemcr.2018.04.004. Epub 2018 May 3.

Pluripotent Stem Cell Model of Nakajo-Nishimura Syndrome Untangles Proinflammatory Pathways Mediated by Oxidative Stress.

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Nakajo-Nishimura syndrome (NNS) is an immunoproteasome-associated autoinflammatory disorder caused by a mutation of the PSMB8 gene. Although dysfunction of the immunoproteasome causes various cellular stresses attributed to the overproduction of inflammatory cytokines and chemokines in NNS, the underlying mechanisms of the autoinflammation are still largely unknown. To investigate and understand the mechanisms and signal pathways in NNS, we established a panel of isogenic pluripotent stem cell (PSC) lines with PSMB8 mutation. Activity of the immunoproteasome in PSMB8-mutant PSC-derived myeloid cell lines (MT-MLs) was reduced even without stimulation compared with non-mutant-MLs. In addition, MT-MLs showed an overproduction of inflammatory cytokines and chemokines, with elevated reactive oxygen species (ROS) and phosphorylated p38 MAPK levels. Treatment with p38 MAPK inhibitor and antioxidants decreased the abnormal production of cytokines and chemokines. The current PSC model revealed a specific ROS-mediated inflammatory pathway, providing a platform for the discovery of alternative therapeutic options for NNS and related immunoproteasome disorders.

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DOI: 10.1016/j.stemcr.2018.04.004

PMCID: PMC5989695

PMID: 29731430

327. An Bras Dermatol. 2018 Mar;93(2):191-196. doi: 10.1590/abd1806-4841.20186068.

Macrophage migration inhibitory factor as an incriminating agent in vitiligo.

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**BACKGROUND:** Vitiligo is an autoimmune skin disorder in which the loss of melanocytes is mainly attributed to defective autoimmune mechanisms and, lately, there has been more emphasis on autoinflammatory mediators. Among these is the macrophage migration inhibitory factor, which is involved in many autoimmune skin diseases. However, little is known about the contribution of this factor to vitiligo vulgaris.

**OBJECTIVE:** To determine the hypothesized role of migration inhibitory factor in vitiligo via estimation of serum migration inhibitory factor levels and migration inhibitory factor mRNA concentrations in patients with vitiligo compared with healthy controls. We also aimed to assess whether there is a relationship between the values of serum migration inhibitory factor and/or migration inhibitory factor mRNA with disease duration, clinical type and severity in vitiligo patients.

**METHODS:** Evaluation of migration inhibitory factor serum level and migration inhibitory factor mRNA expression by ELISA and real-time PCR, respectively, were performed for 50 patients with different degrees of vitiligo severity and compared to 15 age- and gender-matched healthy volunteers as controls.

**RESULTS:** There was a highly significant increase in serum migration inhibitory factor and migration inhibitory factor mRNA levels in vitiligo cases when compared to controls ( $p < 0.001$ ). There was a significant positive correlation between both serum migration inhibitory factor and migration inhibitory factor mRNA concentrations in vitiligo patients, and each of them with duration and severity of vitiligo. In addition, patients with generalized vitiligo have significantly elevated serum migration inhibitory factor and mRNA levels than control subjects.

**STUDY LIMITATIONS:** Small number of investigated subjects.

**CONCLUSIONS:** Migration inhibitory factor may have an active role in the development of vitiligo, and it may also be a useful index of disease severity. Consequently, migration inhibitory factor may be a new treatment target for vitiligo patients.



DOI: 10.1590/abd1806-4841.20186068  
PMCID: PMC5916389  
PMID: 29723363 [Indexed for MEDLINE]

328. Pathog Dis. 2018 Apr 1;76(3). doi: 10.1093/femspd/fty020.

The pyrin inflammasome: from sensing RhoA GTPases-inhibiting toxins to triggering autoinflammatory syndromes.

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Numerous pathogens including *Clostridium difficile* and *Yersinia pestis* have evolved toxins or effectors targeting GTPases from the RhoA subfamily (RhoA/B/C) to inhibit or hijack the host cytoskeleton dynamics. The resulting impairment of RhoA GTPases activity is sensed by the host via an innate immune complex termed the pyrin inflammasome in which caspase-1 is activated. The cascade leading to activation of the pyrin inflammasome has been recently uncovered. In this review, following a brief presentation of RhoA GTPases-modulating toxins, we present the pyrin inflammasome and its regulatory mechanisms. Furthermore, we discuss how some pathogens have developed strategies to escape detection by the pyrin inflammasome. Finally, we present five monogenic autoinflammatory diseases associated with pyrin inflammasome deregulation. The molecular insights provided by the study of these diseases and the corresponding mutations on pyrin inflammasome regulation and activation are presented.

DOI: 10.1093/femspd/fty020  
PMID: 29718184 [Indexed for MEDLINE]

## Therapeutic Delivery Specifications Identified Through Compartmental Analysis of a Mesenchymal Stromal Cell-Immune Reaction.

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Despite widespread preclinical success, mesenchymal stromal cell (MSC) therapy has not reached consistent pivotal clinical endpoints in primary indications of autoinflammatory diseases. Numerous studies aim to uncover specific mechanisms of action towards better control of therapy using in vitro immunomodulation assays. However, many of these immunomodulation assays are imperfectly designed to accurately recapitulate microenvironment conditions where MSCs act. To increase our understanding of MSC efficacy, we herein conduct a systems level microenvironment approach to define compartmental features that can influence the delivery of MSCs' immunomodulatory effect in vitro in a more quantitative manner than ever before. Using this approach, we notably uncover an improved MSC quantification method with predictive cross-study applicability and unveil the key importance of system volume, time exposure to MSCs, and cross-communication between MSC and T cell populations to realize full therapeutic effect. The application of these compartmental analysis can improve our understanding of MSC mechanism(s) of action and further lead to administration methods that deliver MSCs within a compartment for predictable potency.

DOI: 10.1038/s41598-018-24971-2

PMCID: PMC5931547

PMID: 29717209

330. Int Ophthalmol. 2018 Apr 30. doi: 10.1007/s10792-018-0924-0. [Epub ahead of print]

Case report: acute hydrops and spontaneous corneal perforation in a patient with keratoconus treated with colchicine for familial Mediterranean fever.

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**PURPOSE:** To report a rare case of spontaneous corneal perforation after hydrops in keratoconus patients who suffer from familial Mediterranean fever and was treated systemically with Colchicine.

**METHODS:** Case report.

**RESULTS:** We report a case of a 30-year-old male with keratoconus and familial Mediterranean fever treated with colchicine, presented with acute hydrops in his left eye, which progressed to a spontaneous corneal perforation. Attempts to treat the perforation with cyanoacrylate glue failed, and he underwent penetrating keratoplasty with an excellent visual outcome.

**CONCLUSION:** Colchicine treatment may have had a role in the pathogenesis of this rare case.

DOI: 10.1007/s10792-018-0924-0

PMID: 29713855

331. J Immunol. 2018 Jun 15;200(12):3950-3961. doi: 10.4049/jimmunol.1701643. Epub 2018 Apr 30.

REDD1/Autophagy Pathway Is Associated with Neutrophil-Driven IL-1 $\beta$  Inflammatory

## Response in Active Ulcerative Colitis.

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Infiltration of neutrophils into colonic mucosa has been associated with the severity of ulcerative colitis (UC). We investigated the effect of disease microenvironment on the release of neutrophil extracellular traps (NETs) as well as the involved mechanisms in NETosis and whether certain NET proteins are correlated with disease phenotype. Peripheral blood neutrophils, sera, and colonic tissue were collected from treatment-naïve and mesalazine-treated patients with active UC, treatment-naïve patients with active Crohn's disease, patients suffering from infectious colitis, or healthy individuals (controls). Analysis of colonic biopsy specimens and peripheral blood neutrophils for the presence of NET-related markers using immunofluorescence confocal microscopy, ELISA, immunoblotting, flow cytometry, and quantitative PCR were performed. In vitro cell and tissue culture systems were further deployed. The local inflammatory response in colon in UC, but not Crohn's disease, is characterized by the presence of NETs carrying bioactive IL-1 $\beta$  and thrombogenic tissue factor. The inflammatory environment of UC is able to induce neutrophil activation, IL-1 $\beta$  expression, and NET release, as shown both ex vivo and in vitro. REDD1 expression, as a mediator linking inflammation, autophagy, and NET release, was also specifically associated with the inflammatory response of UC. We show that

neutrophil expression of REDD1 in colon tissue and the presence of IL-1 $\beta$  in neutrophils/NETs provide candidate biomarkers for the differential diagnosis of inflammatory colitis and possible targets for the treatment of UC, suggesting that UC shares common features with autoinflammatory disorders.

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DOI: 10.4049/jimmunol.1701643

PMID: 29712770

332. Cancer Cell. 2018 May 14;33(5):862-873.e5. doi: 10.1016/j.ccell.2018.03.027. Epub 2018 Apr 26.

Extrinsic Phagocyte-Dependent STING Signaling Dictates the Immunogenicity of Dying Cells.

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The ability of dying cells to activate antigen-presenting cells (APCs) is carefully controlled to avoid unwarranted inflammatory responses. Here, we show that engulfed cells containing cytosolic double-stranded DNA species (viral or synthetic) or cyclic di-nucleotides (CDNs) are able to stimulate APCs via extrinsic STING (stimulator of interferon genes) signaling, to promote antigen cross-presentation. In the absence of STING agonists, dying cells were ineffectual in the stimulation of APCs in trans. Cytosolic STING activators, including CDNs, constitute cellular danger-associated molecular patterns (DAMPs) only generated by viral infection or following DNA damage events that rendered tumor cells highly immunogenic. Our data shed insight into the molecular mechanisms that drive appropriate anti-tumor adaptive immune responses, while averting harmful autoinflammatory disease, and provide a therapeutic strategy for

cancer treatment.

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DOI: 10.1016/j.ccell.2018.03.027

PMCID: PMC6177226 [Available on 2019-05-14]

PMID: 29706455

333. Int Immunol. 2018 Apr 25;30(5):181-182. doi: 10.1093/intimm/dxy022.

Introduction: Autoinflammatory Syndromes Special Issue-hidden mysteries in the corners of autoinflammation.

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DOI: 10.1093/intimm/dxy022

PMCID: PMC6281335 [Available on 2019-04-25]

PMID: 29697820

334. Front Immunol. 2018 Apr 11;9:735. doi: 10.3389/fimmu.2018.00735. eCollection 2018.

Cutaneous Vasculitis and Recurrent Infection Caused by Deficiency in Complement Factor I.

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Cutaneous leukocytoclastic vasculitis arises from immune complex deposition and dysregulated complement activation in small blood vessels. There are many causes, including dysregulated host response to infection, drug reactions, and various autoimmune conditions. It is increasingly recognised that some monogenic autoinflammatory diseases cause vasculitis, although genetic causes of vasculitis are extremely rare. We describe a child of consanguineous parents who presented with chronic cutaneous leukocytoclastic vasculitis, recurrent upper respiratory tract infection, and hypocomplementaemia. A homozygous p.His380Arg mutation in the complement factor I (CFI) gene CFI was identified as the cause, resulting in complete absence of alternative complement pathway activity, decreased classical complement activity, and low levels of serum factor I, C3, and factor H. C4 and C2 levels were normal. The same homozygous mutation and immunological defects were also identified in an asymptomatic sibling. CFI deficiency is thus now added to the growing list of monogenic causes of vasculitis and should always be considered in vasculitis patients found to have persistently low levels of C3 with normal C4.

DOI: 10.3389/fimmu.2018.00735

PMCID: PMC5904195

PMID: 29696024

335. Cell Rep. 2018 Apr 24;23(4):1112-1123. doi: 10.1016/j.celrep.2018.03.115.

Pro-inflammation Associated with a Gain-of-Function Mutation (R284S) in the Innate Immune Sensor STING.

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The cellular sensor stimulator of interferon genes (STING) initiates type I interferon (IFN) and cytokine production following association with cyclic dinucleotides (CDNs) generated from intracellular bacteria or via a cellular synthase, cGAS, after binding microbial or self-DNA. Although essential for protecting the host against infection, unscheduled STING signaling is now known to be responsible for a variety of autoinflammatory disorders. Here, we report a gain-of-function mutation in STING (R284S), isolated from a patient who did not require CDNs to augment activity and who manifested a constitutively active phenotype. Control of the Unc-51-like autophagy activating kinase 1 (ULK1) pathway, which has previously been shown to influence STING function, was potentially able to suppress STING (R284S) activity to alleviate cytokine production. Our findings add to the growing list of inflammatory syndromes associated with spontaneous STING signaling and provide a therapeutic strategy for the treatment of STING-induced inflammatory disease.

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DOI: 10.1016/j.celrep.2018.03.115

PMCID: PMC6092751



PMID: 29694889

336. Hum Mol Genet. 2018 Aug 1;27(R2):R108-R118. doi: 10.1093/hmg/ddy139.

Neurodegenerative diseases have genetic hallmarks of autoinflammatory disease.

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The notion that one common pathogenic pathway could account for the various clinically distinguishable, typically late-onset neurodegenerative diseases might appear unlikely given the plethora of diverse primary causes of neurodegeneration. On the contrary, an autoinflammatory pathogenic mechanism allows diverse genetic and environmental factors to converge into a common chain of causality. Inflammation has long been known to correlate with neurodegeneration. Until recently this relationship was seen as one of consequence rather than cause-with inflammatory cells and events acting to 'clean up the mess' after neurological injury. This explanation is demonstrably inadequate and it is now clear that inflammation is at the very least, rate-limiting for neurodegeneration (and more likely, a principal underlying cause in most if not all neurodegenerative diseases), protective in its initial acute phase, but pernicious in its latter chronic phase.

DOI: 10.1093/hmg/ddy139

PMCID: PMC6061832 [Available on 2019-08-01]

PMID: 29684205

337. Prenat Diagn. 2018 Apr 23. doi: 10.1002/pd.5272. [Epub ahead of print]

Clinical experience with multigene carrier panels in the reproductive setting.

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**OBJECTIVES:** Expanded carrier testing is acknowledged as an acceptable strategy for carrier testing by the American College of Obstetrics and Gynecology. Limited studies have investigated positivity rates of expanded carrier panels. We describe our experience with 3 commercial laboratory panels varying in size from 3 to 218 disorders.

**METHODS:** We reviewed outcomes for 3 multigene carrier screening panels: trio (3 diseases), standard (23 diseases), and global (218 diseases). All panels used targeted genotype analysis of preselected mutations via next-generation sequencing. We calculated positivity rates for each panel.

**RESULTS:** Positivity rates were 7.2% for Preparent Trio, 13.2% for Preparent Standard, and 35.8% for Preparent Global. The most frequent positive results in the global panel were (in descending order): abnormal hemoglobin electrophoresis, familial Mediterranean fever, cystic fibrosis, fragile X, glucose-6-phosphate dehydrogenase deficiency, alpha-thalassemia, and nonsyndromic hearing loss.

**CONCLUSIONS:** While genetic diseases are individually rare, they are cumulatively common. Our experience illustrates that, with a panel of 218 diseases, the likelihood of identifying a carrier can be as high as 36%. Understanding panel positivity rates is one important factor for providers when choosing the right test for their practice, setting appropriate expectations for patients, and planning for follow-up counseling.

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DOI: 10.1002/pd.5272

PMCID: PMC6099294

PMID: 29683194

338. Biores Open Access. 2018 Apr 1;7(1):47-51. doi: 10.1089/biores.2017.0025. eCollection 2018.

# Possible Association of Multicentric Castleman's Disease with Autoimmune Lymphoproliferative Syndrome.

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Multicentric Castleman's disease (MCD) is lymphoproliferative disorder characterized by systemic inflammatory symptoms such as fever and weight loss. Human herpes virus-8 (HHV-8) is thought to be a causable pathogen in all HIV-positive and some HIV-negative MCD patients. Furthermore, the term idiopathic MCD (iMCD) was recently proposed to represent a group of HIV-negative and HHV-8-negative patients with unknown etiologies. Although the international diagnostic criteria for iMCD require exclusion of infection-related disorders, autoimmune/autoinflammatory diseases and malignant/lymphoproliferative disorders to make an iMCD diagnosis, the relationships and differences between these disorders and MCD have not yet been clarified. We recently reported the first case of MCD with autoimmune lymphoproliferative syndrome (ALPS). Although ALPS was included in the iMCD exclusion criteria as an autoimmune/autoinflammatory disease according to the international diagnostic criteria, there is a lack of evidence on the association between MCD and ALPS. In this study, we review the recent understanding of MCD and discuss the possible association between MCD with ALPS.

DOI: 10.1089/biores.2017.0025

PMCID: PMC5908426

PMID: 29682404

Conflict of interest statement: No competing financial interests exist.

339. Eur J Hum Genet. 2018 Jul;26(7):960-971. doi: 10.1038/s41431-018-0130-6. Epub 2018 Apr 23.

A decision tree for the genetic diagnosis of deficiency of adenosine deaminase 2

(DADA2): a French reference centres experience.

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Deficiency of adenosine deaminase 2 (DADA2) is a recently described autoinflammatory disorder. Genetic analysis is required to confirm the diagnosis. We aimed to describe the identifying symptoms and genotypes of patients referred to our reference centres and to improve the indications for genetic testing. DNA from 66 patients with clinically suspected DADA2 were sequenced by Sanger or next-generation sequencing. Detailed epidemiological, clinical and biological features were collected by use of a questionnaire and were compared between patients with and without genetic confirmation of DADA2. We identified 13 patients (19.6%) carrying recessively inherited mutations in ADA2 that were predicted to be deleterious. Eight patients were compound heterozygous for mutations. Seven mutations were novel (4 missense variants, 2 predicted to affect mRNA splicing and 1 frameshift). The mean age of the 13 patients with genetic confirmation was 12.7 years at disease onset and 20.8 years at diagnosis. Phenotypic manifestations included fever (85%), vasculitis (85%) and neurological disorders (54%). Features best associated with a confirmatory genotype included fever with neurologic or cutaneous attacks (odds ratio [OR] 10.71,  $p = 0.003$  and OR 10.9,  $p < 0.001$ ), fever alone (OR 8.1,  $p = 0.01$ ), and elevated C-reactive protein (CRP) level with neurologic involvement (OR 6.63,  $p = 0.017$ ). Our proposed decision tree may help improve obtaining genetic confirmation of DADA2 in the context of autoinflammatory symptoms. Prerequisites for quick and low-cost Sanger analysis include one typical cutaneous or neurological sign, one marker of inflammation (fever or elevated CRP level), and recurrent or chronic attacks in adults.

DOI: 10.1038/s41431-018-0130-6

PMCID: PMC6018671 [Available on 2019-07-01]

PMID: 29681619

340. J Autoimmun. 2018 Jul;91:55-60. doi: 10.1016/j.jaut.2018.04.002. Epub 2018 Apr 17.

Efficacy of tocilizumab in Takayasu arteritis: Multicenter retrospective study of 46 patients.

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**OBJECTIVES:** To assess the efficacy of tocilizumab in patients with Takayasu arteritis (TA).

**METHODS:** We conducted a retrospective multicenter study in 46 TA patients treated with tocilizumab. We analyzed factors associated with response to tocilizumab

(assessed using NIH score).

**RESULTS:** Forty-six patients with TA were included, with a median age of 43 years [29-54], and 35 (76%) females. We observed a decrease in the median NIH scale (from 3 [2-3] at baseline to 0 [0-1] and 0 at 3 and 6 months, respectively;  $p < 0.0001$ ). The daily prednisone dose also decreased from 15 mg [8-19] at baseline to 4 mg [5-21] and 5 mg [4.5-9] at 3 and 6 months, respectively ( $p < 0.0001$ ) under tocilizumab. The overall tocilizumab failure free survival was 81% [CI 95%; 0.7-0.95], 72% [CI 95%; 0.55-0.95] and 48% [CI 95%; 0.2-0.1] at 12, 24 and 48 months, respectively. The presence of constitutional symptoms (HR 5.6 [CI 95%; 1.08-29],  $p = 0.041$ ), and C-reactive protein level (HR 1.16 [CI 95%; 1.01-1.31],  $P = 0.003$ ) at the time of tocilizumab initiation were significantly associated with tocilizumab event-free survival. The event-free survival was significantly better under tocilizumab therapy in comparison to DMARDs ( $p = 0.02$ ).

**CONCLUSION:** This large multicenter study shows that tocilizumab is efficient and may reduce the incidence of relapses in TA.

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DOI: 10.1016/j.jaut.2018.04.002

PMID: 29678346

341. Immunology. 2018 Apr 19. doi: 10.1111/imm.12937. [Epub ahead of print]

Autoinflammatory disease in the lung.

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Ascertaining the dominant cell type driving an immunological disease is essential to understanding the causal pathology and, therefore, selecting or developing an effective treatment. Classifying immunological diseases in this way has led to successful treatment regimens for many monogenic diseases; however, when the dominant cell type is unclear and there is no obvious causal genetic mutation, then identifying the correct disease classification and appropriate therapy can be challenging. In this review we focus on pulmonary immunological diseases where an innate immune signature has been identified as a predominant aspect of the immunopathology. We describe the molecular pathology of 'autoinflammatory diseases of the lung' and propose that small molecule and biological therapies, including recombinant interleukin-1 receptor antagonist, that target key innate immune pathways, are likely to be beneficial in the control of pulmonary and systemic inflammation in these conditions. In addition, the successful use of macrolide antibiotics to treat lung infections in these conditions further confirms that the innate immune system is the key conductor of inflammation in these pulmonary diseases, as there is a strong body of evidence that macrolides are able to modulate the NLRP3 inflammasome and interleukin-1 $\beta$  and interleukin-18 secretion, both of which are central players in the innate immune response. Throughout this review we highlight the published evidence of autoinflammatory disease in chronic obstructive pulmonary disease, bronchiectasis, cystic fibrosis and rheumatoid lung disease and suggest that the fundamental pathology of these diseases places them towards the autoinflammatory pole of the immunological disease continuum.

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DOI: 10.1111/imm.12937

PMCID: PMC6050210 [Available on 2019-08-01]

PMID: 29676014

342. Clin Rheumatol. 2018 Jun;37(6):1715-1720. doi: 10.1007/s10067-018-4092-4. Epub 2018 Apr 18.

Predictors of sustained clinical response in patients with Behçet's disease-related uveitis treated with infliximab and adalimumab.

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To identify clinical variables capable of predicting long-term treatment duration of TNF- $\alpha$  inhibition in patients with Behçet's disease (BD)-related uveitis. Demographic, clinical, and therapeutic data were retrospectively collected from BD patients treated with the tumor necrosis factor (TNF)- $\alpha$  blockers infliximab and adalimumab. Patients still continuing TNF- $\alpha$  inhibitors at 48-month follow-up visits were classified as long-term responders and were statistically compared to patients discontinuing treatment before the 48-month visit. Forty-five patients (75 eyes) were enrolled. Thirty-two patients continued anti-TNF- $\alpha$  treatment for

more than 48 months; 13 patients discontinued the treatment after a mean time of  $12.3 \pm 10.44$  months due to lack (61.5%) or loss (38.5%) of efficacy. Baseline value of BD current activity form was the only variable discriminating long- and short-term responsive patients ( $p = 0.048$ , OR = 0.656, C.I. 95% 0.433-0.996). Disease activity levels at the start of treatment predict duration of response to monoclonal TNF antagonists in ocular BD.

DOI: 10.1007/s10067-018-4092-4

PMID: 29671190 [Indexed for MEDLINE]

343. Drug Des Devel Ther. 2018 Apr 9;12:795-813. doi: 10.2147/DDDT.S158018. eCollection 2018.

Transethosomal gels as carriers for the transdermal delivery of colchicine: statistical optimization, characterization, and ex vivo evaluation.

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**Introduction:** Colchicine is used for the treatment of gout, pseudo-gout, familial Mediterranean fever, and many other illnesses. Its oral administration is associated with poor bioavailability and severe gastrointestinal side effects. The drug is also known to have a low therapeutic index. Thus to overcome these drawbacks, the transdermal delivery of colchicine was investigated using transethosomal gels as potential carriers.

**Methods:** Colchicine-loaded transethosomes (TEs) were prepared by the cold method and statistically optimized using three sets of 24 factorial design experiments. The optimized formulations were incorporated into Carbopol 940® gel base. The prepared colchicine-loaded transethosomal gels were further characterized for vesicular size, dispersity, zeta potential, drug content, pH, viscosity, yield, rheological behavior, and ex vivo skin permeation through Sprague Dawley rats' back skin.

**Results:** The results showed that the colchicine-loaded TEs had aspherical irregular shape, nanometric size range, and high entrapment efficiency. All the formulated gels exhibited non-Newtonian plastic flow without thixotropy.

Colchicine-loaded transethosomal gels were able to significantly enhance the skin permeation parameters of the drug in comparison to the non-ethosomal gel.

Conclusion: These findings suggested that the transethosomal gels are promising carriers for the transdermal delivery of colchicine, providing an alternative route for drug administration.

DOI: 10.2147/DDDT.S158018

PMCID: PMC5898596

PMID: 29670336 [Indexed for MEDLINE]

Conflict of interest statement: Disclosure The authors report no conflicts of interest in this work.

344. *Pediatr Rheumatol Online J*. 2018 Apr 18;16(1):27. doi: 10.1186/s12969-018-0246-9.

An international delphi survey for the definition of the variables for the development of new classification criteria for periodic fever aphthous stomatitis pharyngitis cervical adenitis (PFAPA).

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**BACKGROUND:** Diagnosis of Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) is currently based on a set of criteria proposed in 1999 modified from Marshall's criteria. Nevertheless no validated evidence based set of classification criteria for PFAPA has been established so far. The aim of this study was to identify candidate classification criteria PFAPA syndrome using international consensus formation through a Delphi questionnaire survey.

**METHODS:** A first open-ended questionnaire was sent to adult and pediatric clinicians/researchers, asking to identify the variables thought most likely to be helpful and relevant for the diagnosis of PFAPA. In a second survey, respondents were asked to select, from the list of variables coming from the first survey, the 10 features that they felt were most important, and to rank them in descending order from most important to least important.

**RESULTS:** The response rate to the first and second Delphi was respectively 109/124 (88%) and 141/162 (87%). The number of participants that completed the first and second Delphi was 69/124 (56%) and 110/162 (68%). From the first Delphi we obtained a list of 92 variables, of which 62 were selected in the second Delphi. Variables reaching the top five position of the rank were regular

periodicity, aphthous stomatitis, response to corticosteroids, cervical adenitis, and well-being between flares.

CONCLUSION: Our process led to identification of features that were felt to be the most important as candidate classification criteria for PFAPA by a large sample of international rheumatologists. The performance of these items will be tested further in the next phase of the study, through analysis of real patient data.

DOI: 10.1186/s12969-018-0246-9

PMCID: PMC5907175

PMID: 29669569 [Indexed for MEDLINE]

345. Cell Death Differ. 2019 Jan;26(1):146-161. doi: 10.1038/s41418-018-0106-7. Epub 2018 Apr 17.

Single-cell analysis of pyroptosis dynamics reveals conserved GSDMD-mediated subcellular events that precede plasma membrane rupture.

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Pyroptosis is rapidly emerging as a mechanism of anti-microbial host defense, and of extracellular release of the inflammasome-dependent cytokines interleukin (IL)-1 $\beta$  and IL-18, which contributes to autoinflammatory pathology. Caspases 1, 4, 5 and 11 trigger this regulated form of necrosis by cleaving the pyroptosis effector gasdermin D (GSDMD), causing its pore-forming amino-terminal domain to

oligomerize and perforate the plasma membrane. However, the subcellular events that precede pyroptotic cell lysis are ill defined. In this study, we triggered primary macrophages to undergo pyroptosis from three inflammasome types and recorded their dynamics and morphology using high-resolution live-cell spinning disk confocal laser microscopy. Based on quantitative analysis of single-cell subcellular events, we propose a model of pyroptotic cell disintegration that is initiated by opening of GSDMD-dependent ion channels or pores that are more restrictive than recently proposed GSDMD pores, followed by osmotic cell swelling, commitment of mitochondria and other membrane-bound organelles prior to sudden rupture of the plasma membrane and full permeability to intracellular proteins. This study provides a dynamic framework for understanding cellular changes that occur during pyroptosis, and charts a chronological sequence of GSDMD-mediated subcellular events that define pyroptotic cell death at the single-cell level.

DOI: 10.1038/s41418-018-0106-7

PMCID: PMC6294780

PMID: 29666477

346. Turk Kardiyol Dern Ars. 2018 Apr;46(3):184-190. doi: 10.5543/tkda.2018.93762.

Lipid profile and atherogenic indices and their association with platelet indices in familial Mediterranean fever.

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Comment in

Turk Kardiyol Dern Ars. 2018 Dec;46(8):739.

Turk Kardiyol Dern Ars. 2018 Dec;46(8):739-740.

**OBJECTIVE:** The aim of this study was to investigate lipid profiles and atherogenic indices and their association with platelet indices in Familial Mediterranean Fever (FMF) patients.

**METHODS:** A total of 63 FMF patients and 51 healthy individuals were included in

this retrospective study. Inflammatory marker values (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP] and fibrinogen), platelet indices (mean platelet volume, plateletcrit value, platelet large cell ratio, and platelet distribution width), lipid profiles (levels of total cholesterol, triglycerides, high-density lipoprotein [HDL] cholesterol, and low-density lipoprotein cholesterol) were recorded. Atherogenic indices (atherogenic index of plasma [AIP], atherogenic coefficient [AC], Castelli's risk indices I and II [CRI I and II]) were calculated using lipid parameters.

RESULTS: In FMF patients, while AIP, AC, and CRI I and II values were significantly higher than in the healthy control group, the HDL cholesterol level was significantly lower (all  $p < 0.05$ ). However, no significant difference was determined in terms of the other studied parameters (all  $p > 0.05$ ). In male FMF patients, whereas AIP, AC, and CRI I and II values were significantly higher than in female FMF patients, the platelet count, ESR, and HDL cholesterol levels were significantly lower (all  $p < 0.05$ ). The level of CRP was negatively correlated with HDL cholesterol ( $r = -0.275$ ;  $p = 0.032$ ) and total cholesterol level ( $r = -0.313$ ;  $p = 0.014$ ) in FMF patients. HDL cholesterol level was negatively correlated with disease duration ( $r = -0.269$ ;  $p = 0.049$ ).

CONCLUSION: The use of atherogenic indices may be recommended to identify patients with an increased risk of atherosclerotic cardiovascular disease in FMF, especially in male patients.

DOI: 10.5543/tkda.2018.93762

PMID: 29664424 [Indexed for MEDLINE]

347. Bratisl Lek Listy. 2018;119(4):198-200. doi: 10.4149/BLL\_2018\_036.

Canakinumab as monotherapy for treatment of familial Mediterranean fever - first report in Central and Eastern Europe region.

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Autoinflammatory disorders (AID) are characterized by spontaneous attacks of acute inflammation with a broad spectrum of clinical symptoms. Ongoing inflammation and reoccurrence of acute flares can lead to the development of amyloidosis. One group of AID is represented by monogenic periodic fever syndromes while familial Mediterranean fever (FMF) is the most common form of AID from this group. Its prevalence in Central and Eastern Europe was reported to be



very low. We report a case of FMF patient with a very severe clinical course of FMF and intolerance to colchicine, which is a gold standard for FMF treatment. The clinical effect of the application of anakinra was insufficient and accompanied with side effects and low tolerability. Switching to canakinumab (human monoclonal antibody against IL-1 $\beta$ ) at dose of 150 mg every 4 weeks induced a rapid remission of the disease activity and inflammatory markers. However, due to relapse of acute flares after three weeks from application, the escalation of dose to 300 mg every 4 weeks induced a complete remission of symptoms and significantly improved the quality of life. This is the first report of successful canakinumab administration in FMF patient in Central and Eastern Europe, a region with very low incidence of FMF (Tab. 1, Ref. 16).

DOI: 10.4149/BLL\_2018\_036

PMID: 29663815 [Indexed for MEDLINE]

348. Clin Rheumatol. 2018 Dec;37(12):3329-3335. doi: 10.1007/s10067-018-4095-1. Epub 2018 Apr 16.

Anakinra treatment in macrophage activation syndrome: a single center experience and systemic review of literature.

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Our aim was to report our experiences of pediatric macrophage activation syndrome (MAS) patients treated with anakinra and to review previous studies reporting anakinra treatment in pediatric MAS patients associated with systemic juvenile idiopathic arthritis (sJIA) or autoinflammatory diseases (AIDs). The study group consisted of pediatric MAS patients due to sJIA or AIDs, followed up in the Pediatric Rheumatology Unit of Hacettepe University between January 2015 and January 2017 and treated with anakinra (anti-IL1). We conducted a systematic review of the published literature involving pediatric MAS patients associated with sJIA or AIDs, treated with anakinra. Thirteen sJIA patients and two AIDs

patients were included the study. Nineteen MAS episodes were observed in 15 patients. Anakinra (2 mg/kg/day) was started in with a median 1 day after admission. Clinical symptoms resolved, and laboratory findings normalized within median (minimum-maximum) 2 (1-4) and 6 (4-9) days, respectively after the introduction of anakinra. Steroid treatment was stopped in a median of 10 (4-13) weeks after the initiation of anakinra treatment. Patients were followed up for a median of 13 (6-24) months. Two patients developed recurrent MAS episodes when the anakinra dose was reduced, while the other patients achieved remission. In the literature review, we identified nine articles, describing 35 pediatric MAS patients associated with sJIA or AIDs and treated with anakinra. Except for two, all the patients reached remission. Our study and systematic literature review may help to improve the knowledge on the role of anakinra treatment in the management of MAS.

DOI: 10.1007/s10067-018-4095-1

PMID: 29663156

349. Immunity. 2018 Apr 17;48(4):787-798.e4. doi: 10.1016/j.immuni.2018.03.019. Epub 2018 Apr 10.

An Interleukin-25-Mediated Autoregulatory Circuit in Keratinocytes Plays a Pivotal Role in Psoriatic Skin Inflammation.

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Psoriasis is a chronic autoinflammatory skin disease. Although interleukin-17, derived from lymphocytes, has been shown to be critical in psoriasis, the initiation and maintenance of chronic skin inflammation has not been well understood. IL-25 (also called IL-17E), another IL-17 family cytokine, is well known to regulate allergic responses and type 2 immunity. Here we have shown that IL-25, also highly expressed in the lesional skin of psoriasis patients, was regulated by IL-17 in murine skin of a imiquimod (IMQ)-induced psoriasis model. IL-25 injection induced skin inflammation, whereas germline or keratinocyte-specific deletion of IL-25 caused resistance to IMQ-induced psoriasis. Via IL-17RB expression in keratinocytes, IL-25 stimulated the proliferation of keratinocytes and induced the production of inflammatory cytokines and chemokines, via activation of the STAT3 transcription factor. Thus, our data demonstrate that an IL-17-induced autoregulatory circuit in keratinocytes is mediated by IL-25 and suggest that this circuit could be targeted in the treatment of psoriasis patients.

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DOI: 10.1016/j.immuni.2018.03.019

PMID: 29653697

350. Plast Reconstr Surg. 2018 Jul;142(1):186-192. doi: 10.1097/PRS.0000000000004494.

Chronic Recurrent Multifocal Osteomyelitis of the Mandible: A Diagnostic Challenge.

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Chronic recurrent multifocal osteomyelitis is a rare autoinflammatory bone disorder of children and adolescents characterized by monofocal or multifocal inflammatory bone lesions that are culture-negative on biopsy, associated with periods of exacerbation and resolution that can last over several months to years. Although it is predominantly a disease of long bones and the spine, craniofacial involvement is not uncommon, affecting the mandible in up to one-fifth of cases. Similarities with other causes of osteitis in clinical presentation and imaging, and the lack of specific symptoms or laboratory tests, make chronic recurrent multifocal osteomyelitis mainly a diagnosis of exclusion. An accurate diagnosis is required for appropriate treatment to induce remission. This article highlights the challenges faced by plastic and oral surgeons in diagnosing mandibular chronic recurrent multifocal osteomyelitis, and describes two pediatric patients affected with the disease. Both cases were initially confused with other entities, leading to unnecessary initial treatments and a delayed diagnosis. A review aimed at surgeons summarizes the major aspects of this condition so that it is considered as a differential diagnosis in young patients presenting with a facial bony mass. CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, V.

DOI: 10.1097/PRS.00000000000004494

PMID: 29652766 [Indexed for MEDLINE]

351. J Clin Invest. 2018 Jul 2;128(7):3041-3052. doi: 10.1172/JCI98814. Epub 2018 Jun 11.

JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies.

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**BACKGROUND:** Monogenic IFN-mediated autoinflammatory diseases present in infancy with systemic inflammation, an IFN response gene signature, inflammatory organ damage, and high mortality. We used the JAK inhibitor baricitinib, with IFN-blocking activity in vitro, to ameliorate disease.

**METHODS:** Between October 2011 and February 2017, 10 patients with CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperatures), 4 patients with SAVI (stimulator of IFN genes-associated [STING-associated] vasculopathy with onset in infancy), and 4 patients with other interferonopathies were enrolled in an expanded access program. The patients underwent dose escalation, and the benefit was assessed by reductions in daily disease symptoms and corticosteroid requirement. Quality of life, organ inflammation, changes in IFN-induced biomarkers, and safety were longitudinally assessed.

**RESULTS:** Eighteen patients were treated for a mean duration of 3.0 years (1.5-4.9 years). The median daily symptom score decreased from 1.3 (interquartile range [IQR], 0.93-1.78) to 0.25 (IQR, 0.1-0.63) ( $P < 0.0001$ ). In 14 patients receiving corticosteroids at baseline, daily prednisone doses decreased from 0.44 mg/kg/day (IQR, 0.31-1.09) to 0.11 mg/kg/day (IQR, 0.02-0.24) ( $P < 0.01$ ), and 5 of 10 patients with CANDLE achieved lasting clinical remission. The patients' quality of life and height and bone mineral density Z-scores significantly improved, and their IFN biomarkers decreased. Three patients, two of whom had genetically undefined conditions, discontinued treatment because of lack of efficacy, and one CANDLE patient discontinued treatment because of BK viremia and azotemia. The most common adverse events were upper respiratory infections, gastroenteritis, and BK viruria and viremia.

**CONCLUSION:** Upon baricitinib treatment, clinical manifestations and inflammatory and IFN biomarkers improved in patients with the monogenic interferonopathies CANDLE, SAVI, and other interferonopathies. Monitoring safety and efficacy is important in benefit-risk assessment.

**TRIAL REGISTRATION:** ClinicalTrials.gov NCT01724580 and NCT02974595.

**FUNDING:** This research was supported by the Intramural Research Program of the NIH, NIAID, and NIAMS. Baricitinib was provided by Eli Lilly and Company, which is the sponsor of the expanded access program for this drug.

DOI: 10.1172/JCI98814

PMCID: PMC6026004

PMID: 29649002

352. Medicine (Baltimore). 2018 Apr;97(15):e0333. doi: 10.1097/MD.00000000000010333.

A case of adult onset Still's disease with mutations of the MEFV gene who is partially responsive to colchicine.

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**RATIONALE:** Familial Mediterranean fever (FMF) and adult onset Still's disease (AOSD) have overlapping features, and are categorized as being on the spectrum of autoinflammatory diseases (AIDs). FMF is more prevalent in the Mediterranean region but rarely, described in the Chinese population.

**PATIENT CONCERNS:** We present an interesting case of a Han Chinese AOSD patient with episodic fever, wheals, and polyarthritis for 2 years.

**DIAGNOSIS:** Sequencing analysis found exon 2 mutations of the MEFV gene (c.329T>C [L110P], and c.442G>C [E148Q]).

**INTERVENTION:** Her arthritis was well-controlled with colchicine treatment, but fever, and rashes were not.

**OUTCOMES:** She eventually received tocilizumab, in addition to colchicine, and her symptoms completely disappeared.

**LESSONS:** MEFV mutations may exist in AOSD patients, and treatment with colchicine might be helpful in such patients.

DOI: 10.1097/MD.00000000000010333

PMCID: PMC5908639

PMID: 29642170 [Indexed for MEDLINE]

353. J Interferon Cytokine Res. 2018 Apr;38(4):171-185. doi: 10.1089/jir.2017.0127.

Development of a Validated Interferon Score Using NanoString Technology.

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Chronic elevation of interferon (IFN)-response genes (IRG) in a subset of patients with systemic immune-dysregulatory diseases, including the Mendelian Type-I IFN-mediated autoinflammatory diseases and some autoimmune diseases suggest a causative role of excessive IFN signaling in the disease pathogenesis and as target for treatment. We developed a 28-IFN response gene scoring system to calculate either a standardized or geomean score by customizing a NanoString assay to quantify the expression of putative IRGs. The gene targets were selected in patients with the IFN-mediated disease chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) and an adult patient with chronic hepatitis C who received the first dose of pegylated interferon alpha-2a. The putative target genes were validated in patients with STING-associated vasculopathy with onset in infancy (SAVI), a monogenic autoinflammatory disease caused by gain-of-function mutations in TMEM173 that encodes the viral sensor stimulator of IFN genes (STING), and had low expression in clinically active patients with the monogenic IL-1-mediated autoinflammatory disease, neonatal-onset multisystem inflammatory disease (NOMID) and in healthy controls. The score calculation on the NanoString assay is rapid and showed high reproducibility and low intra-, and interassay variability. The utility of this 28-gene IFN score may be explored in the diagnosis of patients with presumed interferonopathies and as a biomarker to assess disease activity, long-term outcome, and treatment responses.

DOI: 10.1089/jir.2017.0127

PMCID: PMC5963606 [Available on 2019-04-01]

PMID: 29638206



354. Intern Emerg Med. 2018 Jun;13(4):475-489. doi: 10.1007/s11739-018-1842-x. Epub 2018 Apr 9.

Management of idiopathic recurrent pericarditis in adults and in children: a role for IL-1 receptor antagonism.

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Recurrent pericarditis is one of the most frequent pericardial diseases, affecting up to 30% of the patients who have experienced acute pericarditis. While the diagnosis of acute pericarditis is sometime straight forward, its etiology and therapeutic management are still a challenge for physicians. In developed countries, the idiopathic form is the most frequent, and the search for an infectious etiology is almost invariably negative. Nevertheless, since standard treatment with nonsteroidal anti-inflammatory drugs and colchicine is not always able to neutralize pericardial inflammation in recurrent pericarditis, anakinra, an IL-1 receptor antagonist, has been proposed as a possible

therapeutic alternative for refractory forms. IL-1 is a cytokine that exerts a pivotal role in innate immunity and in the pathogenesis of some autoimmune diseases, such as rheumatoid arthritis, and in autoinflammatory disorders, as familial Mediterranean fever and cryopyrin-associated periodic syndromes. The successful management of patients with acute idiopathic recurrent pericarditis (IRP) needs a teamwork approach, where cardiologists, rheumatologists, clinical immunologists and internists are involved. In this review, we will discuss the clinical and therapeutical challenges of IRP both in adults and children from a clinical practice standpoint. We will also briefly illustrate the main pathogenic mechanisms of IRP to provide internists and cardiologists with the rationale for approaching the use of anakinra in selected clinical cases.

DOI: 10.1007/s11739-018-1842-x

PMID: 29633070 [Indexed for MEDLINE]

355. Joint Bone Spine. 2018 Apr 6. pii: S1297-319X(18)30053-8. doi: 10.1016/j.jbspin.2018.03.010. [Epub ahead of print]

Biological agents in the management of adult-onset Still's disease.

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DOI: 10.1016/j.jbspin.2018.03.010

PMID: 29631071

356. Pediatr Rheumatol Online J. 2018 Apr 5;16(1):22. doi: 10.1186/s12969-018-0236-y.

IL-6 blockade in systemic juvenile idiopathic arthritis - achievement of inactive disease and remission (data from the German AID-registry).

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**BACKGROUND:** Systemic juvenile idiopathic arthritis (sJIA) is a complex disease with an autoinflammatory component of unknown etiology related to the innate immune system. A major role in the pathogenesis has been ascribed to proinflammatory cytokines like interleukin-6 (IL-6), and effective drugs inhibiting their signaling are being developed. This study evaluates sJIA patients treated with the IL-6 inhibitor tocilizumab (TCZ) concerning clinical response rate, disease course and adverse effects in a real-life clinical setting.

**METHODS:** In 2009 a clinical and research consortium was established, including an online registry for autoinflammatory diseases (AID) ( <https://aid-register.de> ).

Data for this retrospective TCZ study were documented by 13 centers.

**RESULTS:** From 7/2009 to 4/2014, 200 patients with sJIA were recorded in the AID-registry. Out of these, 46 (19 m, 27 f, age 1-18 years) received therapy with TCZ. Long term treatment (median 23 months) has been documented in 24/46 patients who were evaluated according to Wallace criteria (active disease 6/24, inactive disease 5/24, remission 13/24 cases). Under observation co-medication were used in 40/46 cases. Adverse events were reported in 11/46 patients. The clinical response rate (no clinical manifestation, no increased inflammation parameters) within the first 12 weeks of treatment was calculated to be 35%.

**CONCLUSION:** Out of 200 sJIA children reported in the German AID-registry, 46 were treated with TCZ, showing a clinical response rate of 35% during the first 12 weeks, and inactive disease and/or remission under medication in 75% after one year. Adverse events were seen in 24% and severe adverse events in 4%.

**TRIAL REGISTRATION:** The AID-Registry is funded by the BMBF (01GM08104, 01GM1112D, 01GM1512D).

DOI: 10.1186/s12969-018-0236-y

PMCID: PMC5887199

PMID: 29622022 [Indexed for MEDLINE]

357. Int Immunol. 2018 Apr 25;30(5):183-193. doi: 10.1093/intimm/dxy009.

Novel aspects of the assembly and activation of inflammasomes with focus on the NLRC4 inflammasome.

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Inflammasomes are multiprotein structures that activate caspase-1, support secretion of pro-inflammatory cytokines, IL-1 $\beta$  and IL-18, and also induce inflammatory programmed cell death, termed pyroptosis. Inflammasomes are activated in response to the detection of endogenous and microbially derived danger signals and are mediated by several classes of inflammasome-forming sensors. These include several nucleotide-binding proteins of the NOD-like receptor (NLR) family, including NLRP1, NLRP3 and NLRC4, as well as the proteins Absent in Melanoma 2 (AIM2) and Pyrin. Mutations in genes encoding some of these sensors have been found to be associated with gain-of-function monogenetic inflammatory disorders in humans. Genetic, biochemical and structural studies have begun to demonstrate how these proteins sense danger signals and to shed light on the step-by-step processes that are necessary for the assembly of inflammasomes, in both physiologic responses to pathogens and potentially in autoinflammatory conditions. Recent biochemical studies of pro-caspase-1 and an adapter protein known as ASC suggest that inflammasomes act to initiate self-generating effector filaments responsible for activating caspase-1 and initiating downstream signaling. These studies have suggested a model of molecular events from sensor activation to inflammasome formation that may describe processes that are universal to inflammasome formation.

DOI: 10.1093/intimm/dxy009

PMCID: PMC5915955 [Available on 2019-02-14]

PMID: 29617808

358. Biomarkers. 2018 Sep;23(6):558-562. doi: 10.1080/1354750X.2018.1460764. Epub 2018 Apr 16.

Increased circulating endothelial microparticles in children with FMF.

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**OBJECTIVE:** Endothelial microparticles (EMPs) are considered as markers of endothelial dysfunction. In this study, we aimed to examine whether there is endothelial dysfunction in children with familial Mediterranean fever (FMF), hypothesizing that endothelial dysfunction would be present especially with acute-phase response in the active period of the disease.

**METHODS:** This cross-sectional study included 65 FMF patients (41 attack free, 24 attack period) and 35 healthy controls. Circulating EMPs, serum amyloid A (SAA), and other inflammation markers were measured in all groups. Circulating EMPs were measured using flow cytometry. Study groups were compared for circulating EMP and inflammatory markers. The relationship between EMPs and the activation of the disease was evaluated.

**RESULTS:** The levels of CD144+ and CD146+ EMPs in the FMF attack period group were significantly higher than those of the control group ( $p < 0.05$ ). The levels of inflammation markers in the attack period group were significantly higher than those of the control and attack-free groups ( $p < 0.05$ ). In the FMF attack group, the CD144+ and CD146+ EMP were significantly correlated with CRP.

**CONCLUSIONS:** Our results suggest that endothelial damage is present especially in the active period of the disease in children with FMF. The endothelial dysfunction becomes an overt parallel with inflammation.

DOI: 10.1080/1354750X.2018.1460764

PMID: 29611726 [Indexed for MEDLINE]

359. Clin Rheumatol. 2018 Apr 3. doi: 10.1007/s10067-018-4069-3. [Epub ahead of print]

Long-term retention rates of adalimumab and infliximab in non-infectious intermediate, posterior, and panuveitis.

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The aim of the present study was to compare long-term adalimumab (ADA) and infliximab (IFX) retention rates in patients with intermediate, posterior, or panuveitis. Additional aims are as follows: (i) to identify any difference in the causes of treatment discontinuation between patients treated with ADA and IFX; (ii) to assess any impact of demographic features, concomitant treatments, and different lines of biologic therapy on ADA and IFX retention rates; and (iii) to identify any correlation between ADA and IFX treatment duration and the age at uveitis onset, the age at onset of the associated systemic diseases, and the age at the start of treatment. Clinical, therapeutic, and demographic data from patients with non-infectious intermediate, posterior, or panuveitis treated with ADA or IFX were retrospectively collected. Kaplan-Meier plot and log-rank (Mantel-Cox) test were used to assess survival curves. One hundred eight patients (188 eyes) were enrolled; in 87 (80.6%) patients, uveitis was associated with a

systemic disease. ADA and IFX were administered in 62 and 46 patients, respectively. No statistically significant differences were identified between ADA and IFX retention rates (p value = 0.22). Similarly, no differences were identified between ADA and IFX retention rates in relation to gender (p value = 0.61 for males, p value = 0.09 for females), monotherapy (p value = 0.08), combination therapy with conventional disease-modifying antirheumatic drugs (log-rank p value = 0.63), and different lines of biologic therapy (p value = 0.79 for biologic-naïve patients; p value = 0.81 for subjects previously treated with other biologics). In conclusion, ADA and IFX have similar long-term retention rates in patients with non-infectious intermediate, posterior, and panuveitis. Demographic, clinical, and therapeutic features do not affect their long-term effectiveness.

DOI: 10.1007/s10067-018-4069-3

PMID: 29611087

360. Pediatrics. 2018 Apr;141(Suppl 5):S496-S500. doi: 10.1542/peds.2017-0213.

Inherited Immunodeficiency: A New Association With Early-Onset Childhood Panniculitis.

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We report on 4 children who presented with aseptic panniculitis associated with inherited immunodeficiency. Three patients had a B-cell immunodeficiency



resulting from mutations in the TRNT1 and NF- $\kappa$ B genes (no mutation was found in the third patient), and 1 had a T-cell deficiency (mutation in the LCK gene). Panniculitis occurred before the age of 2 years in the 4 patients and preceded the onset of recurrent infections because of immunodeficiency in 2. It presented either as nodules, which resolved spontaneously within 1 to 2 weeks (3 patients), or chronic ulcerative lesions (1 patient) associated with unexplained fever and elevated acute phase reactants, without evidence of infection or high-titer autoantibodies. Febrile nodules relapsed in 2 patients, and recurrent attacks of unexplained fever (without relapse of panniculitis) occurred in the third. Skin biopsy revealed predominantly lympho-histiocytic or septal neutrophilic panniculitis in 1 and 3 patients, respectively. Panniculitis was associated with dermal involvement in the 4 patients. Patients with B-cell deficiency received monthly intravenous immunoglobulin replacement. Two patients who underwent bone marrow transplant died of bone marrow transplant-related complications. The 2 remaining patients had persistent, mild autoinflammatory disease, which did not require specific treatment. In these cases, the need for careful immunologic evaluation of patients who present with unexplained panniculitis, especially early-onset panniculitis before the age of 2 years, is highlighted.

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DOI: 10.1542/peds.2017-0213

PMID: 29610179

Conflict of interest statement: POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

361. J Autoimmun. 2018 Jul;91:13-22. doi: 10.1016/j.jaut.2018.03.002. Epub 2018 Mar 30.

Gain of function mutation and inflammasome driven diseases in human and mouse models.

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Activation of the NLRP3 inflammasome, a multiprotein complex, leading to caspase activation with production of proinflammatory IL-1 $\beta$  represents a major pathway of inflammation. Recent studies in mice and human patients uncovered several gain-of-function (GOF) mutations in inflammasome sensor proteins that allow inflammasome assembly in the absence of cognate ligands to trigger autoinflammatory syndromes. Cryopyrin-associated periodic syndromes (CAPS) are rare autoinflammatory diseases, comprising a broad disease spectrum with varying severity. CAPS are associated with GOF mutations in the NLRP3 inflammasome and activation of IL-1 $\beta$  leading to episodes of fever, cutaneous, musculoskeletal, articular, ocular, and neurological symptoms. Here, we review current knowledge on different mutations leading to CAPS and related clinical syndromes. Homologous gene mutations in mice provide insights into the regulation and consequences of the activation of different inflammasomes in several autoinflammatory syndrome. In view of the critical role of IL-1 $\beta$  in the pathogenesis of autoinflammatory GOF mutations such as CAPS, blockade of the action of IL-1 $\beta$  is critical. Therapeutic administration of recombinant IL-1 receptor antagonists or monoclonal anti-IL-1 $\beta$  antibody had a beneficial effect. Furthermore, novel inhibitors of inflammasome complex formation such as MCC950 and related compounds attenuate experimental and clinical disease. The discovery of new GOF mutants of inflammasomes leading to further insights in pathomechanisms and the development of novel inhibitors represent a great challenge.

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DOI: 10.1016/j.jaut.2018.03.002

PMID: 29610014

362. *Pediatr Dermatol*. 2018 Jul;35(4):482-485. doi: 10.1111/pde.13488. Epub 2018 Mar 30.

Hyper-immunoglobulin D syndrome with novel mutations in an afebrile infant.

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Hyper-immunoglobulin D syndrome is a rare autosomal-recessive autoinflammatory syndrome in which a mevalonate kinase deficiency results due to mutations of the mevalonate kinase gene. We report a case of an Asian male infant who was found to have hyper-immunoglobulin D syndrome in the absence of fever. His skin manifestations included cephalic pustulosis as well recurrent transient and fixed pink plaques and nodules on the face and extremities. Subsequent examination revealed hyper-immunoglobulin D syndrome with two novel allelic mutations in the mevalonate kinase gene: c.895G > A (p.D299N) and c.1168C > T (p.Q390). It is important for dermatologists to recognize the varied cutaneous presentations of hyper-immunoglobulin D syndrome because rapid diagnosis and treatment can significantly affect outcomes.

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DOI: 10.1111/pde.13488

PMID: 29600537 [Indexed for MEDLINE]

363. J Med Genet. 2018 Aug;55(8):530-537. doi: 10.1136/jmedgenet-2017-105216. Epub 2018 Mar 29.

New workflow for classification of genetic variants' pathogenicity applied to hereditary recurrent fevers by the International Study Group for Systemic Autoinflammatory Diseases (INSAID).

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**BACKGROUND:** Hereditary recurrent fevers (HRFs) are rare inflammatory diseases sharing similar clinical symptoms and effectively treated with anti-inflammatory biological drugs. Accurate diagnosis of HRF relies heavily on genetic testing.

**OBJECTIVES:** This study aimed to obtain an experts' consensus on the clinical significance of gene variants in four well-known HRF genes: MEFV, TNFRSF1A, NLRP3 and MVK.

**METHODS:** We configured a MOLGENIS web platform to share and analyse pathogenicity classifications of the variants and to manage a consensus-based classification process. Four experts in HRF genetics submitted independent classifications of 858 variants. Classifications were driven to consensus by recruiting four more expert opinions and by targeting discordant classifications in five iterative rounds.

**RESULTS:** Consensus classification was reached for 804/858 variants (94%). None of the unsolved variants (6%) remained with opposite classifications (eg, pathogenic vs benign). New mutational hotspots were found in all genes. We noted a lower pathogenic variant load and a higher fraction of variants with unknown or

unsolved clinical significance in the MEFV gene.

**CONCLUSION:** Applying a consensus-driven process on the pathogenicity assessment of experts yielded rapid classification of almost all variants of four HRF genes.

The high-throughput database will profoundly assist clinicians and geneticists in the diagnosis of HRFs. The configured MOLGENIS platform and consensus evolution protocol are usable for assembly of other variant pathogenicity databases. The MOLGENIS software is available for reuse at <http://github.com/molgenis/molgenis>; the specific HRF configuration is available at <http://molgenis.org/said/>. The HRF pathogenicity classifications will be published on the INFEVERS database at <https://fmf.igh.cnrs.fr/ISSAID/infevers/>.

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DOI: 10.1136/jmedgenet-2017-105216

PMID: 29599418

Conflict of interest statement: Competing interests: None declared.

364. Rheumatology (Oxford). 2018 Mar 27. doi: 10.1093/rheumatology/key058. [Epub ahead of print]

The multifaceted presentation of chronic recurrent multifocal osteomyelitis: a series of 486 cases from the Eurofever international registry.

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#### Erratum in

Rheumatology (Oxford). 2018 Aug 1;57(8):1504.

**Objectives:** Chronic non-bacterial osteomyelitis (CNO) or chronic recurrent multifocal osteomyelitis (CRMO) is an autoinflammatory disorder characterized by sterile bone osteolytic lesions. The aim of this study was to evaluate the demographic data and clinical, instrumental and therapeutic features at baseline in a large series of CNO/CRMO patients enrolled in the Eurofever registry.

**Methods:** A web-based registry collected retrospective data on patients affected by CRMO/CNO. Both paediatric and adult centres were involved.

**Results:** Complete baseline information on 486 patients was available (176 male,

310 female). The mean age of onset was 9.9 years. Adult onset (>18 years of age) was observed in 31 (6.3%) patients. The mean time from disease onset to final diagnosis was 1 year (range 0-15). MRI was performed at baseline in 426 patients (88%), revealing a mean number of 4.1 lesions. More frequent manifestations not directly related to bone involvement were myalgia (12%), mucocutaneous manifestations (5% acne, 5% palmoplantar pustulosis, 4% psoriasis, 3% papulopustular lesions, 2% urticarial rash) and gastrointestinal symptoms (8%). A total of 361 patients have been treated with NSAIDs, 112 with glucocorticoids, 61 with bisphosphonates, 58 with MTX, 47 with SSZ, 26 with anti-TNF and 4 with anakinra, with a variable response.

**Conclusion:** This is the largest reported case series of CNO patients, showing that the range of associated clinical manifestations is rather heterogeneous. The study confirms that the disease usually presents with an early teenage onset, but it may also occur in adults, even in the absence of mucocutaneous manifestations.

DOI: 10.1093/rheumatology/key058

PMID: 29596638

365. J Clin Rheumatol. 2018 Mar 29. doi: 10.1097/RHU.0000000000000770. [Epub ahead of print]

Sacroiliitis in Children With Familial Mediterranean Fever.

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**BACKGROUND/OBJECTIVE:** Familial Mediterranean fever (FMF) is an autosomal recessive disease, characterized by recurrent, self-limited attacks of fever with serositis. Various diseases were reported to be associated with FMF. The aim of this study was to investigate the frequency and characteristics of sacroiliitis in children with FMF.

**METHODS:** Files of FMF patients who had been seen in 2 reference hospitals in Ankara were retrospectively evaluated. Patients with FMF and concomitant sacroiliitis were included to the study. All patients had magnetic resonance imaging evidence of sacroiliitis.

**RESULTS:** Among 650 FMF patients, 17 (11 females, 6 males; mean age,  $13.32 \pm 4.24$  years) (2.6%) of them were found to have sacroiliitis. Familial Mediterranean fever diagnosis was done prior to sacroiliitis diagnosis in 11 patients (65%) and concurrently or afterward in 6 patients (35%). Ten patients had isolated

sacroiliitis, and 7 had associated diseases (5 enthesitis-related arthritis, 1 psoriatic arthritis, and 1 ulcerative colitis). Arthritis (59%), arthralgia (77%), leg pain (71%), heel pain (41%), and enthesitis (29%) were common complaints. Sacroiliac tenderness was detected in 77%, and M694V mutation in almost 90% of the patients. All patients received colchicine therapy. Additionally, 14 of them were treated with nonsteroidal anti-inflammatory drugs, 10 were on sulfasalazine treatment, and 7 of them were on biological agents. CONCLUSIONS: Sacroiliitis can be seen in patients with FMF during childhood, and M694V mutation seems to be a susceptibility factor for its development. Inflammatory low-back pain and leg and heel pain could suggest sacroiliitis.

DOI: 10.1097/RHU.0000000000000770

PMID: 29596210

366. Acta Dermatovenereol Alp Pannonica Adriat. 2018 Mar;27(1):9-16.

Oral manifestations of autoinflammatory and autoimmune diseases.

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Autoimmune diseases may also be reflected in changes in the oral cavity that represent the first sign of the disease, or they may occur simultaneously with or later in the course of the disease. Oral findings are mostly non-specific, and therefore further investigations are needed to exclude or confirm possible diagnoses. This article presents the most important diseases in this research area, divides them into meaningful groups, and highlights the importance of examining the oral cavity for possible manifestations.

PMID: 29589639 [Indexed for MEDLINE]



367. Eur Radiol. 2018 Sep;28(9):3963-3976. doi: 10.1007/s00330-018-5304-7. Epub 2018 Mar 26.

Conventional radiography in juvenile idiopathic arthritis: Joint recommendations from the French societies for rheumatology, radiology and paediatric rheumatology.

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**BACKGROUND:** Juvenile idiopathic arthritis (JIA) can cause structural damage. However, data on conventional radiography (CR) in JIA are scant.

**OBJECTIVE:** To provide pragmatic guidelines on CR in each non-systemic JIA subtype.

**METHODS:** A multidisciplinary task force of 16 French experts (rheumatologists, paediatricians, radiologists and one patient representative) formulated research questions on CR assessments in each non-systemic JIA subtype. A systematic literature review was conducted to identify studies providing detailed information on structural joint damage. Recommendations, based on the evidence found, were evaluated using two Delphi rounds and a review by an independent committee.

**RESULTS:** 74 original articles were included. The task force developed four principles and 31 recommendations with grades ranging from B to D. The experts felt strongly that patients should be selected for CR based on the risk of structural damage, with routine CR of the hands and feet in rheumatoid factor-positive polyarticular JIA but not in oligoarticular non-extensive JIA.

**CONCLUSION:** These first pragmatic recommendations on CR in JIA rely chiefly on expert opinion, given the dearth of scientific evidence. CR deserves to be viewed as a valuable tool in many situations in patients with JIA.

**KEY POINTS:** • CR is a valuable imaging technique in selected indications. • CR is routinely recommended for peripheral joints, when damage risk is high. • CR is recommended according to the damage risk, depending on JIA subtype. • CR is not the first-line technique for imaging of the axial skeleton.

DOI: 10.1007/s00330-018-5304-7

PMCID: PMC6096609

PMID: 29582130 [Indexed for MEDLINE]

368. PLoS One. 2018 Mar 26;13(3):e0194693. doi: 10.1371/journal.pone.0194693. eCollection 2018.

Genetics in TNF-TNFR pathway: A complex network causing spondyloarthritis and conditioning response to anti-TNF $\alpha$  therapy.

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**OBJECTIVES:** We investigated whether polymorphisms (SNPs) in the promoter region of TNFA, or in the autoinflammatory TNFRSF1A and MEFV genes, concur with HLA-B27 in enhancing the risk of Spondyloarthritis (SpA) and/or in predicting the response to anti-TNF $\alpha$  treatment.

**METHODS:** 373 controls and 137 SpA (82 with Psoriatic Arthritis-PsA and 55 with Ankylosing Spondylitis- AS; 98/137 under TNF $\alpha$  inhibitor therapy) from the Veneto Region (Italy) were studied. TNFA polymorphisms (-1031T>C;-857C>T;-376G>A;-308G>A;-238G>A) and HLA-B27 were assayed by RT-PCR. Direct sequencing of MEFV (exons 2,3,5 and 10) and TNFRSF1A (exons 2,3,4 and 6) genes were performed.

**RESULTS:** HLA-B27 was associated with AS ( $\chi^2 = 120.1$ ;  $p = 0.000$ ). Only the TNFA -1031T>C was singly associated with SpA, and the haplotype C/G, resulting from -1031T>C/-308G>A combination, was significantly associated with a reduced risk of SpA (OR: 0.67, CI: 0.46-0.97;  $p = 0.035$ ). Two SNPs were identified in TNFRSF1A, the R92Q (Minor allele frequency-MAF = 0.034) and c.625+10A>G (MAF = 0.479). None of them was associated with SpA ( $p>0.05$ ). The TNFRSF1A c.625+10 G allele was associated with late response to anti-TNF $\alpha$  therapy ( $p = 0.031$ ). Twenty-one SNPs were identified in MEFV gene, 10 with a known potential functional significance. Variant alleles were extremely rare in our population (MAF<0.025) except for R202Q (MAF = 0.27). None was associated with SpA diagnosis ( $p>0.05$ ).

**CONCLUSION:** TNFRSF1A and MEFV gene SNPs are not associated with SpA in the North-East of Italy. AS risk appears to depend not only on HLA-B27, but also on the protective TNFA haplotype -1031C/-308G. The TNFRSF1A c.625+10A>G impacts on the response to anti-TNF $\alpha$  therapy.

DOI: 10.1371/journal.pone.0194693

PMCID: PMC5868803

PMID: 29579081 [Indexed for MEDLINE]

369. Mod Rheumatol. 2018 Apr 27:1-4. doi: 10.1080/14397595.2018.1457469. [Epub ahead of print]

Efficacy and safety of interleukin-1 inhibitors in familial Mediterranean fever patients complicated with amyloidosis.

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**BACKGROUND:** Colchicine is the mainstay of the treatment of familial Mediterranean fever (FMF). However, 10% of FMF patients do not respond well to colchicine. Efficacy of interleukin (IL)-1 inhibitors in reducing attacks have been demonstrated in colchicine-resistant FMF (crFMF) patients recently. Colchicine is still the only approved drug for the prevention of amyloidosis in FMF and utility of IL-1 inhibitors in crFMF cases who already has amyloidosis remain to be elucidated. Herein, we evaluated efficacy and safety of IL-1 inhibitors in patients with crFMF-associated AA amyloidosis in a relatively large single center study.

**METHODS:** Medical records of FMF patients complicated with AA amyloidosis in our dedicated FMF center were retrospectively reviewed and those patients who ever treated with IL-1 inhibitors were enrolled into the study. Patient global, physician global assessments (on 0-10 cm visual analog scale), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum creatinine and 24-h urinary protein excretion values for each visit were recruited from computer-based hospital records. Treatment response of patients were assessed with clinical symptoms, serum albumin, CRP and ESR values. Renal outcome parameters were analyzed on those not receiving renal replacement therapy.

**RESULTS:** Seventeen patients were identified with crFMF-amyloidosis that ever treated with IL-1 inhibitors. Background colchicine therapy was continued in all patients in maximal-tolerated dose along with IL-1 inhibitors. All patients benefit from IL-1 antagonists assessed by patient and physician global assessments. Inflammatory markers, CRP and ESR, were significantly reduced in all

and normalized in 12 out of 17 patients. More importantly, the amount of proteinuria was remarkably improved following IL-1 inhibitor therapy (1606 mg/day to 519 mg/day,  $p = .008$ ). Both anakinra and canakinumab were well-tolerated without severe side effects. All patients were initially treated with anakinra but switched to canakinumab in seven patients (one leukopenia, four injection site reaction, two inefficacy).

**CONCLUSION:** We evaluated the clinical and laboratory responses to IL-1 inhibitors in crFMF-associated amyloidosis patients. We found significant decreases in CRP, ESR and proteinuria after IL-1 inhibitor therapy. This study confirmed that IL-1 inhibitors are effective for controlling attacks and inflammatory activity in FMF patients complicated with AA amyloidosis. Moreover, they reduce or stabilize amount of proteinuria and preserve renal function in short-term follow-up. Prolonged prospective clinical trials are warranted to assess their long-term efficacy in this particular patient group.

DOI: 10.1080/14397595.2018.1457469

PMID: 29578360

370. Proteins. 2018 Jun;86(6):676-683. doi: 10.1002/prot.25494. Epub 2018 Apr 1.

Complex formation dynamics of native and mutated pyrin's B30.2 domain with caspase-1.

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Pyrin protein is the product of the MEFV gene, mutations in which cause manifestation of familial Mediterranean fever (FMF). Functions of pyrin are not completely clear. The secondary structure of the pyrin is represented with four domains and two motifs. Mutations p.M680I, p.M694V, p.M694I, p.K695R, p.V726A, and p.A744S, which are located in the B30.2 domain of pyrin protein, are responsible for manifestation of the most common and severe forms of FMF. All the domains and the motifs of pyrin, are directly or indirectly, involved in the

protein-protein interaction with proteins of apoptosis and regulate the cascade of inflammatory reactions, which is impaired due to pyrin mutations. It is well known, that malfunction of the pyrin-caspase-1 complex is the main reason of inflammation during FMF. Complete tertiary structure of pyrin and the effects of mutations in it are experimentally not studied yet. The aim of this study was to identify possible effects of the abovementioned mutations in the B30.2 domain tertiary structure and to determine their potential consequences in formation of the B30.2-caspase-1 complex. Using in silico methods, it was found, that these mutations led to structural rearrangements in B30.2 domain tertiary structure, causing shifts of binding sites and altering the interaction energy between B30.2 and caspase-1.

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DOI: 10.1002/prot.25494

PMID: 29575132

371. *Pediatr Dermatol*. 2018 May;35(3):e170-e172. doi: 10.1111/pde.13464. Epub 2018 Mar 25.

Neutrophilic urticarial dermatosis as a presenting feature of systemic juvenile idiopathic arthritis.

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This report describes a case of chronic neutrophilic urticarial dermatosis as a presenting feature of systemic juvenile idiopathic arthritis. When encountered in children, neutrophilic urticarial dermatosis should raise suspicion of autoimmune or autoinflammatory disease.

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DOI: 10.1111/pde.13464

PMID: 29574969 [Indexed for MEDLINE]

372. Ann Rheum Dis. 2018 Mar 24. pii: annrheumdis-2018-213359. doi: 10.1136/annrheumdis-2018-213359. [Epub ahead of print]

Response to: 'A20 haploinsufficiency (HA20): clinical phenotypes and disease course of patients with a newly recognised NF- $\kappa$ B-mediated autoinflammatory disease' by Aeschlimann et al.

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DOI: 10.1136/annrheumdis-2018-213359

PMID: 29574415

Conflict of interest statement: Competing interests: None declared.

373. Clin Immunol. 2018 Jun;191:44-51. doi: 10.1016/j.clim.2018.03.009. Epub 2018 Mar 20.

TNFAIP3 haploinsufficiency is the cause of autoinflammatory manifestations in a patient with a deletion of 13Mb on chromosome 6.

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There is scarce literature about autoinflammation in syndromic patients. We describe a patient who, in addition to psychomotor and growth delay, presented with fevers, neutrophilic dermatosis, and recurrent orogenital ulcers. Comparative Genomic Hybridization (CGH) array permitted to identify a 13.13Mb



deletion on chromosome 6, encompassing 53 genes, and including TNFAIP3 gene (A20). A20 is a potent inhibitor of the NF- $\kappa$ B signalling pathway and restricts inflammation via its deubiquitinase activity. Western blotting and immunoprecipitation assays showed decreased A20 expression and increased phosphorylation of p65 and I $\kappa$ B $\alpha$ . Patient's cells displayed increased levels of total K63-linked ubiquitin and increased levels of ubiquitinated RIP and NEMO after stimulation with TNF. We describe the molecular characterization of an autoinflammatory disease due to a large chromosomal deletion and review the phenotypes of patients with A20 haploinsufficiency. CGH arrays should be the first diagnostic method for comprehensive analysis of patients with syndromic features and immune dysregulation.

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DOI: 10.1016/j.clim.2018.03.009

PMID: 29572183

374. Semin Cell Dev Biol. 2018 Nov;83:12-21. doi: 10.1016/j.semcdb.2018.03.011. Epub 2018 Apr 5.

The unconventional secretion of IL-1 $\beta$ : Handling a dangerous weapon to optimize inflammatory responses.

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Interleukin 1 $\beta$  (IL-1 $\beta$ ) is a major mediator of inflammation, with a causative role in many diseases. Unlike most other cytokines, however, it lacks a secretory signal sequence, raising intriguing mechanistic, functional and evolutionary questions. Despite decades of strenuous efforts in many laboratories, how IL-1 $\beta$  is secreted is still a matter of intense debate. Here, we summarize the different mechanisms and pathways that have been proposed for IL-1 $\beta$  secretion. At least two of them, namely the endolysosomal vesicle-based and gasdermin D-dependent

pathways (types III and I in the recent Rabouille's classification of unconventional protein secretion), can be triggered in monocytes, the main source of IL-1 $\beta$  in humans, according to the type and strength of the pro-inflammatory stimuli. As during the escalation of human conflicts, monocytes deploy secretory mechanisms of increasing efficiency and dangerousness, shifting from the specific and controlled type III pathway to the much faster release of type I. Thus, the different mechanisms are activated depending on the severity of the conditions, from the self-limiting type III pathways in response of low pathogen load or small trauma, to the uncontrolled responses that underlie autoinflammatory disorders and sepsis.

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DOI: 10.1016/j.semcd.2018.03.011

PMID: 29571971

375. Arthritis Rheumatol. 2018 Jul;70(7):1167. doi: 10.1002/art.40497. Epub 2018 May 14.

Familial Mediterranean Fever: New Insights Into Cancer Immunoprevention? Comment on the Article by Brenner et al.

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DOI: 10.1002/art.40497

PMID: 29569856

376. Pediatr Rheumatol Online J. 2018 Mar 21;16(1):19. doi: 10.1186/s12969-018-0235-z.

The safety of live-attenuated vaccines in patients using IL-1 or IL-6 blockade: an international survey.

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**BACKGROUND:** Withholding live-attenuated vaccines in patients using interleukin (IL)-1 or IL-6 blocking agents is recommended by guidelines for both pediatric and adult rheumatic diseases, since there is a risk of infection in an immune suppressed host. However, this has never been studied. This retrospective, multicenter survey aimed to evaluate the safety of live-attenuated vaccines in patients using IL-1 or IL-6 blockade.

**METHODS:** We contacted physicians involved in the treatment of autoinflammatory diseases to investigate potential cases. Patients were included if a live-attenuated vaccine had been administered while they were on IL-1 or IL-6 blockade.

**RESULTS:** Seventeen patients were included in this survey (7 systemic juvenile idiopathic arthritis (sJIA), 5 cryopyrin associated periodic syndrome (CAPS), 4 mevalonate kinase deficiency (MKD) and 1 familial Mediterranean fever (FMF). Three patients experienced an adverse event, of which two were serious adverse events (a varicella zoster infection after varicella zoster booster vaccination, and a pneumonia after MMR booster). One additional patient had diarrhea after oral polio vaccine. Further, seven patients experienced a flare of their disease, which were generally mild. Eight patients did not experience an adverse event or

a flare.

**CONCLUSION:** We have described a case series of seventeen patients who received a live-attenuated vaccine while using IL-1 or IL-6 blocking medication. The findings of this survey are not a reason to adapt the existing guidelines. Prospective trials are needed in order to acquire more evidence about the safety and efficacy before considering adaptation of guidelines.

DOI: 10.1186/s12969-018-0235-z

PMCID: PMC5863478

PMID: 29562920 [Indexed for MEDLINE]

377. Ochsner J. 2018 Spring;18(1):94-97.

Polyarteritis Nodosa in Pregnancy.

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**Background:** Polyarteritis nodosa (PAN) is a rare disease that occurs predominantly in middle-aged males; its onset during pregnancy is exceptional.

**Case Report:** We present a case of PAN with peripartum onset in a patient with a twin pregnancy after ovarian stimulation for primary infertility. The pregnancy outcome was good in terms of the children's health. In the case of the mother, however, the presence of nonspecific signs and symptoms, a noncontributory

ovarian biopsy, and mimics of a puerperal infection delayed the diagnosis of PAN. The emergence of a tender subcutaneous nodule on the forearm and its histopathologic findings were diagnostic. Treatment with pulse methylprednisolone and intravenous cyclophosphamide resulted in the patient's prompt recovery. Conclusion: We present the case to stress the value of careful physical examination in unveiling the presence of a rare disease.

PMCID: PMC5855434

PMID: 29559879

378. Int Med Case Rep J. 2018 Mar 13;11:37-40. doi: 10.2147/IMCRJ.S148205. eCollection 2018.

A rare cause of fever in an adult: a case of familial Mediterranean fever.

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Background: Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease characterized by recurrent fever attacks and serositis. Nonspecific manifestations of the FMF can mimic many common acquired disorders such as infections and acute abdomen. This can delay recognition for many years and lead to comprehensive assessments and even unnecessary surgeries. Untreated FMF may lead to serious complications such as end-stage renal disease and malabsorption due to amyloid deposits in the kidneys and the digestive system. Colchicine has been used successfully to treat FMF since the 1970s.

Case presentation: A 30-year-old male was admitted to our hospital with the complaints of fever, nausea, vomiting, and generalized myalgia and weakness for

15 days. The day after hospitalization, the patient had abdominal pain. Approximately a month before, the patient was treated for a diagnosis of urinary tract infection, with similar complaints. MEFV gene mutation analysis revealed homozygosity for the R202Q mutation. FMF was considered in the patient due to the presence of recurrent febrile serositis attacks and R202Q homozygous mutation in the FMF gene analyses. Colchicine was started 3×0.5 mg/day by consulting rheumatology on day 8 of admission. After the colchicine treatment, the patient's complaints markedly improved and the inflammatory markers returned to normal levels. At his follow-up visit at 6 months, the patient remained asymptomatic. Conclusion: We present a case of adult-onset FMF accompanied by peritonitis as a disease among the rare causes of fever in an adult who was treated with colchicine. Based on this case, we suggest that FMF should be kept in mind in the differential diagnosis of patients with periodic fever syndromes.

DOI: 10.2147/IMCRJ.S148205

PMCID: PMC5856027

PMID: 29559814

Conflict of interest statement: Disclosure The authors report no conflicts of interest in this work.

379. Future Med Chem. 2018 Jun 1;10(11):1301-1317. doi: 10.4155/fmc-2017-0322. Epub 2018 Mar 21.

Suramin potently inhibits cGAMP synthase, cGAS, in THP1 cells to modulate IFN- $\beta$  levels.

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AIM: Persistent activation of STING pathway is the basis for several autoimmune diseases. STING is activated by cGAMP, which is produced by cGAS in the presence of DNA. Results/methodology: HPLC-based medium throughput screening for inhibitors of cGAS identified suramin as a potent inhibitor. Unlike other reported cGAS inhibitors, which bind to the ATP/GTP binding site, suramin displaced the bound DNA from cGAS. Addition of suramin to THP1 cells reduced the levels of IFN- $\beta$  mRNA and protein. Suramin did not inhibit lipopolysaccharide- or Pam3CSK4-induced IL-6 mRNA expression.

CONCLUSION: Suramin inhibits STING pathway via the inhibition of cGAS enzymatic activity. Suramin or analogs thereof that displace DNA from cGAS could be used as anti-inflammatory drugs.

DOI: 10.4155/fmc-2017-0322

PMID: 29558821

380. Front Immunol. 2018 Mar 5;9:422. doi: 10.3389/fimmu.2018.00422. eCollection 2018.

Regulation of Cytokine Production by the Unfolded Protein Response; Implications for Infection and Autoimmunity.

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Protein folding in the endoplasmic reticulum (ER) is an essential cell function. To safeguard this process in the face of environmental threats and internal stressors, cells mount an evolutionarily conserved response known as the unfolded protein response (UPR). Invading pathogens induce cellular stress that impacts protein folding, thus the UPR is well situated to sense danger and contribute to immune responses. Cytokines (inflammatory cytokines and interferons) critically mediate host defense against pathogens, but when aberrantly produced, may also drive pathologic inflammation. The UPR influences cytokine production on multiple levels, from stimulation of pattern recognition receptors, to modulation of

inflammatory signaling pathways, and the regulation of cytokine transcription factors. This review will focus on the mechanisms underlying cytokine regulation by the UPR, and the repercussions of this relationship for infection and autoimmune/autoinflammatory diseases. Interrogation of viral and bacterial infections has revealed increasing numbers of examples where pathogens induce or modulate the UPR and implicated UPR-modulated cytokines in host response. The flip side of this coin, the UPR/ER stress responses have been increasingly recognized in a variety of autoimmune and inflammatory diseases. Examples include monogenic disorders of ER function, diseases linked to misfolding protein (HLA-B27 and spondyloarthritis), diseases directly implicating UPR and autophagy genes (inflammatory bowel disease), and autoimmune diseases targeting highly secretory cells (e.g., diabetes). Given the burgeoning interest in pharmacologically targeting the UPR, greater discernment is needed regarding how the UPR regulates cytokine production during specific infections and autoimmune processes, and the relative place of this interaction in pathogenesis.

DOI: 10.3389/fimmu.2018.00422

PMCID: PMC5844972

PMID: 29556237

381. Ann Rheum Dis. 2018 Mar 16. pii: annrheumdis-2018-213347. doi: 10.1136/annrheumdis-2018-213347. [Epub ahead of print]

Response to: 'A20 haploinsufficiency (HA20): clinical phenotypes and disease course of patients with a newly recognised NF- $\kappa$ B-mediated autoinflammatory disease'.

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DOI: 10.1136/annrheumdis-2018-213347

PMID: 29549169

Conflict of interest statement: Competing interests: None declared.

382. Genet Med. 2018 Mar 15. doi: 10.1038/gim.2018.46. [Epub ahead of print]

Clinical and genetic heterogeneity in a large cohort of Armenian patients with late-onset familial Mediterranean fever.

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**Purpose**This work aimed at investigating demographic, clinical, and genetic characteristics of individuals experiencing their first familial Mediterranean fever (FMF) attack at age  $\geq 40$  years in a very large cohort of Armenian FMF patients.**Methods**In total, 10,370 Armenian patients diagnosed with FMF based on the Tel Hashomer criteria and carrying at least one MEFV mutant allele were included in this study.**Results**A total of 354 (3.40%) patients had late-onset FMF. Of these, 194 (54.80%) were female and 160 (45.20%) were male. The following genotypes were significantly associated with the late-onset variant: M680I/E148Q ( $P = 0.004$ ), M694V/E148Q ( $P < 0.001$ ), and V726A/V726A ( $P < 0.001$ ). Of note, 12/354 (3.40%) patients were found to be homozygous for the M694V mutation. Individuals with late-onset FMF had a milder disease phenotype presenting significantly less

frequent fever, skin manifestation, and chest pain compared to individuals with a disease onset before 40 years of age. Abdominal pain was found more often in the late-onset FMF group, whereas arthritis, proteinuria, and amyloidosis did not differ significantly between the two groups. Conclusion Our data suggest that late-onset FMF is more prevalent in women and is of greater clinical as well as genetic heterogeneity than previously reported. GENETICS in MEDICINE advance online publication, 15 March 2018; doi:10.1038/gim.2018.46.

DOI: 10.1038/gim.2018.46

PMID: 29543225

383. Int Immunol. 2018 Apr 25;30(5):205-213. doi: 10.1093/intimm/dxy021.

Using genes to triangulate the pathophysiology of granulomatous autoinflammatory disease: NOD2, PLCG2 and LACC1.

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The intersection of granulomatosis and autoinflammatory disease is a rare occurrence that can be generally subdivided into purely granulomatous phenotypes and disease spectra that are inclusive of granulomatous features. NOD2 (nucleotide-binding oligomerization domain-containing protein 2)-related disease, which includes Blau syndrome and early-onset sarcoidosis, is the prototypic example of granulomatous inflammation in the context of monogenic autoinflammation. Granulomatous inflammation has also been observed in two related autoinflammatory diseases caused by mutations in PLCG2 (phospholipase Cy2). More recently, mutations in LACC1 (laccase domain-containing protein 1) have been identified as the cause of a monogenic form of systemic juvenile idiopathic arthritis, which does not itself manifest granulomatous inflammation, but the same LACC1 mutations have also been shown to cause an early-onset, familial form of a well-known granulomatous condition, Crohn's disease (CD). Rare genetic variants of PLCG2 have also been shown to cause a monogenic form of CD,

and moreover common variants of all three of these genes have been implicated in polygenic forms of CD. Additionally, common variants of NOD2 and LACC1 have been implicated in susceptibility to leprosy, a granulomatous infection. Although no specific mechanistic link exists between these three genes, they form an intriguing web of susceptibility to both monogenic and polygenic autoinflammatory and granulomatous phenotypes.

DOI: 10.1093/intimm/dxy021

PMCID: PMC6281334 [Available on 2019-03-12]

PMID: 29538758

384. *Mediterr J Hematol Infect Dis*. 2018 Mar 1;10(1):e2018019. doi: 10.4084/MJHID.2018.019. eCollection 2018.

Chemotherapy-Colchicine Interaction in a Child with Familial Mediterranean Fever and Hodgkin Lymphoma.

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Familial Mediterranean fever (FMF) has been associated with hematological malignancies but has not been reported in association with Hodgkin lymphoma (HL). We hereby describe the first pediatric patient with FMF and stage IIA nodular sclerosis HL. She was treated with prednisone, doxorubicin, vincristine and etoposide (OEPA) being on therapy with colchicine. However, she suffered more than expected treatment-related toxicity attributed either to chemotherapy (severe neutropenia) or colchicine (Abdominal pains and diarrhoea). Colchicine had to be discontinued. In the absence of colchicine, she tolerated very well the

second cycle of chemotherapy. Currently, she is in remission at 17 months after her HL diagnosis, and her FMF is under control with colchicine without any signs of toxicity.

DOI: 10.4084/MJHID.2018.019

PMCID: PMC5841933

PMID: 29531656

Conflict of interest statement: Competing interests: The authors have declared that no competing interests exist.

385. Open Access Maced J Med Sci. 2018 Feb 9;6(2):310-313. doi: 10.3889/oamjms.2018.079. eCollection 2018 Feb 15.

Immunological Evaluation in Patients with Familial Mediterranean fever.

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**OBJECTIVE:** This study aimed to investigate T & B lymphocyte subsets and Natural Killer (NK) cells patterns in children with FMF versus normal control subjects, to estimate the immunoglobulins IgG, IgM, and IgA levels, and to scrutinize the possible use of Neutrophil / Lymphocyte ratio (NLR) as a marker for subclinical inflammation in FMF patients.

**PATIENTS AND METHODS:** A group of 42 patients with FMF attending the Genetics Clinic at National Research Centre were included in this study. They were 13 males and 19 females; their age ranged from 2 to 17 years old. Normal healthy subjects within the same age and sex range were included as a control group. Complete blood picture was done for all cases, and neutrophil/ lymphocyte ratio was calculated. Flow cytometer analysis was done for CD3, CD4, CD8, CD19 and CD16 using monoclonal antibodies. Immunoglobulins IgG, IgA and IgM were estimated in serum using nephelometry.

RESULTS: Positive consanguinity was present in 20 patients (47.6%). Abdominal pain was the most common manifestation followed by fever, arthritis, and red rash. CD3, CD4 and CD8 were statistically increased in patients group as compared to normal control group, while CD16 was statistically decreased.

CONCLUSION: The study suggests that quantitative measurement of CD expressions of CD3, CD4 and CD8 as well as NLR might be used as valuable markers for subclinical inflammation in FMF.

DOI: 10.3889/oamjms.2018.079

PMCID: PMC5839438

PMID: 29531594

386. EMBO Mol Med. 2018 Apr;10(4). pii: e8689. doi: 10.15252/emmm.201708689.

Tranilast directly targets NLRP3 to treat inflammasome-driven diseases.

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The dysregulation of NLRP3 inflammasome can cause uncontrolled inflammation and drive the development of a wide variety of human diseases, but the medications targeting NLRP3 inflammasome are not available in clinic. Here, we show that tranilast (TR), an old anti-allergic clinical drug, is a direct NLRP3 inhibitor.

TR inhibits NLRP3 inflammasome activation in macrophages, but has no effects on AIM2 or NLRC4 inflammasome activation. Mechanismly, TR directly binds to the NACHT domain of NLRP3 and suppresses the assembly of NLRP3 inflammasome by blocking NLRP3 oligomerization. In vivo experiments show that TR has remarkable preventive or therapeutic effects on the mouse models of NLRP3 inflammasome-related human diseases, including gouty arthritis, cryopyrin-associated autoinflammatory syndromes, and type 2 diabetes. Furthermore, TR is active ex vivo for synovial fluid mononuclear cells from patients with gout. Thus, our study identifies the old drug TR as a direct NLRP3 inhibitor and provides a potentially practical pharmacological approach for treating NLRP3-driven diseases.

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DOI: 10.15252/emmm.201708689

PMCID: PMC5887903

PMID: 29531021

387. Intern Med. 2018 Aug 15;57(16):2425-2429. doi: 10.2169/internalmedicine.0057-17. Epub 2018 Mar 9.

Five Cases of Familial Mediterranean Fever in Japan: The Relationship with MEFV Mutations.

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Familial Mediterranean fever (FMF) is the most common genetic autoinflammatory disease, but it has been considered a rare disease in Japan. We herein describe five patients with FMF who were diagnosed both clinically and genetically at a single Japanese institute. A genetic investigation of Mediterranean fever (MEFV) detected heterozygosity for the compound mutations L110P/E148Q (n=2) and L110P/148Q/P369S/R406Q (n=1), and heterozygosity for M694I (n=1) and S503C (n=1). Colchicine prevented febrile attacks and accompanying symptoms in four patients. One patient with an S503C mutation showed resistance. Physicians should be aware of the characteristic symptoms, as well as the more unusual symptoms such as headache, when diagnosing FMF.

DOI: 10.2169/internalmedicine.0057-17

PMCID: PMC6148168

PMID: 29526930 [Indexed for MEDLINE]

388. Autoimmun Rev. 2018 May;17(5):435-439. doi: 10.1016/j.autrev.2017.11.033. Epub 2018 Mar 8.

Perspective: Scientific and ethical concerns pertaining to animal models of autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA).

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The autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA) was first described in 2011. The aluminium containing adjuvants of vaccines were stated to be one of the main causes of the condition. Other disorders associated with ASIA include siliconosis, Gulf war syndrome, sick building syndrome and the macrophagic myositis syndrome. We have recently reviewed ASIA as defined by its authors. We have shown that the definition of ASIA is imprecise and includes all patients with an autoimmune disorder as well as potentially the entire population. Application of the Bradford Hill criteria for causality does not support ASIA as an outcome of exposure to aluminium containing adjuvants in vaccines. The advocates of ASIA highlight animal models as evidence for the existence of the disorder. However, as this review will demonstrate, animal models purporting to support the existence of ASIA have methodological, analytical and ethical flaws which, in our view, refute the existence of the condition. Three publications by the advocates of ASIA were recently retracted from peer-reviewed journals. We call for an immediate moratorium on animal experiments of ASIA until an independent inquiry has been conducted to determine the existence of a clinically relevant syndrome, identifiable as ASIA in humans.

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DOI: 10.1016/j.autrev.2017.11.033

PMID: 29526635 [Indexed for MEDLINE]

389. Rev Med Interne. 2018 Apr;39(4):240-255. doi: 10.1016/j.revmed.2018.02.005. Epub 2018 Mar 8.

[Familial Mediterranean fever].

[Article in French]

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Familial Mediterranean Fever (FMF) is the most frequent monogenic auto-inflammatory disease. FMF is an autosomal recessive disease, which affects populations from Mediterranean origin and is associated with MEFV gene mutations encoding for the protein pyrin. Pyrin activation enhances the secretion of interleukin 1 by myelo-monocytic cells. Main features of the disease are acute attacks of serositis mainly located on the abdomen, less frequently on chest and joints, accompanied by fever and biological inflammatory markers elevation. Usually attacks last 1 to 3 days and spontaneously stop. A daily oral colchicine intake of 1 to 2mg/day is able to prevent attack's occurrence, frequency, intensity and duration among most patients. Colchicine is also able to prevent the development of inflammatory amyloidosis, the most severe complication of FMF. This state of the art article will focus on the diagnosis of FMF, the treatment and an update on the pathophysiology including the recent described dominant form of MEFV-associated new auto-inflammatory diseases.

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DOI: 10.1016/j.revmed.2018.02.005

PMID: 29526329 [Indexed for MEDLINE]

390. Rev Med Interne. 2018 Apr;39(4):256-264. doi: 10.1016/j.revmed.2018.02.002. Epub 2018 Mar 7.

[Tumor necrosis receptor associated periodic syndrome (TRAPS): State of the art].

[Article in French]

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Tumour necrosis receptor associated periodic syndrome (TRAPS) is a rare cosmopolitan dominant autosomal disease that belongs to the group of recurrent autoinflammatory syndromes. TRAPS is characterized by recurrent bouts of fever lasting more than 7 days, with arthralgia, myalgia, abdominal pain, erythematous rash and sometimes ocular symptoms. During flares, raised inflammatory markers are constant. The age of onset may occur during childhood but also during

adulthood. TRAPS is caused by mutations in the TNF receptor 1 (TNFRSF1A) gene that may occur in most of the populations over the world. In the majority of patients, history shows affected relatives, even if sporadic cases do exist. Management of TRAPS usually involves corticosteroid therapy during inflammatory flares. The most severe cases require a treatment with biological agents (mainly interleukin 1 inhibitors). The prognosis of TRAPS is overall good; the main risk is represented by the development of secondary inflammatory amyloidosis. This risk is greatest in patients with structural mutations leading to conformation abnormalities of the TNFRSF1A receptor. Regular clinical and biological monitoring is essential in the follow-up of TRAPS patients.

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DOI: 10.1016/j.revmed.2018.02.002  
PMID: 29525418 [Indexed for MEDLINE]

391. Acta Otorrinolaringol Esp. 2018 Mar 7. pii: S0001-6519(18)30012-8. doi: 10.1016/j.otorri.2017.08.008. [Epub ahead of print]

Immune-Mediated Inner Ear Disease: Diagnostic and therapeutic approaches.

[Article in English, Spanish]

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**INTRODUCTION:** Immune Mediated Inner Ear Disease (IMIED) is a rare form of sensorineural bilateral hearing loss, usually progressing in weeks to months and responsive to immunosuppressive treatment. Despite recent advances, there is no consensus on diagnosis and optimal treatment.

**METHODS:** A review of articles on IMIED from the last 10 years was conducted using

PubMed® database.

**RESULTS:** IMIED is a rare disease, mostly affecting middle aged women. It may be a primary ear disease or secondary to autoimmune systemic disease. A dual immune response (both cellular and humoral) seems to be involved. Cochlin may be the inner ear protein targeted in this disease. Distinction from other (core common) forms of neurosensory hearing loss is a challenge. Physical examination is mandatory for exclusion of other causes of hearing loss; audiometry identifies characteristic hearing curves. Laboratory and imaging studies are controversial since no diagnostic marker is available.

**CONCLUSION:** Despite recent research, IMIED diagnosis remains exclusive. Steroids are the mainstay treatment; other therapies need further investigation. For refractory cases, cochlear implantation is an option and with good relative outcome.

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DOI: 10.1016/j.otorri.2017.08.008

PMID: 29525415

392. J Periodontol. 2018 Apr;89(4):456-465. doi: 10.1002/JPER.17-0243. Epub 2018 Feb 27.

Serum, salivary, and tissue levels of plasminogen in familial Mediterranean fever, amyloidosis, and chronic periodontitis.

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**BACKGROUND:** There are no published studies regarding the role of the plasminogen (PLG) system in familial Mediterranean fever (FMF), FMF-associated secondary amyloidosis, or chronic periodontitis (CP), although recent limited data have focused on the association between FMF and chronic periodontitis. Therefore, the aim of this study was to evaluate the serum, salivary, and gingival tissue levels of PLG in patients with CP, FMF, and amyloidosis.

**METHODS:** The study population included 122 patients with FMF (only FMF, and FMF and amyloidosis and 128 individuals who were systemically healthy controls. Blood and salivary samples were obtained from the cases and controls, and clinical periodontal parameters were recorded. Serum and salivary PLG levels were assessed. The gingival tissue samples of the case and control groups were analyzed histopathologically and immunohistochemically for amyloid deposition and PLG.

**RESULTS:** The amyloidosis group had significantly more severe clinical periodontal parameters than those of the FMF and systemically healthy groups ( $P < 0.05$ ). Salivary levels of PLG were significantly higher in the FMF and amyloidosis groups compared with those in the control group ( $P < 0.001$ ). The FMF with periodontitis and amyloidosis with periodontitis groups had higher salivary PLG levels compared with those in the CP group. Serum and salivary PLG levels were significantly associated with the clinical periodontal parameters in the FMF group. The amyloidosis cases had hyperplasia, severe inflammation, and activation of the gingiva.

**CONCLUSION:** The PLG system could play an important role in inflammatory diseases, such as chronic periodontitis, FMF, and FMF-associated secondary amyloidosis.

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DOI: 10.1002/JPER.17-0243

PMID: 29520774

393. Zhonghua Er Ke Za Zhi. 2018 Mar 2;56(3):179-185. doi: 10.3760/cma.j.issn.0578-1310.2018.03.005.

[Stimulator of interferon genes-associated vasculopathy with onset in infancy: first case report in China].

[Article in Chinese; Abstract available in Chinese from the publisher]

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Objective: To summarize the clinical characteristics and treatment efficacy of the first reported case of a Chinese boy with stimulator of interferon genes (STING) associated vasculopathy with onset in infancy (SAVI). Methods: Sanger sequencing of the gene TMEM173 was performed based on systemic evaluation and clinical analysis of a highly suspected SAVI child admitted to Peking Union Medical College Hospital. A literature search (search terms included 'STING"SAVI"autoinflammatory diseases' and 'interferonopathy') was conducted using Chinese literature database, EMBASE and PubMed to include recently published SAVI studies (searched from January 2010 to December 2017). Results: A 14-year-old boy who had a history of chronic dry cough along with decreased activity tolerance after birth presented with growth retardation, chilblain lesions on the ear, telangiectasia of multiple skin areas and long clubbed fingers. His C-reactive protein was 21 mg/L, erythrocyte sedimentation rate was 78 mm/1h, and IgG was 22.16 g/L. The high-resolution computed tomography (HRCT) revealed interstitial lung diseases and echocardiography showed pulmonary artery hypertension, with a level of 61 mmHg (1 mmHg=0.133 kPa). Genetic mutation of TMEM173 (c.463G>A, p.V155M) was confirmed by Sanger sequencing. His activity tolerance increased to some extent after treatment with tofacitinib at a dose of 5 mg twice a day. Our review yielded 8 publications (8 English and 0 Chinese) . To date 20 cases have been reported worldwide, who mostly presented with skin and lung involvement as well as growth retardation. Conclusions: SAVI has been included within the spectrum of interferonopathy, which is a kind of autoinflammatory diseases as well. Typical clinical features include chilblain skin lesions, interstitial lung disease, growth retardation, elevated IgG levels, and increased inflammation markers. Janus kinase (JAK) inhibitors may offer benefit for SAVI patients.

Publisher: 目的：总结中国首例干扰素基因刺激蛋白（STING）相关婴儿期起病的血管病（SAVI）的病例特点和初步疗效观察。方法：

分析2017年11月北京协和医院儿科收治的1例高度疑似SAVI患儿的病例特点，并用Sanger测序进行患儿及其生物学父母相应突变位点验证明确诊断。以"STING"

"SAVI""自身炎症性疾病""干扰素通路疾病"为检索词，检索2010年1月至2017年12月中文数据库及Embase、Pubmed数据库进行文献复习。结果：

患儿 男，14岁，生后起病，以反复干咳伴活动耐力下降为主要表现，伴有生长受限、反复冻疮样皮疹、毛细血管扩张和长的杵状指，实验室检查：红细胞沉降率78 mm/1 h，C反应蛋白21 mg/L，免疫球蛋白G 22.16 g/L，胸部高分辨CT提示间质性肺病，超声心动提示肺动脉高压[61 mmHg（1 mmHg=0.133

kPa）]。经Sanger测序发现患儿TMEM173基因新生杂合突变：c.463G>A, p.V155M，经托法替尼5

mg，2次/d治疗后患儿活动耐力较前增加。文献检索共8篇，中文0篇，英文8篇，全世界目前共有20例SAVI病例，多伴有生长受限、皮肤和肺部的受累。结论：

SAVI是自身炎症性疾病中干扰素通路疾病中的一种，多以反复冻疮样皮疹、间质性肺病、生长受限、免疫球蛋白G升高、炎性指标升高为临床表现，Janus激酶抑制剂对该病有一定疗效。.

DOI: 10.3760/cma.j.issn.0578-1310.2018.03.005

PMID: 29518827 [Indexed for MEDLINE]

394. Front Immunol. 2018 Feb 20;9:298. doi: 10.3389/fimmu.2018.00298. eCollection 2018.

The Potential Role of Trained Immunity in Autoimmune and Autoinflammatory Disorders.

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During induction of trained immunity, monocytes and macrophages undergo a functional and transcriptional reprogramming toward increased activation. Important rewiring of cellular metabolism of the myeloid cells takes place during induction of trained immunity, including a shift toward glycolysis induced through the mTOR pathway, as well as glutaminolysis and cholesterol synthesis. Subsequently, this leads to modulation of the function of epigenetic enzymes, resulting in important changes in chromatin architecture that enables increased gene transcription. However, in addition to the beneficial effects of trained immunity as a host defense mechanism, we hypothesize that trained immunity also plays a deleterious role in the induction and/or maintenance of autoimmune and autoinflammatory diseases if inappropriately activated.

DOI: 10.3389/fimmu.2018.00298

PMCID: PMC5826224

PMID: 29515591

395. Front Immunol. 2018 Feb 21;9:104. doi: 10.3389/fimmu.2018.00104. eCollection 2018.

A20/Tumor Necrosis Factor  $\alpha$ -Induced Protein 3 in Immune Cells Controls Development of Autoinflammation and Autoimmunity: Lessons from Mouse Models.

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Immune cell activation is a stringently regulated process, as exaggerated innate and adaptive immune responses can lead to autoinflammatory and autoimmune diseases. Perhaps the best-characterized molecular pathway promoting cell activation is the nuclear factor- $\kappa$ B (NF- $\kappa$ B) signaling pathway. Stimulation of this pathway leads to transcription of numerous pro-inflammatory and cell-survival genes. Several mechanisms tightly control NF- $\kappa$ B activity, including



the key regulatory zinc finger (de)ubiquitinating enzyme A20/tumor necrosis factor  $\alpha$ -induced protein 3 (TNFAIP3). Single nucleotide polymorphisms (SNPs) in the vicinity of the TNFAIP3 gene are associated with a spectrum of chronic systemic inflammatory diseases, indicative of its clinical relevance. Mice harboring targeted cell-specific deletions of the *Tnfaip3* gene in innate immune cells such as macrophages spontaneously develop autoinflammatory disease. When immune cells involved in the adaptive immune response, such as dendritic cells or B-cells, are targeted for A20/TNFAIP3 deletion, mice develop spontaneous inflammation that resembles human autoimmune disease. Therefore, more knowledge on A20/TNFAIP3 function in cells of the immune system is beneficial in our understanding of autoinflammation and autoimmunity. Using the aforementioned mouse models, novel A20/TNFAIP3 functions have recently been described including control of necroptosis and inflammasome activity. In this review, we discuss the function of the A20/TNFAIP3 enzyme and its critical role in various innate and adaptive immune cells. Finally, we discuss the latest findings on TNFAIP3 SNPs in human autoinflammatory and autoimmune diseases and address that genotyping of TNFAIP3 SNPs may guide treatment decisions.

DOI: 10.3389/fimmu.2018.00104

PMCID: PMC5826380

PMID: 29515565

396. Pract Neurol. 2018 Aug;18(4):278-290. doi: 10.1136/practneurol-2017-001792. Epub 2018 Mar 6.

POEMS neuropathy: optimising diagnosis and management.

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POEMS syndrome is a rare and disabling autoinflammatory condition characterised by a typical peripheral neuropathy and the presence of a monoclonal plasma cell disorder. The acronym 'POEMS' represents the complex and multisystem features of the disease, including polyneuropathy, organomegaly, endocrinopathy, a monoclonal plasma cell disorder and skin disease. The diagnosis of POEMS is a significant challenge because of the heterogeneity of clinical presentations and variation of POEMS features. Patients are often misdiagnosed with another cause of inflammatory neuropathy and receive one or more ineffective immunomodulatory medications, resulting in delayed diagnosis and further clinical deterioration before a diagnosis is made. University College London Hospitals sees one of the largest reported POEMS cohorts in Europe, and runs a multispecialist clinic to assist with diagnosis, treatment and ongoing support. This review draws upon our experience to present the typical features of POEMS syndrome and highlight diagnostic conundrums commonly experienced, supplemented with clinical cases. We provide an investigative guide for clinicians when considering POEMS as the diagnosis, and propose a treatment algorithm that centres on the site and degree of monoclonal cell proliferation.

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DOI: 10.1136/practneurol-2017-001792

PMID: 29511110 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: None declared.

397. Scott Med J. 2018 May;63(2):63-66. doi: 10.1177/0036933018760763. Epub 2018 Mar 5.

Adult-onset Still's disease with prominent polyserositis.

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Adult-onset Still's disease is a systemic autoinflammatory disease the presentation of which can often mimic infection. As a consequence, there is often a delay in diagnosis. Serositis is a recognised but less common clinical feature that can result in complications including cardiac tamponade and constrictive pericarditis. We describe a case of adult-onset Still's disease without the hallmark rash or significant arthritis, presenting with polyserositis that showed a good response to initial steroid treatment and sustained remission with anakinra. An elevated procalcitonin level was due to active adult-onset Still's disease, not bacterial infection.

DOI: 10.1177/0036933018760763

PMID: 29506437 [Indexed for MEDLINE]

398. Am J Ophthalmol. 2018 May;189:77-85. doi: 10.1016/j.ajo.2018.02.019. Epub 2018 Mar 2.

Autoimmunity, Autoinflammation, and Infection in Uveitis.

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Hospital and UCL-Institute of Ophthalmology, London, United Kingdom.

**PURPOSE:** To review the pathogenesis of uveitis in light of recent advances in our understanding of innate and adaptive immune responses and their regulation.

**DESIGN:** Perspective.

**METHODS:** Methods included a review of prevailing views on the pathogenesis of uveitis and an analysis of developments in immunology that impact on its conceptual basis, particularly the concept of immunologic tolerance and its loss in autoimmunity. Importantly, the role of infection in the pathogenesis of uveitis is evaluated.

**RESULTS:** The results comprise a reappraisal of the pathogenesis of anterior vs posterior uveitis in the context of the blood-retinal barrier and its relation to autoimmune, autoinflammatory, and infectious uveitis. Autoimmunity is seen as a possible cause of certain forms of uveitis but definitive proof is lacking.

Autoinflammatory disease, involving activated innate immune mechanisms, is considered causative in a second set of uveitis conditions. A place for infection in uveitis generally is proposed within a unifying concept for the pathogenesis of uveitis.

**CONCLUSION:** Infection may be implicated directly or indirectly in many forms of noninfectious or undifferentiated uveitis. In addition to the growing recognition that foreign antigen, including reactivatable infectious agents, might hide within ocular tissues, the possibility that a dysregulated microbiome might generate T cells that cause immune-mediated ocular inflammation has now been demonstrated experimentally. An uncontrolled, overexuberant host immune response may cause continuing irreversible tissue damage even after the infection has been cleared.

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DOI: 10.1016/j.ajo.2018.02.019

PMID: 29505775

399. Medicine (Baltimore). 2018 Jan;97(1):e9547. doi: 10.1097/MD.00000000000009547.

Familial Mediterranean fever mimicking Crohn disease: A case report.

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**RATIONALE:** Familial Mediterranean fever (FMF) is the most common form of autoinflammatory disease. We report a rare case of FMF with gastrointestinal lesions mimicking Crohn disease.

**PATIENT CONCERNS:** A 21-year-old Japanese man was referred to our institution, complaining of refractory diarrhea and weight loss of 14 kg during the past two years. He had presented with recurrent fever, abdominal pain, anal fistula and stomatitis. His father and one of his brothers had ulcerative colitis.

Colonoscopy revealed longitudinal ulcers in the terminal ileum and aphthous erosions in the colorectum. Esophagogastroduodenoscopy revealed multiple linear erosions in the gastric corpus and circular erosions in the duodenal second portion. Biopsy from these lesions failed to detect epithelioid cell granulomas.

**DIAGNOSES:** Analysis of the genomic DNA revealed compound heterozygous mutations of E148Q/L110P in exon 2 of MEFV gene, suggesting a diagnosis of FMF.

**INTERVENTIONS:** The patient was subsequently given 0.5 mg of colchicine per day.

**OUTCOMES:** Follow-up colonoscopy 6 months later demonstrated that both the longitudinal ulcers in the terminal ileum and aphthous lesions in the colorectum had completely disappeared.

**LESSONS:** Our case suggests that patients with FMF possibly manifest gastrointestinal lesions mimicking Crohn disease.

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DOI: 10.1097/MD.00000000000009547

PMCID: PMC5943120

PMID: 29505533 [Indexed for MEDLINE]

[Clinical overview of auto-inflammatory diseases].

[Article in French]

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Monogenic auto-inflammatory diseases are characterized by genetic abnormalities coding for proteins involved in innate immunity. They were initially described in mirror with auto-immune diseases because of the absence of circulating autoantibodies. Their main feature is the presence of peripheral blood inflammation in crisis without infection. The best-known auto-inflammatory diseases are mediated by interleukines that consisted in the 4 following diseases familial Mediterranean fever, cryopyrinopathies, TNFRSF1A-related intermittent fever, and mevalonate kinase deficiency. Since 10 years, many other diseases have been discovered, especially thanks to the progress in genetics. In this review, we propose the actual panorama of the main known auto-inflammatory diseases. Some of them are recurrent fevers with crisis and remission; some others evaluate more chronically; some are associated with immunodeficiency. From a physiopathological point of view, we can separate diseases mediated by interleukine-1 and diseases mediated by interferon. Then some polygenic inflammatory diseases will be shortly described: Still disease, Schnitzler syndrome, aseptic abscesses syndrome. The diagnosis of auto-inflammatory disease is largely based on anamnesis, the

presence of peripheral inflammation during attacks and genetic analysis, which are more and more performant.

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DOI: 10.1016/j.revmed.2018.01.004  
PMID: 29501512 [Indexed for MEDLINE]

401. J Allergy Clin Immunol. 2018 May;141(5):1953. doi: 10.1016/j.jaci.2018.01.010.  
Epub 2018 Mar 2.

Hidradenitis suppurativa as an autoinflammatory keratinization disease.

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DOI: 10.1016/j.jaci.2018.01.010  
PMID: 29501350

402. Rheumatol Int. 2018 May;38(5):887-893. doi: 10.1007/s00296-018-4002-8. Epub 2018  
Mar 2.

Multigene sequencing reveals heterogeneity of NLRP12-related autoinflammatory  
disorders.

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NLRP12-related autoinflammatory disease (NLRP12-AID) is an exceptionally rare autosomal dominant disorder caused by germline mutations in NLRP12 gene. Very few patients with NLRP12-AD have been identified worldwide; therefore, there is a scarcity of data on phenotypic presentation of this syndrome. Here we provide evidence that NLRP12-AID may have clinical manifestations characteristic for primary immune deficiencies (PID). 246 children with periodic fever (PF) of unknown origin were subjects to the next generation sequencing (NGS) analysis; 213 of these patients had signs of primary immunodeficiency (PID) manifested by recurrent infections, while 33 kids had isolated PF. The NGS panel was composed of 302 genes implicated in PID and/or AID. 15 patients (9 girls and 6 boys) with NLRP12-AID were identified. Median age of first AID-related fever episode was 12 months, ranging from 2 months to 13 years. Main clinical features of NLRP12-related AID were periodic fever (100%), abdominal pain and diarrhea (47%), arthralgia (20%), headache (20%) and failure to thrive (33%). Nine patients demonstrated increased susceptibility to infection and two children suffered from Crohn's disease. Administration of short courses of NSAID or corticosteroids resulted in resolution of the disease flare. In one severe case, canakinumab (anti-interleukin-1 $\beta$  antibody) was successfully used. Significant number of patients with genetically assigned diagnosis of NLRP12-AID has clinical features which close resemble primary immune deficiency. This phenotypic overlap may result in underdiagnosis of NLRP12-AID among patients with PID.

DOI: 10.1007/s00296-018-4002-8

PMID: 29500522 [Indexed for MEDLINE]

403. Rev Med Interne. 2018 Apr;39(4):279-286. doi: 10.1016/j.revmed.2018.02.003. Epub 2018 Feb 26.

[NLRC4 associated autoinflammatory diseases: A systematic review of the current literature].

[Article in French]

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The auto-inflammatory diseases linked to NLRC4 mutations are recently described entities. Transmission is autosomal dominant in 80 % of cases; cases of somatic mutation have already been reported. The disease may display two very different clinical phenotypes: the phenotype 1 (30 %), severe, is dominated by a multisystemic inflammation starting in the first year of life with symptoms of chronic inflammatory bowel disease (IBD), macrophagic activation syndrome (MAS), or even a presentation suggesting a cryopyrinopathy in its CINCA form; the mortality of this phenotype is high (25 %). The phenotype 2 (70 %), mild, usually starts after the age of 3 and is characterized by cold urticaria, arthralgia, ocular features and fever in 50 % of cases without visceral failure. Anti-interleukin-1 inhibitors are effective in most cases (83 %). Interleukin-18 (IL-18) levels are very high in both clinical forms. Interleukin-18 inhibitors and anti-interferon-gamma inhibitors were remarkably effective in two very severe phenotype 1 patients. Thus, NLRC4 mutations can induce various clinical manifestations with two distinct phenotypes. Although still rare, because very recently described, this group of diseases could be evoked by an internist in front of cold familial urticarial; probably more and more cases will be diagnosed thanks to the major progresses of genetic diagnostic tools such as next generation sequencing.

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DOI: 10.1016/j.revmed.2018.02.003

PMID: 29496273 [Indexed for MEDLINE]

404. J Med Case Rep. 2018 Mar 1;12(1):53. doi: 10.1186/s13256-017-1552-4.

A novel single variant in the MEFV gene causing Mediterranean fever and Behçet's disease: a case report.

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**BACKGROUND:** Familial Mediterranean fever is an autoinflammatory disease of unknown etiology, characterized clinically by recurrent attacks of sudden-onset fever with arthralgia and/or thoracoabdominal pain and pathogenetically by autosomal recessive inheritance due to a mutation in the MEFV gene. Behçet's disease is an inflammatory disease characterized by recurrent oral and genital aphthous ulcerations, uveitis, and skin lesions. Preliminarily, our literature review suggested that patients with familial Mediterranean fever who also have Behçet's disease have only a single mutated familial Mediterranean fever gene. The MEFV gene mutation responsible for familial Mediterranean fever is probably a susceptibility factor for Behçet's disease, particularly for patients with vascular involvement, and both disorders can occur concurrently in a patient, as in the present case.

**CASE PRESENTATION:** A 10-year-old girl of Moroccan origin presented to our institution for genetic consultation for genetic testing of the MEFV gene. She had fever associated with abdominal and diffuse joint pain in addition to headache. These symptoms have oriented pediatricians to familial Mediterranean fever. The evolution was marked by Behçet's syndrome symptoms. Sanger sequencing followed by complete exome sequencing analysis of the MEFV gene for the proband mutation revealed a novel variant. We conclude that the novel single variant c.2078 T > A (p.Met693Lys) could be responsible for the association of familial Mediterranean fever and Behçet's disease.

**CONCLUSION:** To the best of our knowledge, this is the first report of a new variant in exon 10 of the MEFV gene in a Moroccan family. This novel variant should be listed in the MEFV sequence variant databases.

DOI: 10.1186/s13256-017-1552-4

PMCID: PMC5831228

PMID: 29490685 [Indexed for MEDLINE]

405. Orphanet J Rare Dis. 2018 Feb 27;13(1):37. doi: 10.1186/s13023-018-0774-x.

TRAPPED - an insight into two sisters' struggle to access treatment for a rare genetic disease.

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Medical student training is largely focused on acquiring knowledge of diseases and their management, which may leave one with a naïve perception of what is achievable in practice, particularly in the field of rare diseases. Tumour Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) is a rare autoinflammatory disorder with a prevalence of one in a million. Its features include recurrent disabling episodes of high-grade fever associated with rash and arthralgia. Its rarity, combined with its somewhat vague and heterogenous clinical presentation, means that patients often suffer with TRAPS for years before they are diagnosed. Although it has a licensed treatment, Interleukin-1 blocker Anakinra, this is not currently funded by the NHS. This report provides an insight into the experiences of two sisters recently diagnosed with TRAPS, and the barriers they face preventing them from accessing the treatment they need, without which they are likely to suffer life-threatening organ failure. I have argued that the commissioning policy model for rare diseases needs reconsideration to improve access to Anakinra on a national level, and have highlighted the significant impact that clinicians can have on an individual level by being advocates for their patients.

DOI: 10.1186/s13023-018-0774-x

PMCID: PMC5828179

PMID: 29482660

406. Cell. 2018 Feb 22;172(5):952-965.e18. doi: 10.1016/j.cell.2018.02.019.

Inborn Errors of RNA Lariat Metabolism in Humans with Brainstem Viral Infection.

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Viruses that are typically benign sometimes invade the brainstem in otherwise healthy children. We report bi-allelic DBR1 mutations in unrelated patients from different ethnicities, each of whom had brainstem infection due to herpes simplex virus 1 (HSV1), influenza virus, or norovirus. DBR1 encodes the only known RNA lariat debranching enzyme. We show that DBR1 expression is ubiquitous, but strongest in the spinal cord and brainstem. We also show that all DBR1 mutant alleles are severely hypomorphic, in terms of expression and function. The fibroblasts of DBR1-mutated patients contain higher RNA lariat levels than control cells, this difference becoming even more marked during HSV1 infection. Finally, we show that the patients' fibroblasts are highly susceptible to HSV1. RNA lariat accumulation and viral susceptibility are rescued by wild-type DBR1. Autosomal recessive, partial DBR1 deficiency underlies viral infection of the brainstem in humans through the disruption of tissue-specific and cell-intrinsic immunity to viruses.

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DOI: 10.1016/j.cell.2018.02.019

PMCID: PMC5886375 [Available on 2019-02-22]



407. Ann Rheum Dis. 2018 Jun;77(6):840-847. doi: 10.1136/annrheumdis-2017-212608. Epub 2018 Feb 22.

Open-label, multicentre, dose-escalating phase II clinical trial on the safety and efficacy of tadekinig alfa (IL-18BP) in adult-onset Still's disease.

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**OBJECTIVES:** Adult-onset Still's disease (AOSD) is a rare systemic autoinflammatory disease; its management is largely empirical. This is the first clinical study to determine if interleukin (IL)-18 inhibition, using the recombinant human IL-18 binding protein, tadekinig alfa, is a therapeutic option in AOSD.

**METHODS:** In this phase II, open-label study, patients were  $\geq 18$  years with active AOSD plus fever or C reactive protein (CRP) levels  $\geq 10$  mg/L despite treatment with prednisone and/or conventional synthetic disease-modifying antirheumatic drugs (DMARDs). Previous biological DMARD treatment was permitted. Patients received tadekinig alfa 80 mg or 160 mg subcutaneously three times per week for 12 weeks; those receiving 80 mg not achieving early predicted response criteria (reduction of  $\geq 50\%$  CRP values from baseline and fever resolution) were up-titrated to 160 mg for a further 12 weeks. The primary endpoint was the occurrence of adverse events (AEs) throughout the study.

**RESULTS:** Ten patients were assigned to receive 80 mg tadekinig alfa and 13 patients to the 160 mg dose. One hundred and fifty-five treatment-emerging AEs were recorded, and 47 were considered related to the study drug. Most AEs were mild and resolved after drug discontinuation. Three serious AEs occurred, one possibly related to treatment (toxic optic neuropathy). At week 3, 5 of 10 patients receiving 80 mg and 6 of 12 patients receiving 160 mg achieved the predefined response criteria.

**CONCLUSIONS:** Our results indicate that tadekinig alfa appears to have a favourable safety profile and is associated with early signs of efficacy in patients with AOSD.

**TRIAL REGISTRATION NUMBER:** NCT02398435.

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DOI: 10.1136/annrheumdis-2017-212608

PMCID: PMC5965361

PMID: 29472362

Conflict of interest statement: Competing interests: CG has received grants and personal fees from AB2 Bio Ltd, grants and personal fees from Roche and Pfizer, and personal fees from Merck Sharp & Dohme (MSD), Novartis, Sanofi and AbbVie; BF has received grants from AbbVie, MSD, Pfizer and Roche, and personal fees from AbbVie, Biogen, Bristol-Myers Squibb (BMS), Celgene, Janssen, Lilly, MSD, MEDAC, Nordic, Pfizer, Roche, Swedish Orphan Biovitrum AB (publ) (Sobi), Novartis and Union Chimique Belge (UCB); FS has received grants from AB2 Bio Ltd; EF has received financial and non-financial support from AB2 Bio Ltd; IK has received personal fees from AbbVie, Actelion, BMS, Celgene, GlaxoSmithKline, Janssen, Novartis, Pfizer, Roche and Sobi; TS has received grants and personal fees from Pfizer and Roche, and personal fees from AbbVie, Biogen, BMS, Lilly, MSD, Novartis, Sanofi and UCB; BH has received personal fees from AbbVie, BMS, Novartis, Roche, Pfizer, Celgene and MSD; PL has received non-financial support from AB2 Bio Ltd; DSC has received grants from AB2 Bio Ltd and personal fees from Pfizer, BMS and Janssen; AS and EJS are employees of AB2 Bio Ltd.

408. Cold Spring Harb Mol Case Stud. 2018 Jun 1;4(3). pii: a002519. doi: 10.1101/mcs.a002519. Print 2018 Jun.

A novel de novo CAPN5 mutation in a patient with inflammatory vitreoretinopathy, hearing loss, and developmental delay.

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Mutations that activate the protease calpain-5 (CAPN5) cause a nonsyndromic adult-onset autoinflammatory eye disease characterized by uveitis, altered synaptic signaling, retinal degeneration, neovascularization, and intraocular fibrosis. We describe a pediatric patient with severe inflammatory vitreoretinopathy accompanied by hearing loss and developmental delay associated with a novel, de novo CAPN5 missense mutation (c.865C>T, p.Arg289Trp) that shows greater hyperactivation of the calpain protease, indicating a genotype-phenotype correlation that links mutation severity to proteolytic activity and the possibility of earlier onset syndromic disease with auditory and neurological abnormalities.

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DOI: 10.1101/mcs.a002519

PMCID: PMC5983175

PMID: 29472286

409. Autoimmunity. 2018 Mar;51(2):53-61. doi: 10.1080/08916934.2018.1442442. Epub 2018 Feb 22.

Alterations in nucleotide-binding oligomerization domain-2 expression, pathway activation, and cytokine production in Yao syndrome.

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Yao syndrome (YAOS) is a systemic autoinflammatory disease (SAID), formerly termed nucleotide-binding oligomerization domain-2 (NOD2)-associated autoinflammatory disease. Due to the recent identification of YAOS, the molecular mechanisms underlying its disease pathogenesis are unclear. With specific NOD2 variants as characteristic genotypic features of YAOS, our study examined NOD2 expression, transcript splicing, signaling pathway activation, and cytokine profiles in peripheral blood mononuclear cells (PBMCs) from 10 YAOS patients and six healthy individuals. All participants were genotyped for NOD2 variants; all YAOS patients were heterozygous for the NOD2 IVS8+158 variant (IVS8+158) and four patients also carried a concurrent NOD2 R702W variant (IVS8+158/R702W haplotype). Resembling other SAIDs, plasma levels of TNF $\alpha$ , IL-1 $\beta$ , IL-6, IFN $\gamma$ , and S100A12 were unaltered in YAOS patients. Intron-8 splicing of NOD2 transcripts was unaffected by carriage of NOD2 IVS8+158. However, NOD2 transcript level and basal p38 mitogen-activated protein kinase (MAPK) activity were significantly elevated in PBMCs from IVS8+158 YAOS patients. Moreover, these patients' cells had elevated basal IL-6 secretion that was enhanced by muramyl dipeptide (MDP) stimulation. Tocilizumab treatment of a YAOS IVS8+158 patient resulted in marked clinical improvement. In contrast, MDP-stimulated NF- $\kappa$ B activity was uniquely suppressed in haplotype IVS8+158/R702W patients, as was TNF $\alpha$  secretion. Our study demonstrates for the first time that NOD2 expression and pathway activation are aberrant in YAOS, and specific NOD2 genotypes result in distinct NOD2 expression and cytokine profiles. These findings may also help select therapeutic strategies in the future.

DOI: 10.1080/08916934.2018.1442442

PMCID: PMC6036904

PMID: 29471675

410. J Pathol. 2018 May;245(1):114-125. doi: 10.1002/path.5061. Epub 2018 Apr 2.

Proinflammatory role of blister fluid-derived exosomes in bullous pemphigoid.

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Bullous pemphigoid is an autoimmune inflammatory disorder characterized by the presence of autoantibodies against bullous pemphigoid autoantigens, leading to dermal-epidermal separation with consequent blister formation. However, whether and how the components of blister fluid exacerbate the progression of bullous pemphigoid is unclear. Exosomes are nanometre-sized vesicles released from cells into the body fluid, where they can transmit signals throughout the body. In the present study, we isolated and characterized exosomes from blister fluids of patients with bullous pemphigoid, evaluated their proinflammatory role, and identified the underlying molecular mechanisms. We found that exosomes isolated from blister fluids of patients with bullous pemphigoid showed the expected size and expressed the marker proteins CD63, CD81, and CD9. Additionally, blister fluid-derived exosomes were internalized by human primary keratinocytes, inducing the production of critical inflammatory cytokines and chemokines. Western blotting analysis showed robust and rapid activation of the extracellular signal-regulated kinase 1/2 and signal transducer and activator of transcription 3 signalling pathways in human primary keratinocytes after stimulation with blister fluid-derived exosomes. We also found that blister fluid-derived exosomes indirectly induced neutrophil trafficking by upregulating C-X-C motif chemokine ligand 8 *in vitro*. Furthermore, CD63 was localized mostly to keratinocytes and infiltrative granulocytes in skin lesions, suggesting that these cells were the possible sources of exosomes in blister fluid. Using mass spectrometry, we analysed the proteomes of blister fluid-derived exosomes and identified a variety of proteins implicated in inflammatory and immune responses. Together, our findings provide strong evidence that blister fluid-derived exosomes are involved in the local autoinflammatory responses of the skin associated with bullous pemphigoid. Copyright © 2018 Pathological Society of Great Britain and Ireland. Published by John Wiley & Sons, Ltd.

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DOI: 10.1002/path.5061

PMID: 29468680

411. Front Immunol. 2018 Feb 6;9:173. doi: 10.3389/fimmu.2018.00173. eCollection 2018.

Inositol-Requiring Enzyme 1-Mediated Downregulation of MicroRNA (miR)-146a and miR-155 in Primary Dermal Fibroblasts across Three TNFRSF1A Mutations Results in Hyperresponsiveness to Lipopolysaccharide.

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Tumor necrosis factor (TNF)-receptor-associated periodic fever syndrome (TRAPS) is a rare monogenic autoinflammatory disorder characterized by mutations in the TNFRSF1A gene, causing TNF-receptor 1 (TNFR1) misfolding, increased cellular stress, activation of the unfolded protein response (UPR), and hyperresponsiveness to lipopolysaccharide (LPS). Both microRNA (miR)-146a and miR-155 provide negative feedback for LPS-toll-like receptor 2/4 signaling and cytokine production, through regulation of nuclear factor kappa B (NF- $\kappa$ B). In this study, we hypothesized that proinflammatory cytokine signaling in TRAPS downregulates these two miRs, resulting in LPS-induced hyperresponsiveness in TRAPS dermal fibroblasts (DFs), irrespective of the underlying genetic mutation. Primary DF were isolated from skin biopsies of TRAPS patients and healthy controls (HC). TNFR1 cell surface expression was measured using immunofluorescence. DF were stimulated with LPS, interleukin (IL)-1 $\beta$ , thapsigargin, or TNF, with and without inositol-requiring enzyme 1 (IRE1) inhibitor (4u8C), following which miR-146a and miR-155 expression was measured by RT-qPCR. IL-1 $\beta$ , IL-6, and TNF secretion was measured by enzyme-linked

immunosorbent assays, and baseline expression of 384 different miRs was assessed using microfluidics assays. TNFR1 was found to be expressed on the surface of HC DF but expression was deficient in all samples with TRAPS-associated mutations. HC DF showed significant dose-dependent increases in both miR-146a and miR-155 expression levels in response to LPS; however, TRAPS DF failed to upregulate either miR-146a or miR-155 under the same conditions. This lack of miR-146a and miR-155 upregulation was associated with increased proinflammatory cytokine production in TRAPS DF in response to LPS challenge, which was abrogated by 4u8C. Incubation of HC DF with IL-1 $\beta$  led to downregulation of miR-146a and miR-155 expression, which was dependent on IRE1 enzyme. We observed global dysregulation of hundreds of other miRs at baseline in the TRAPS DF. In summary, these data suggest a mechanism whereby IL-1 $\beta$ , produced in response to activation of the UPR in TRAPS DF, downregulates miR-146a and miR-155, by inducing IRE1-dependent cleavage of both these miRs, thereby impairing negative regulation of NF- $\kappa$ B and increasing proinflammatory cytokine production.

DOI: 10.3389/fimmu.2018.00173

PMCID: PMC5808292

PMID: 29467762

412. Pharmacol Ther. 2018 Jul;187:133-149. doi: 10.1016/j.pharmthera.2018.02.011. Epub 2018 Feb 18.

Inflammasome biology, molecular pathology and therapeutic implications.

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Inflammasomes are intracellular multiprotein signaling complexes, mainly present in myeloid cells. They commonly assemble around a cytoplasmic receptor of the nucleotide-binding leucine-rich repeat containing receptor (NLR) family, although other cytoplasmic receptors like pyrin have been shown to form inflammasomes. The nucleation of the multiprotein scaffolding platform occurs upon detection of a microbial, a danger or a homeostasis pattern by the receptor that will, most commonly, associate with the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD) through homotypic domain interactions resulting in recruitment of procaspase-1. This will lead to the autoproteolytic activation of caspase-1, which regulates the secretion of proinflammatory IL1 $\beta$  and IL18 cytokines and pyroptosis, a caspase-1-mediated form of cell death. Pyroptosis occurs through cleavage of Gasdermin D, a membrane pore forming protein. Recently, non-canonical inflammasomes have been described, which directly sense intracellular pathogens through caspase-4 and -5 in humans, leading to pyroptosis. Inflammasomes are important in host defense; however, a deregulated activity is associated with a number of inflammatory, immune and metabolic disorders. Furthermore, mutations in inflammasome receptor coding genes are causal for an increasing number of rare autoinflammatory diseases. Biotherapies targeting the products of inflammasome activation as well as molecules that directly or indirectly inhibit inflammasome nucleation and activation are promising therapeutic areas. This review discusses recent advances in inflammasome biology, the molecular pathology of several inflammasomes, and current therapeutic approaches in autoinflammatory diseases and in selected common multifactorial inflammasome-mediated disorders.

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DOI: [10.1016/j.pharmthera.2018.02.011](https://doi.org/10.1016/j.pharmthera.2018.02.011)

PMID: 29466702

413. Clin Exp Rheumatol. 2018 Mar-Apr;36 Suppl 111(2):135-142. Epub 2018 Feb 20.

Polyarteritis nodosa revisited: a review of historical approaches, subphenotypes

and a research agenda.

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Polyarteritis nodosa (PAN) is a rare form of primary systemic vasculitis with heterogeneous presentations, treatments and disease course. Historical approaches to classification and diagnostic terminology are reviewed. Since differentiation of PAN from microscopic polyangiitis (MPA) and other ANCA vasculitides by the Chapel Hill conference statements, and with hepatitis associated PAN defined as a secondary vasculitis, the phenotyping and subclassification of PAN has received little attention. Monogenic disorders similar to PAN have been described (familial Mediterranean fever, Adenosine Deaminase-2 deficiency), and cutaneous PAN and single organ vasculitis, discussed. The overlapping phenotypes between PAN and other primary vasculitic syndromes and subphenotypes within PAN are explored. This work will underpin development of newer treatment regimens and future genetic and related aetiological studies.

PMID: 29465365 [Indexed for MEDLINE]

414. Rev Med Suisse. 2018 Feb 14;14(594):378-383.

[Recurrent auto-inflammatory fevers : a practical diagnostic flow chart].

[Article in French; Abstract available in French from the publisher]

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Recurrent autoinflammatory fever syndromes are characterized by an abnormal activation of the innate immune system pathways, leading to inappropriate systemic inflammation responsible for clinical symptoms. The diagnosis of these conditions is difficult because of their low prevalence, but also because of their nonspecific clinical signs. The presence of clinical inflammatory signs such as fever associated to serositis (arthritis, peritonitis ...) or recurrent cutaneous manifestations and elevated acute phase reactants should help the clinician to make the correct diagnosis. The purpose of this article is to provide a practical management flow chart for children with a suspected autoinflammatory recurrent fever syndrome.

Publisher: Les fièvres récurrentes auto-inflammatoires sont un groupe de pathologies qui ont comme point commun une activation anormale du système immunitaire inné, en bonne partie liées à des mutations dans les gènes régulateurs des cascades inflammatoires. Le diagnostic de ces pathologies est difficile en raison de leur faible prévalence, mais aussi de leurs signes cliniques peu spécifiques. La présence de signes cliniques et biologiques inflammatoires tels que de la fièvre associée à une inflammation des séreuses (arthrite, péritonite...) et de signes cliniques cutanés récurrents doit faire évoquer le diagnostic et conduire à une analyse sémiologique fine afin de pouvoir poser un diagnostic précis. Cet article propose une conduite à tenir de pratique clinique courante devant un enfant atteint d'une fièvre à répétition.

PMID: 29461752

Conflict of interest statement: Les auteurs n'ont déclaré aucun conflit d'intérêts en relation avec cet article.

415. Curr Opin Cell Biol. 2018 Jun;52:66-72. doi: 10.1016/j.ceb.2018.02.001. Epub 2018 Feb 21.

Nuclear envelope rupture: little holes, big openings.

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The nuclear envelope (NE), which is a critical barrier between the DNA and the cytosol, is capable of extensive dynamic membrane remodeling events in interphase. One of these events, interphase NE rupture and repair, can occur in both normal and disease states and results in the loss of nucleus compartmentalization. NE rupture is not lethal, but new research indicates that it could have broad impacts on genome stability and activate innate immune responses. These observations suggest a new model for how changes in NE structure could be pathogenic in cancer, laminopathies, and autoinflammatory syndromes, and redefine the functions of nucleus compartmentalization.

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DOI: 10.1016/j.ceb.2018.02.001

PMCID: PMC5988944 [Available on 2019-06-01]

PMID: 29459181

416. World J Clin Pediatr. 2018 Feb 8;7(1):49-55. doi: 10.5409/wjcp.v7.i1.49. eCollection 2018 Feb 8.

Neither hereditary periodic fever nor periodic fever, aphthae, pharyngitis, adenitis: Undifferentiated periodic fever in a tertiary pediatric center.

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AIM: To describe the frequency and clinical characteristics of patients with undifferentiated periodic fever (UPF) and to investigate whether a clinical classification of UPF based on the PRINTO-Eurofever score can help predicting the response to treatment and the outcome at follow-up.

**METHODS:** Clinical and therapeutic information of patients with recurrent fever who presented at a single pediatric rheumatology center from January 2006 through April 2016 were retrospectively collected. Patients with a clinical suspicion of hereditary periodic fever (HPF) syndrome and patients with clinical picture of periodic fever, aphthae, pharyngitis, adenitis (PFAPA) who were refractory to tonsillectomy underwent molecular analysis of five HPF-related genes: MEFV (NM\_000243.2), MVK (NM\_000431.3), TNFRSF1A (NM\_001065.3), NLRP3 (NM\_001079821.2), NLRP12 (NM\_001277126.1). All patients who had a negative genetic result were defined as UPF and further investigated. PRINTO-Eurofever score for clinical diagnosis of HPF was calculated in all cases.

**RESULTS:** Of the 221 patients evaluated for periodic fever, twelve subjects with a clinical picture of PFAPA who were refractory to tonsillectomy and 22 subjects with a clinical suspicion of HPF underwent genetic analysis. Twenty-three patients (10.4%) resulted negative and were classified as UPF. The median age at presentation of patients with UPF was 9.5 mo (IQR 4-24). Patients with UPF had a higher frequency of aphthae (52.2% vs 0%,  $P = 0.0026$ ) and musculoskeletal pain (65.2% vs 18.2%,  $P = 0.0255$ ) than patients with genetic confirmed HPF. Also, patients with UPF had a higher frequency of aphthous stomatitis (52.2% vs 10.7%,  $P < 0.0001$ ), musculoskeletal pain (65.2% vs 8.0%,  $P < 0.0001$ ), and abdominal pain (52.2% vs 4.8%,  $P < 0.0001$ ) and a lower frequency of pharyngitis (56.6% vs 81.3%,  $P = 0.0127$ ) compared with typical PFAPA in the same cohort. Twenty-one of 23 patients with UPF (91.3%) received steroids, being effective in 16; 13 (56.2%) were given colchicine, which was effective in 6. Symptoms resolution occurred in 2 patients with UPF at last follow-up. Classification according to the PRINTO-Eurofever score did not correlate with treatment response and prognosis.

**CONCLUSION:** UPF is not a rare diagnosis among patients with periodic fever. Clinical presentation place UPF half way on a clinical spectrum between PFAPA and HPF. The PRINTO-Eurofever score is not useful to predict clinical outcome and treatment response in these patients.

DOI: 10.5409/wjcp.v7.i1.49

PMCID: PMC5803565

PMID: 29456932

**Conflict of interest statement:** Conflict-of-interest statement: The authors declare no conflict of interest.

19.

Delicate regulation of the cGAS-MITA-mediated innate immune response.

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Although it has long been demonstrated that cytosolic DNA is a potent immune stimulant, it is only in recent years that the molecular mechanisms of DNA-stimulated innate immune responses have emerged. Studies have established critical roles for the DNA sensor cyclic GMP-AMP synthase (cGAS) and the adapter protein MITA/STING in the innate immune response to cytosolic DNA or DNA viruses. Although the regulation of cGAS-MITA/STING-mediated signaling remains to be fully investigated, understanding the processes involved may help to explain the mechanisms of innate immune signaling events and perhaps autoinflammatory diseases and to provide potential therapeutic targets for drug intervention. In this review, we summarize recent progress on the regulation of the cGAS-MITA/STING-mediated innate immune response to DNA viruses at the organelle-trafficking, post-translational and transcriptional levels.

DOI: 10.1038/cmi.2016.51

PMCID: PMC6123429

PMID: 29456253

418. Joint Bone Spine. 2018 Dec;85(6):733-739. doi: 10.1016/j.jbspin.2018.01.010. Epub 2018 Feb 13.

Boundaries between familial Mediterranean fever and juvenile spondyloarthritis: Analysis of three French retrospective cohorts.

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**OBJECTIVES:** Children with Familial Mediterranean fever may suffer from musculoskeletal involvement, somewhat difficult to distinguish from juvenile spondyloarthritis. The association of these two diseases has been scarcely reported in children. Objective of this work was to define the association of familial Mediterranean fever and juvenile spondyloarthritis in France.

**METHODS:** Three cohorts of children with familial Mediterranean fever, juvenile spondyloarthritis, familial Mediterranean fever related juvenile spondyloarthritis, were retrospectively identified in the French reference center of auto-inflammatory diseases. Familial Mediterranean fever was defined according to Tel-Hashomer or Turkish pediatric criteria with at least one exon-10 MEFV-gene mutation. Juvenile spondyloarthritis was defined according to ILAR criteria. Patients with familial Mediterranean fever or juvenile spondyloarthritis were respectively compared to familial Mediterranean fever related juvenile spondyloarthritis patients.

**RESULTS:** Sixteen children were identified as having familial Mediterranean fever related juvenile spondyloarthritis. The male/female-ratio was 0.6, with median age at spondyloarthritis onset of 7.5years (3-16years). All carried at least one

M694V variant in MEFV gene; 16.7% were HLA-B27-carriers. Compared to 83 familial Mediterranean fever patients, familial Mediterranean fever related juvenile spondyloarthritis patients had less frequently fever ( $P<0.01$ ) and more frequently arthritis ( $P<0.05$ ), enthesitis ( $P<0.001$ ), inflammatory back pain ( $P<0.001$ ), inadequate response to colchicine ( $P<0.05$ ). Compared to 20 juvenile spondyloarthritis patients, familial Mediterranean fever related juvenile spondyloarthritis patients less often received non-steroidal anti-inflammatory drugs ( $P<0.01$ ) and anti-tumor necrosis factor drugs ( $P<0.001$ ).

CONCLUSIONS: Familial Mediterranean fever may be associated with typical pattern of juvenile spondyloarthritis. These patients, with less response to colchicine, should be diagnosed earlier and treated as for jSpA.

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DOI: 10.1016/j.jbspin.2018.01.010

PMID: 29452306

419. Mod Rheumatol. 2018 Mar 2:1-7. doi: 10.1080/14397595.2018.1442639. [Epub ahead of print]

National survey of Japanese patients with mevalonate kinase deficiency reveals distinctive genetic and clinical characteristics.

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**OBJECTIVES:** Mevalonate kinase deficiency (MKD), a rare autosomal recessive autoinflammatory syndrome, is caused by disease-causing variants of the mevalonate kinase (MVK) gene. A national survey was undertaken to investigate clinical and genetic features of MKD patients in Japan.

**METHODS:** The survey identified ten patients with MKD. Clinical information and laboratory data were collected from medical records and by direct interviews with patients, their families, and their attending physicians. Genetic analysis and measurement of MVK activity and urinary excretion of mevalonic acid were performed.

**RESULTS:** None of the 10 patients harbored MVK disease-causing variants that are common in European patients. However, overall symptoms were in line with previous European reports. Continuous fever was observed in half of the patients. Elevated transaminase was observed in four of the 10 patients, two of whom fulfilled the diagnostic criteria for hemophagocytic lymphohistiocytosis. About half of the patients responded to temporary administration of glucocorticoids and NSAIDs; the others required biologics such as anti-IL-1 drugs.

**CONCLUSION:** This is the first national survey of MKD patients in a non-European country. Although clinical symptoms were similar to those reported in Europe, the incidence of continuous fever and elevated transaminase was higher, probably due to differences in disease-causing variants.

DOI: 10.1080/14397595.2018.1442639

PMID: 29451047

Recurrent fever and arthralgia as the presentation of tumor necrosis factor receptor-associated periodic syndrome (TRAPS) in a Chinese girl: a case report and review of the literature.

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Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is characterized by recurrent episodes of inflammation with fever, abdominal pain, chest pain, rash, myalgia, arthralgia, conjunctivitis, and periorbital edema. This condition is a rare autosomal dominant disease that is strongly associated with heterozygous mutations in the tumor necrosis factor (TNF) receptor super family 1A (TNFRSF1A) gene. This condition is believed to be more common in Western countries than in Asian countries, and the AA amyloidosis rate for European countries is estimated to be 10%. Herein, we report the case of a 14-year-old girl with recurrent fever and arthralgia with inflammatory marker elevation for 10 years. After extensive investigation of the infectious etiology with negative results and similar phenomenon observed within her family, the diagnosis of TRAPS was made based on next-generation sequencing, which revealed a T50M mutation; she was also sensitive to corticosteroids. Although none of our TRAPS patients developed AA amyloidosis, we suggest the continual monitoring of urinalysis results and serum amyloid A concentrations during long-term follow-up. Moreover, we also reviewed the related literature and found no Asian patients who had developed AA amyloidosis.

DOI: 10.1007/s10067-018-4023-4

PMID: 29450850 [Indexed for MEDLINE]

421. Rheumatol Int. 2018 May;38(5):879-885. doi: 10.1007/s00296-018-3993-5. Epub 2018 Feb 15.

Canakinumab treatment in children with familial Mediterranean fever: report from a single center.

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Familial Mediterranean fever (FMF), the most common hereditary autoinflammatory disorder is characterized by recurrent episodes of fever, serositis, arthritis.

The major long-term result is amyloidosis. Colchicine remains the principle of the treatment; it not only prevents the acute attacks but also prevents the long-term complications such as amyloidosis; 5-10% of the patients are unresponsive to treatment. Recently new therapeutic options as anti-interleukin 1 agents are successfully used for the patients who do not respond to colchicine treatment. In this study, we retrospectively evaluated 11 pediatric colchicine-resistant FMF patients who were treated with canakinumab. Three of the patients had amyloidosis and two had uveitis. Based on our results, we suggest that canakinumab may be a safe and effective therapy in patients who are resistant to colchicine and even in the patients with amyloidosis. We also suggest that canakinumab might be a safe option for the patients with uveitis.

DOI: 10.1007/s00296-018-3993-5

PMID: 29450637 [Indexed for MEDLINE]

422. Dermatol Online J. 2017 Dec 15;23(12). pii: 13030/qt82d4m2zw.

Pyoderma gangrenosum, acne, and suppurative hidradenitis syndrome in end-stage renal disease successfully treated with adalimumab.

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PASH syndrome (pyoderma gangrenosum, acne, and suppurative hidradenitis) forms part of the spectrum of autoinflammatory diseases. We report an unusual case of PASH syndrome in a patient with end-stage renal disease (ESRD) who was successfully treated with the tumor necrosis factor inhibitor, adalimumab. The case underscores the challenges associated with the treatment of PASH syndrome as well as the ongoing search to establish a genetic basis for the syndrome. Renal impairment has been reported in association with pyoderma gangrenosum but has not been described in PASH syndrome. We believe this to be the first reported case of a patient who developed PASH syndrome in the setting of ESRD.

PMID: 29447652 [Indexed for MEDLINE]

423. Dermatol Online J. 2017 Nov 15;23(11). pii: 13030/qt3mq1b1cx.

Crohn disease-associated neutrophilic urticarial dermatosis: report and literature review of neutrophilic urticarial dermatosis.

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Neutrophilic urticarial dermatosis (NUD) is a useful diagnostic term for urticarial lesions that are less pruritic and more painful than conventional urticaria. The histopathologic features include neutrophilic infiltrates in the interstitial dermis with a higher density than idiopathic urticaria. NUD has been associated with several systemic conditions, which are predominantly autoimmune and autoinflammatory in nature. A woman with Crohn disease who developed NUD is described. Literature reports of other conditions in which neutrophilic urticarial dermatosis have been observed are also reviewed and summarized. NUD has not only been described in the setting of inflammatory bowel disease, but also in patients who have systemic lupus erythematosus, adult-onset Still disease, and IgA gammopathy. NUD is usually associated with an underlying disease. Therapeutic agents that target neutrophils (such as dapsone and colchicine) and antagonists to interleukin-1 receptor (such as anakinra) may be effective modalities for affected patients. NUD can be added to the list of dermatologic manifestations associated with systemic inflammation, particularly inflammatory bowel disease.

PMID: 29447637 [Indexed for MEDLINE]

424. J Nephrol. 2018 Jun;31(3):453-455. doi: 10.1007/s40620-018-0475-5. Epub 2018 Feb 14.

Canakinumab treatment in renal transplant recipients with familial Mediterranean fever.

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Colchicine is the first-line treatment for familial Mediterranean fever (FMF), preventing both inflammatory attacks as well as the development of amyloidosis in the majority of the patients. However approximately 5-10% of patients are

colchicine resistant/intolerant. Side effects of colchicine are more prominent in renal transplant recipients due to interaction with immunosuppressive drugs. Anti-interleukin (IL)-1 drugs (anakinra, canakinumab and rilonacept) have emerged as the most promising drugs in the treatment of colchicine-resistant and/or intolerant FMF. There are no existing reports in the literature on canakinumab use in renal transplant recipients with FMF. We report here the efficacy and safety of canakinumab in three renal transplant recipients who achieved a complete clinical response with elimination of attacks and normalization of serum C-reactive protein (CRP) levels without significant side effects. This highlights the advantage of use of this drug in this setting, which has a better tolerability compared to anakinra.

DOI: 10.1007/s40620-018-0475-5

PMID: 29446001

425. Clin Rheumatol. 2018 Feb 13. doi: 10.1007/s10067-017-3914-0. [Epub ahead of print]

Evaluation of the effects of miRNAs in familial Mediterranean fever.

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Erratum in

Familial Mediterranean fever (FMF) is an inherited autoinflammatory disorder that can result in attacks with accompanying recurrent episodes of fever, serositis, and skin rash. MiRNAs are demonstrated to be associated with a number of other diseases; however, no comprehensive study has revealed its association with FMF disease. The aim is to investigate the role of microRNAs in FMF. We included 51 patients with genetically diagnosed FMF who had clinical symptoms and 49 healthy volunteers. Fifteen miRNAs that were found to be associated with autoinflammatory diseases and have a part in immune response were evaluated. The expression levels of 11 miRNAs (miR-125a, miR-132, miR-146a, miR-155, miR-15a, miR-16, miR-181a, miR-21, miR-223, miR-26a, and miR-34a) in the patient group were significantly low, compared with the control group ( $p < 0.05$ ). The patient group was analyzed and compared within itself, and the expression levels of 5 miRNAs (miR-132, miR-15a, miR-181a, miR-23b, miR-26a) in the patients who took colchicine seemed to have increased and levels of 5 miRNAs (miR-146a, miR-15a, miR-16, miR-26a, miR-34a) in the patients who took colchicine were significantly lower ( $p < 0.05$ ). Furthermore, the attack patients were compared with the control group, and their expression levels of 4 miRNAs (miR-132, miR-15a, miR-21, miR-34a) were significantly lower ( $p < 0.05$ ). Levels of 9 miRNAs (miR-132, miR-146a, miR-15a, miR-16, miR-181a, miR-21, miR-223, miR-26a, miR-34a) in non-attack patients decreased significantly ( $p < 0.05$ ). Our study demonstrates that miRNAs could be effective in the pathogenesis of FMF.

DOI: 10.1007/s10067-017-3914-0

PMID: 29442258

426. Front Immunol. 2018 Jan 29;9:80. doi: 10.3389/fimmu.2018.00080. eCollection 2018.

RNA-Seq Analysis of IL-1B and IL-36 Responses in Epidermal Keratinocytes  
Identifies a Shared MyD88-Dependent Gene Signature.

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IL-36 cytokines have recently emerged as mediators of inflammation in autoimmune conditions including psoriasis vulgaris (PsV) and generalized pustular psoriasis (GPP). This study used RNA-seq to profile the transcriptome of primary epidermal keratinocytes (KCs) treated with IL-1B, IL-36A, IL-36B, or IL-36G. We identified some early IL-1B-specific responses (8 h posttreatment), but nearly all late IL-1B responses were replicated by IL-36 cytokines (24 h posttreatment). Type I and II interferon genes exhibited time-dependent response patterns, with early induction (8 h) followed by no response or repression (24 h). Altogether, we identified 225 differentially expressed genes (DEGs) with shared responses to all 4 cytokines at both time points (8 and 24 h). These involved upregulation of ligands (IL1A, IL1B, and IL36G) and activating proteases (CTSS) but also upregulation of inhibitors such as IL1RN and IL36RN. Shared IL-1B/IL-36 DEGs overlapped significantly with genes altered in PsV and GPP skin lesions, as well as genes near GWAS loci linked to autoimmune and autoinflammatory diseases (e.g., PsV, psoriatic arthritis, inflammatory bowel disease, and primary biliary cholangitis). Inactivation of MyD88 adapter protein using CRISPR/Cas9 completely abolished expression responses of such DEGs to IL-1B and IL-36G stimulation. These results provide a global view of IL-1B and IL-36 expression responses in epidermal KCs with fine-scale characterization of time-dependent and cytokine-specific response patterns. Our findings support an important role for IL-1B and IL-36 in autoimmune or autoinflammatory conditions and show that MyD88 adaptor protein mediates shared IL-1B/IL-36 responses.

DOI: 10.3389/fimmu.2018.00080

PMCID: PMC5796909

PMID: 29434599

427. Immunol Rev. 2018 Mar;282(1):265-275. doi: 10.1111/imr.12633.

The role of mast cells in autoinflammation.



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The concept of autoinflammation was proposed to define a new class of immune disorders categorized by self-directed inflammation that is driven via activation of innate immune pathways. Within innate immunity, inflammasomes serve as intracellular signaling platforms to endogenous danger molecules and pathogens. Their key function is the cleavage of pro-interleukin-1 $\beta$  (pro-IL-1 $\beta$ ) into its active form to promote inflammation and programmed cell death. A growing number of inflammasome sensors were described, among which NLR family pyrin domain containing 3 (NLRP3) is the best-studied sensor. Besides macrophages, monocytes, and other innate immune cells, mast cells (MCs) were shown to express functional inflammasomes too. Also, MCs are both, a source and target of IL-1 $\beta$ . Here we review the functional relevance and role of MC inflammasomes and MC-derived IL-1 $\beta$  in contributing to the inflammation at the skin, joints, and central nervous system in rare monogenic autoinflammatory conditions and also common inflammatory and degenerative diseases.

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DOI: 10.1111/imr.12633

PMID: 29431217

428. Australas J Dermatol. 2018 Nov;59(4):278-285. doi: 10.1111/ajd.12795. Epub 2018 Feb 12.

Colchicine in dermatology: A review.

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Colchicine is an anti-inflammatory agent that has been used for decades for the treatment of various diseases including gout, familial Mediterranean fever and pericarditis and in recent years for dermatological indications including chronic urticaria, cutaneous vasculitis and psoriasis. Despite its efficacy in various cutaneous diseases, the use of colchicine may be limited by concerns over its side-effects and the potential for toxicity. This article reviews the current literature on the pharmacology of colchicine and its clinical applications in dermatology.

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DOI: 10.1111/ajd.12795

PMID: 29430631

429. J Neuroinflammation. 2018 Feb 9;15(1):38. doi: 10.1186/s12974-018-1063-2.

Systemic autoinflammation with intractable epilepsy managed with interleukin-1 blockade.

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**BACKGROUND:** Autoinflammatory disorders are distinguished by seemingly random episodes of systemic hyperinflammation, driven in particular by IL-1. Recent

pre-clinical work has shown a key role for IL-1 in epilepsy in animal models, and therapies for autoinflammation including IL-1 blockade are proposed for refractory epilepsy.

**CASE PRESENTATION:** Here, we report an adolescent female with signs of persistent systemic inflammation and epilepsy unresponsive to multiple anti-epileptic drugs (AED). She was diagnosed with generalized epilepsy with a normal brain MRI and an electroencephalogram (EEG) showing occasional generalized spike and slow wave discharges. Her diagnostic evaluation showed no signs of autoimmunity or genetic causes of epilepsy or periodic fever syndromes but persistently elevated serum inflammatory markers including S100 alarmin proteins. She experienced prompt clinical response to IL-1 blockade with first anakinra and then canakinumab, with near complete resolution of clinical seizures. Additionally, she displayed marked improvements in quality of life and social/academic functioning. Baseline gene expression studies on peripheral blood mononuclear cells (PBMC) from this patient showed significantly activated gene pathways suggesting systemic immune activation, including focal adhesion, platelet activation, and Rap1 signaling, which is an upstream regulator of IL-1 $\beta$  production by the NLRP3 inflammasome. It also showed activation of genes that characterize inflammasome-mediated autoinflammatory disorders and no signs of interferon activation. This gene expression signature was largely extinguished after anakinra treatment.

**CONCLUSIONS:** Together, these findings suggest that patients with epilepsy responsive to immune modulation may have distinct autoinflammatory features supporting IL-1 blockade. As such, IL-1 blockade may be highly efficacious adjunctive medication for certain refractory epilepsy syndromes.

DOI: 10.1186/s12974-018-1063-2

PMCID: PMC5807745

PMID: 29426321

430. *Arthritis Rheumatol.* 2018 Jun;70(6):943-956. doi: 10.1002/art.40442. Epub 2018 May 7.

Reversal of Sepsis-Like Features of Neutrophils by Interleukin-1 Blockade in Patients With Systemic-Onset Juvenile Idiopathic Arthritis.

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**OBJECTIVE:** Neutrophils are the most abundant innate immune cells in the blood, but little is known about their role in (acquired) chronic autoinflammatory diseases. This study was undertaken to investigate the role of neutrophils in systemic-onset juvenile idiopathic arthritis (JIA), a prototypical multifactorial autoinflammatory disease that is characterized by arthritis and severe systemic inflammation.

**METHODS:** Fifty patients with systemic-onset JIA who were receiving treatment with recombinant interleukin-1 receptor antagonist (rIL-1Ra; anakinra) were analyzed at disease onset and during remission. RNA sequencing was performed on fluorescence-activated cell-sorted neutrophils from 3 patients with active systemic-onset JIA and 3 healthy controls. Expression of activation markers, apoptosis, production of reactive oxygen species (ROS), and degranulation of secretory vesicles from neutrophils were assessed by flow cytometry in serum samples from 17 patients with systemic-onset JIA and 15 healthy controls.

**RESULTS:** Neutrophil counts were markedly increased at disease onset, and this correlated with the levels of inflammatory mediators. The neutrophil counts normalized within days after the initiation of rIL-1Ra therapy. RNA-sequencing analysis revealed a substantial up-regulation of inflammatory processes in neutrophils from patients with active systemic-onset JIA, significantly overlapping with the transcriptome of sepsis. Correspondingly, neutrophils from patients with active systemic-onset JIA displayed a primed phenotype that was characterized by increased ROS production, CD62L shedding, and secretory vesicle degranulation, which was reversed by rIL-1Ra treatment in patients who had achieved clinical remission. Patients with a short disease duration had high neutrophil counts, more immature neutrophils, and a complete response to rIL-1Ra, whereas patients with symptoms for >1 month had normal neutrophil counts and an unsatisfactory response to rIL-1Ra. In vitro, rIL-1Ra antagonized the priming effect of IL-1 $\beta$  on neutrophils from healthy subjects.

**CONCLUSION:** These results strongly support the notion that neutrophils play an important role in systemic-onset JIA, especially in the early inflammatory phase of the disease. The findings also demonstrate that neutrophil numbers and the

inflammatory activity of systemic-onset JIA are both susceptible to IL-1 blockade.

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DOI: 10.1002/art.40442

PMID: 29426067

431. Intest Res. 2018 Jan;16(1):151-154. doi: 10.5217/ir.2018.16.1.151. Epub 2018 Jan 18.

Duodenal amyloidosis secondary to ulcerative colitis.

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Amyloidosis is defined as the extracellular deposition of non-branching fibrils composed of a variety of serum-protein precursors. Secondary amyloidosis is associated with several chronic inflammatory conditions, such as rheumatologic or intestinal diseases, familial Mediterranean fever, or chronic infectious diseases, such as tuberculosis. Although the association of amyloidosis with inflammatory bowel disease is known, amyloidosis secondary to ulcerative colitis (UC) is rare. A 36-year-old male patient with a 15-year history of UC presented with nausea, vomiting, and abdominal pain. He had been treated with infliximab for 6 years. At the time of admission, he had been undergoing treatment with mesalazine and adalimumab since the preceding 5 months.

Esophagogastroduodenoscopy showed mucosal erythema, edema, and erosions with geographic ulcers at the 2nd and 3rd portions of the duodenum. Duodenal amyloidosis was diagnosed using polarized light microscopy and Congo red stain. Monoclonal gammopathy was not detected in serum and urine tests, while the serum free light chain assay result was not specific. An increase in plasma cells in the bone marrow was not found. Secondary amyloidosis due to UC was suspected. The symptoms were resolved after glucocorticoid therapy.

DOI: 10.5217/ir.2018.16.1.151

PMCID: PMC5797263

PMID: 29422811

Conflict of interest statement: CONFLICT OF INTEREST: No potential conflict of interest relevant to this article was reported.

432. J Dermatol Sci. 2018 May;90(2):105-111. doi: 10.1016/j.jdermsci.2018.01.012. Epub 2018 Feb 1.

Autoinflammatory keratinization diseases: An emerging concept encompassing various inflammatory keratinization disorders of the skin.

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Classifying inflammatory skin diseases is challenging, especially for the expanding group of disorders triggered by genetic factors resulting in hyperactivated innate immunity that result in overlapping patterns of dermal and epidermal inflammation with hyperkeratosis. For such conditions, the umbrella term "autoinflammatory keratinization diseases" (AIKD) has been proposed. AIKD encompasses diseases with mixed pathomechanisms of autoinflammation and autoimmunity, and includes IL-36 receptor antagonist (IL-36Ra)-related pustulosis, CARD14-mediated pustular psoriasis, pityriasis rubra pilaris (PRP) type V, and familial keratosis lichenoides chronica (KLC). Mechanistically, the entities include generalized pustular psoriasis (GPP) without psoriasis vulgaris, impetigo herpetiformis and acrodermatitis continua, which are IL-36Ra-related pustuloses caused by loss-of-function mutations in IL36RN; GPP with psoriasis vulgaris and palmoplantar pustular psoriasis which are CARD14-mediated pustular

psoriasiform dermatoses with gain-of-function variants of CARD14; PRP type V which is caused by gain-of-function mutations in CARD14; and, familial KLC in which mutations in NLRP1, an inflammasome sensor protein predominantly expressed in skin, have been identified. It is likely that further inflammatory keratinization disorders will also fall within the concept of AIKD, as elucidation of novel pathogenic mechanisms of inflammatory keratinization diseases emerges. A better understanding of the pathophysiology of AIKD is likely to lead to innovative, targeted therapies that benefit patients.

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DOI: 10.1016/j.jdermsci.2018.01.012

PMID: 29422292 [Indexed for MEDLINE]

433. Dig Liver Dis. 2018 Jun;50(6):594-600. doi: 10.1016/j.dld.2018.01.127. Epub 2018 Jan 31.

Screen-detected gallstone disease and autoimmune diseases - A cohort study.

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**BACKGROUND:** Gallstone disease is highly prevalent and is associated with systemic inflammation.

**AIMS:** To determine whether screen-detected gallstones or cholecystectomy are associated with the occurrence of autoimmune and autoinflammatory diseases and the most common subgroups thereof.

**METHODS:** A cohort study of three randomly selected general population samples from Copenhagen was performed. Participants (n = 5928) were examined in the period 1982-1992, underwent abdominal ultrasound examination to detect gallstone disease, and followed through national registers until December 2014 (median 24.7 years) for occurrence of immunological diseases. Multivariable Cox regression analyses were performed.

**RESULTS:** Gallstone disease was identified in 10% (591/5928) of participants, of whom 6.8% had gallstones and 3.2% had cholecystectomy at baseline. Gallstone disease was associated with incidence of autoimmune diseases (12.9% versus 7.92%; hazard ratio 1.46; 95% confidence interval [CI], [1.11;1.91]), diabetes mellitus type 1 (5.95% versus 3.67%; 1.53; [1.02;2.30]), and autoimmune thyroid disease (3.70% versus 1.59%; 2.06; [1.26;3.38]). Rheumatoid arthritis, autoinflammatory diseases, or any subgroups thereof were not associated.

**CONCLUSIONS:** In a large general population sample, screen-detected gallstone disease was associated with the development of autoimmune diseases during long-term follow-up. Future research efforts are needed to further explore common disease mechanisms.

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DOI: 10.1016/j.dld.2018.01.127

PMID: 29422240 [Indexed for MEDLINE]

434. Hum Genet. 2018 Feb;137(2):183-193. doi: 10.1007/s00439-018-1871-6. Epub 2018 Feb 7.

Robust identification of mosaic variants in congenital heart disease.



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Mosaicism due to somatic mutations can cause multiple diseases including cancer, developmental and overgrowth syndromes, neurodevelopmental disorders, autoinflammatory diseases, and atrial fibrillation. With the increased use of next generation sequencing technology, multiple tools have been developed to identify low-frequency variants, specifically from matched tumor-normal tissues in cancer studies. To investigate whether mosaic variants are implicated in congenital heart disease (CHD), we developed a pipeline using the cancer somatic variant caller MuTect to identify mosaic variants in whole-exome sequencing (WES) data from a cohort of parent/affected child trios (n = 715) and a cohort of healthy individuals (n = 416). This is a novel application of the somatic variant caller designed for cancer to WES trio data. We identified two cases with mosaic KMT2D mutations that are likely pathogenic for CHD, but conclude that, overall, mosaicism detectable in peripheral blood or saliva does not account for a significant portion of CHD etiology.

DOI: 10.1007/s00439-018-1871-6

PMCID: PMC5997246 [Available on 2019-02-07]

PMID: 29417219

435. Expert Rev Clin Immunol. 2018 Mar;14(3):225-233. doi: 10.1080/1744666X.2018.1438269. Epub 2018 Feb 13.

Pyoderma gangrenosum: a review of pathogenesis and treatment.

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**INTRODUCTION:** Pyoderma gangrenosum (PG) is a complex neutrophilic dermatosis that can occur as an idiopathic disease, in association with systemic conditions such as inflammatory bowel disease, as part of an inherited inflammatory syndrome. It can be challenging to treat, as it occurs in a wide variety of clinical settings and there is a lack of a standardized treatment approach. The main limitations to treatment have been an incomplete understanding of the pathogenesis. However, recent advances have been made in understanding the pathogenesis of this condition, and PG is now considered an autoinflammatory disease process. Areas covered: This review discusses the newest studies that further define our understanding of this disease and the relevant literature on treatment options for pyoderma gangrenosum. Expert commentary: The presence of abnormal neutrophils and T-cells lead to immune dysregulation, leading to lesions of PG. Increased levels of inflammatory mediators including IL-1 $\beta$ , IL-8, IL-17, and TNF- $\alpha$  contribute to the development of the disease but there are still several unknown factors, including the trigger for immune dysregulation and additional contributory components of the immune system. We provide our approach to the management of PG lesions, which involves a multi-faceted approach including wound care, topical therapy, and systemic medications in most cases.

DOI: 10.1080/1744666X.2018.1438269

PMID: 29406827

436. BMC Ophthalmol. 2018 Feb 5;18(1):27. doi: 10.1186/s12886-018-0698-1.

Effect of oral Colchicine on Peripapillary retinal nerve fiber layer thickness in patients with familial Mediterranean fever.

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**BACKGROUND:** The purpose of this study is to investigate whether oral colchicine has an effect on peripapillary retinal nerve fiber layer (pRNFL) thickness of familial Mediterranean fever (FMF) patients.

**METHODS:** We conducted a cross sectional study by comparing pRNFL thickness of FMF patients on colchicine (treated group), newly diagnosed colchicine naïve FMF patients (untreated group) and healthy controls. The study included 66 FMF patients and 32 healthy control subjects. Treated FMF patients were grouped according to colchicine use, duration of use and dosage. pRNFL thickness of the patients and controls were measured by using optical coherence tomography and the measurements were compared.

**RESULTS:** No statistically significant difference was found between the pRNFL thickness in untreated group, treated group and the healthy control group (all  $p > 0.05$ ). No statistically significant difference was found between pRNFL thickness in the healthy control group and FMF patients grouped according to duration or dosage of colchicine use (all  $p > 0.05$ ).

**CONCLUSIONS:** According to our study, FMF and oral colchicine use had no statistically significant effect on pRNFL thickness.

DOI: 10.1186/s12886-018-0698-1

PMCID: PMC5800049

PMID: 29402238 [Indexed for MEDLINE]

437. Curr Opin Rheumatol. 2018 May;30(3):295-300. doi: 10.1097/BOR.0000000000000491.

How does abatacept really work in rheumatoid arthritis?

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**PURPOSE OF REVIEW:** The purpose of this review is to summarize the current knowledge concerning the mechanisms of action of Abatacept in patients with

rheumatoid arthritis.

RECENT FINDINGS: Abatacept (CTLA-4Ig) represents a soluble, recombinant, fully humanized fusion protein, comprising the extracellular domain of CTLA-4 and the Fc portion of IgG1. Abatacept binds to the costimulatory molecules CD80 and CD86 on antigen-presenting cells (APC), thereby blocking interaction with CD28 on T cells. In humans, Abatacept treatment was shown to be effective in patients with various autoinflammatory diseases including rheumatoid arthritis. Although the prevention of T-cell activation by interfering with signaling via CD28 still represents the main mechanism of action Abatacept acts on additional cell populations including regulatory T cells (Treg), monocytes/macrophages, osteoclasts, and B cells.

SUMMARY: Effects of Abatacept on other cell populations besides T cells have to be taken into account and might represent a valuable contribution to the therapeutic success.

DOI: 10.1097/BOR.0000000000000491

PMID: 29401118

438. Cell. 2018 Feb 8;172(4):811-824.e14. doi: 10.1016/j.cell.2017.12.038. Epub 2018 Jan 25.

Human ADAR1 Prevents Endogenous RNA from Triggering Translational Shutdown.

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Type I interferon (IFN) is produced when host sensors detect foreign nucleic

acids, but how sensors differentiate self from nonself nucleic acids, such as double-stranded RNA (dsRNA), is incompletely understood. Mutations in ADAR1, an adenosine-to-inosine editing enzyme of dsRNA, cause Aicardi-Goutières syndrome, an autoinflammatory disorder associated with spontaneous interferon production and neurologic sequelae. We generated ADAR1 knockout human cells to explore ADAR1 substrates and function. ADAR1 primarily edited Alu elements in RNA polymerase II (pol II)-transcribed mRNAs, but not putative pol III-transcribed Alus. During the IFN response, ADAR1 blocked translational shutdown by inhibiting hyperactivation of PKR, a dsRNA sensor. ADAR1 dsRNA binding and catalytic activities were required to fully prevent endogenous RNA from activating PKR. Remarkably, ADAR1 knockout neuronal progenitor cells exhibited MDA5 (dsRNA sensor)-dependent spontaneous interferon production, PKR activation, and cell death. Thus, human ADAR1 regulates sensing of self versus nonself RNA, allowing pathogen detection while avoiding autoinflammation.

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DOI: 10.1016/j.cell.2017.12.038

PMCID: PMC5831367 [Available on 2019-02-08]

PMID: 29395325

439. Clin Genet. 2018 Jul;94(1):81-94. doi: 10.1111/cge.13223. Epub 2018 Mar 9.

Lack of clear and univocal genotype-phenotype correlation in familial Mediterranean fever patients: A systematic review.

Gangemi S(1), Manti S(2), Procopio V(2), Casciaro M(1), Di Salvo E(3), Cutrupi M(2), Ganci G(2), Salpietro C(2), Chimenz R(4), Cuppari C(2).

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Familial Mediterranean fever (FMF) is the most common autosomal recessive autoinflammatory disease. To date, following the isolation of more than 280 MEFV sequence variants, the genotype-phenotype correlation in FMF patients has been intensively investigated; however, an univocal and clear consensus has not been yet reached. Thus, the aim of this systematic review was to analyze the available literature findings in order to provide to scientific community an indirect estimation of the impact of genetic factors on the phenotypic variability of FMF. This systematic review has been conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines. The p.M694V mutation was reported to have a relatively severe clinical course, similarly, patients homozygous for M694I and M680I, or carrying a combination of both at codons 694 and 680, have a severe disease. Also, patients homozygous for M694V and V726A variants experienced more severe clinical picture. Conversely, heterozygous p.V726A and p.E148Q genotypes have been correlated with a milder disease course. At present, doubts remain on the potential pathogenic role of E148Q variant. The heterogeneity in clinical FMF manifestations reflects the changes occurring in repertoire of mutations. We believe that clinical criteria and gene tests, enhancing each other, could better support the diagnosis of FMF.

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DOI: 10.1111/cge.13223

PMID: 29393966

440. Nat Rev Rheumatol. 2018 Feb 1. doi: 10.1038/nrrheum.2018.11. [Epub ahead of print]

Autoinflammatory diseases: Free IL-18 causes macrophage activation syndrome.

Lieben L(1).

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(1)Nature Reviews Disease Primers.

DOI: 10.1038/nrrheum.2018.11

PMID: 29386593

441. Eur Ann Allergy Clin Immunol. 2018 Jul;50(4):187-189. doi: 10.23822/EurAnnACI.1764-1489.31. Epub 2017 Nov 23.

An unusual case of wheat dependent exercise induced anaphylaxis (WDEIA) triggered by Tri a 14 in a pediatric patient: a case report.

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Summary: Anakinra, one of the novel biological agents, is a recombinant human IL-1 receptor antagonist. It is preferred as an alternative drug for familial Mediterranean fever cases where colchicine is not sufficient or cannot be used due to its side effects. Like all other biologics, hypersensitivity reactions to anakinra are quite rare. This is the first case which was successfully desensitized with anakinra after a severe immediate-type hypersensitivity reaction. We report a case of WDEIA in an asthmatic boy admitted to our Unit with suspected mushroom acute toxicity. The symptoms occurred during a gym session, approximately 2 hours after the ingestion of a meal based on pasta and cooked mushroom found in the family's garden. Acute toxicity due to mushroom ingestion was then excluded. Triptase serum levels resulted elevated in acute phase and normal after 24 hours. Food specific IgE showed a sensitization to lipid transfer protein Pru p 3 and to Tri a 14. This case highlights that WDEIA is underdiagnosed, especially when patients are firstly visited in Emergency Unit. Moreover, Tri a 14 is seldom described as responsible for WDEIA, compared to omega 5 gliadin.

DOI: 10.23822/EurAnnACI.1764-1489.31

PMID: 29384105

442. Eur Ann Allergy Clin Immunol. 2018 Mar;50(2):94-96. doi: 10.23822/EurAnnACI.1764-1489.30. Epub 2017 Nov 22.

Successful rapid subcutaneous desensitization to anakinra in a case with a severe



immediate-type hypersensitivity reaction.

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Summary: Anakinra, one of the novel biological agents, is a recombinant human IL-1 receptor antagonist. It is preferred as an alternative drug for familial Mediterranean fever cases where colchicine is not sufficient or cannot be used due to its side effects. Like all other biologics, hypersensitivity reactions to anakinra are quite rare. This is the first case which was successfully desensitized with anakinra after a severe immediate-type hypersensitivity reaction.

DOI: 10.23822/EurAnnACI.1764-1489.30

PMID: 29384104

443. Pharmacol Res. 2018 Jul;133:277-288. doi: 10.1016/j.phrs.2018.01.009. Epub 2018 Jan 31.

Metabolic syndrome, autoimmunity and rheumatic diseases.

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Metabolic syndrome (MetS) is a cluster of metabolic and cardiovascular (CV) risk factors including obesity and visceral adiposity, insulin resistance, dyslipidemia and hypertension contributing to CV mortality. The interface between the metabolic and immune systems has been of great interest recently. These interactions are regulated through genetics, nutritional status, and the intestinal microbiome. Alterations in the immune-metabolic cross-talk contribute to the development of autoimmune diseases. Adipokines exert a variety of metabolic activities contributing to the etiopathogenesis of MetS and are involved in the regulation of both inflammatory processes and autoimmunity occurring in rheumatic diseases. Patients with autoinflammatory disease such as gout and those with autoimmune rheumatic diseases (ARD), such as systemic lupus erythematosus, rheumatoid arthritis, antiphospholipid syndrome, ankylosing spondylitis and vasculitis among others, have increased prevalence of MetS. Despite recent advances in treatment of ARD, incidence of CVD remains high. MetS and altered secretion patterns of proinflammatory adipokines could be the link between CVDs and ARD. In addition, in ARD the activation of proinflammatory signalling pathways results in the induction of several biological markers of chronic inflammation contributing to CVD. In the present paper, we review recent evidences of the interactions between MetS and ARD, as well as novel therapeutic targets.

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DOI: 10.1016/j.phrs.2018.01.009

PMID: 29382608

Jan 31.

Effects of mating patterns on genealogical trees: Assessment of the high carrier rate of Familial Mediterranean Fever in rural Israeli districts.

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We investigate the spread from ancestors to descendants, under a model of sexual reproduction, of hereditary elements distinguishing individuals from their fellow human beings. These hereditary elements, termed labels, are either symbolic, implying a socio-cultural or ethnic self-determined category, or biological, i.e. a DNA sequence (for example founder mutations). The impact of various modes of preferential (assortative) mating on the dissemination of a known ancestral label was studied for both kinds of labels, the symbolic and the biological. For the socio-cultural based labeling, both mathematical modeling and simulation studies were carried out, and disclosed a marked delay in the spread of the labels in future generations, compared to the case where mating was random. The transmission of biological labels (founder mutations) from an ancestor to descendants under various modes and degrees of assortative mating was investigated by simulations and supplemented by an in-depth analysis of allele frequencies of Familial Mediterranean Fever (FMF) in an Israeli Muslim Arab village. The high carrier frequency of FMF in this village was satisfactorily explained solely by the presence of a founder effect and a pronounced high factor of selective mating, causing segregation and consanguinity among its inhabitants. Contribution of further evolutionary mechanisms such as heterozygote advantage, drift, differential reproductive success or selection pressure was not essential to explain these results.

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DOI: 10.1016/j.jtbi.2018.01.029

PMID: 29382538

445. Medicine (Baltimore). 2017 Nov;96(47):e8903. doi: 10.1097/MD.00000000000008903.

Case report: remarkable remission of SAPHO syndrome in response to *Tripterygium wilfordii* hook f treatment.

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**RATIONALE:** SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome is an autoinflammatory disease with no standardized treatment. *Tripterygium wilfordii* hook f (TwHF) is a Chinese herb with immunosuppressive effects and has been used to treat some chronic inflammatory diseases. However, it has not been reported as a therapeutic option in SAPHO syndrome. Here we present the first report in which a remarkable remission of SAPHO syndrome was achieved in response to TwHF.

**PATIENT CONCERNS:** A 57-year-old female patient noted swelling and pain at the anterior chest wall and scattered rashes like psoriasis vulgaris. Bone scintigraphy demonstrated the classic "bull's head" sign and magnetic resonance images indicated bone marrow edema on T5.

**DIAGNOSES:** The diagnosis was made by dermatological and osteoarticular manifestations and classical "bull's head" sign in bone scintigraphy.

**INTERVENTIONS:** TwHF with a priming dose of 20 mg 3 times per day and a gradual dose reduction of 20 mg per day in every 3 months. Four months later, methotrexate was added with 10 mg per week.

**OUTCOMES:** Osteoarticular symptoms and radiological abnormalities were improved dramatically.

**LESSONS:** This case illustrates a promising strategy to treat SAPHO syndrome.

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DOI: 10.1097/MD.00000000000008903

PMCID: PMC5709022

PMID: 29382023 [Indexed for MEDLINE]

446. Br J Dermatol. 2018 Mar;178(3):619-631. doi: 10.1111/bjd.16231. Epub 2018 Jan 30.

Acne and hidradenitis suppurativa.

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Acne and hidradenitis suppurativa (HS) both centre on hair follicles. They often occur together as part of the acne tetrad, but are found in distinct localizations. Acne is primarily defined by the presence of comedones and inflammatory lesions. However, in HS the intertriginous localization and chronicity play equally important roles for the diagnosis to the inflammatory lesions. Genetics, bacteria, environmental factors and innate inflammation have all been found to play a role in acne and/or HS. Surprisingly, there is little overlap between the findings so far. The genetics of acne and HS are distinct, bacteria have not been shown convincingly to play a role in HS, and the important risk factors obesity and smoking in HS cannot be easily translated to acne. The one driving factor central to both diseases is innate inflammation, most strikingly involving interleukin-1. Hence the interleukin-1 family, as already shown in autoinflammatory conditions associated with acne, could represent attractive treatment targets.

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DOI: 10.1111/bjd.16231

PMID: 29380349

447. Mediators Inflamm. 2017;2017:7461426. doi: 10.1155/2017/7461426. Epub 2017 Dec 12.

## Small Intestinal Bacterial Overgrowth Affects the Responsiveness to Colchicine in Familial Mediterranean Fever.

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**Objective:** Familial Mediterranean fever (FMF) is an autosomal recessive disease due to a MEFV gene mutation. Since *Helicobacter pylori* infection has been described to increase the severity and frequency of FMF attacks, we evaluate if overgrowth of small intestinal bacterial (SIBO), associated with a release of bacterial products, can affect the response to colchicine in FMF patients poorly responsive to colchicine.

**Methods:** We revised our Periodic Fever Centre database to detect FMF patients who were poorly responsive to colchicine, without a well-defined cause of drug resistance. They were evaluated for SIBO presence, then treated with decontamination therapy.

**Results:** Among 223 FMF patients, 49 subjects show colchicine resistance, and no other known causes of colchicine unresponsiveness has been found in 25 patients. All 25 patients underwent glucose breath test; 20 (80%) of them were positive, thus affected by SIBO. After a successful decontamination treatment, 11 patients (55%) did not show FMF attacks during the following three months ( $p < 0.01$ ), while 9 of them revealed a significant reduction of the number of attacks compared to three months before ( $p < 0.01$ ).

**Conclusion:** The SIBO eradication improves laboratory and clinical features of FMF patients. Thus, patients with unresponsiveness to colchicine treatment should be investigated for SIBO.

DOI: 10.1155/2017/7461426

PMCID: PMC5742903

PMID: 29379228 [Indexed for MEDLINE]

448. J Leukoc Biol. 2018 Jan 26. doi: 10.1002/JLB.3MIR0917-350R. [Epub ahead of print]

An update on cell intrinsic negative regulators of the NLRP3 inflammasome.

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Inflammasomes are multimeric protein complexes that promote inflammation (through specific cleavage and production of bioactive IL-1 $\beta$  and IL-18) and pyroptotic cell death. The central role of inflammasomes in combating infection and maintaining homeostasis has been studied extensively. Although inflammasome-mediated inflammation and cell death are vital to limit pathogenic insults and to promote wound healing/tissue regeneration, unchecked/uncontrolled inflammation, and cell death can cause cytokine storm, tissue damage, autoinflammatory and autoimmune diseases, and even death in the afflicted individuals. NLRP3 is one of the major cytosolic sensors that assemble an inflammasome. Given the adverse consequences of uncontrolled inflammasome activation, our immune system has developed tiered mechanisms to inhibit NLRP3 inflammasome activation. In this review, we highlight and discuss recent advances and our current understanding of mechanisms by which NLRP3 inflammasome can be negatively regulated.

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DOI: 10.1002/JLB.3MIR0917-350R

PMCID: PMC6202258 [Available on 2019-07-26]

PMID: 29377242

449. Curr Opin Endocrinol Diabetes Obes. 2018 Apr;25(2):94-100. doi: 10.1097/MED.0000000000000399.

Potential role of type I interferon in the pathogenic process leading to type 1 diabetes.

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**PURPOSE OF REVIEW:** Understanding the relationship between viral infections and the development of type 1 diabetes (T1D) is essential for T1D prevention.

Virus-induced innate immune responses, specifically type I interferon (IFN-I) and the IFN gene signature, orchestrate early events of  $\beta$ -cell dysfunction preceding islet autoimmunity. We summarize recent advances in how IFN-I and the IFN gene signature can drive T1D development.

**RECENT FINDINGS:** IFN-I, particularly IFN- $\alpha$ , and the IFN gene signature have been detected in islets and peripheral blood of T1D patients. T1D risk genes in the IFN-I signaling pathway regulate antiviral responses in  $\beta$  cells driven by IFN-I and proinflammatory cytokines. Polymorphisms in these genes may cause chronic dysregulated IFN signaling in islets, characterized by hyperexpression of IFN-I, the IFN gene signature, and major histocompatibility complex class I during viral infection. Islet-cell inflammation mediated by aberrant IFN signaling drives  $\beta$ -cell apoptosis by initiating autoreactivity against  $\beta$ -cell antigens. The profound elevation in IFN-I and the IFN gene signature observed in some forms of T1D are also seen in a novel group of human autoimmune and autoinflammatory diseases called interferonopathies.

**SUMMARY:** Despite significant advances, further studies are required to functionally dissect the mechanisms by which excessive IFN-I contributes to the evolution of autoimmunity that destroys  $\beta$  cells.

DOI: 10.1097/MED.0000000000000399

PMCID: PMC5836805 [Available on 2019-04-01]

PMID: 29369915

450. Am J Ophthalmol. 2018 Apr;188:41-50. doi: 10.1016/j.ajo.2018.01.017. Epub 2018 Jan 31.

Keratoendotheliitis Fugax Hereditaria: A Novel Cryopyrin-Associated Periodic Syndrome Caused by a Mutation in the Nucleotide-Binding Domain, Leucine-Rich Repeat Family, Pyrin Domain-Containing 3 (NLRP3) Gene.



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**PURPOSE:** To describe the phenotype and the genetic defect in keratoendotheliitis fugax hereditaria, an autosomal dominant keratitis that periodically affects the corneal endothelium and stroma, leading in some patients to opacities and decreased visual acuity.

**DESIGN:** Cross-sectional, hospital-based study.

**METHODS:** Patient Population: Thirty affected and 7 unaffected subjects from 7 families, and 4 sporadic patients from Finland.

**OBSERVATION PROCEDURES:** Ophthalmic examination and photography, corneal topography, specular microscopy, and optical coherence tomography in 34 patients, whole exome sequencing in 10 patients, and Sanger sequencing in 34 patients.

**MAIN OUTCOME MEASURES:** Clinical phenotype, disease-causing genetic variants.

**RESULTS:** Unilateral attacks of keratoendotheliitis typically occurred 1-6 times a year (median, 2.5), starting at a median age of 11 years (range, 5-28 years), and lasted for 1-2 days. The attacks were characterized by cornea pseudoguttata and haze in the posterior corneal stroma, sometimes with a mild anterior chamber reaction, and got milder and less frequent in middle age. Seventeen (50%) patients had bilateral stromal opacities. The disease was inherited as an autosomal dominant trait. A likely pathogenic variant c.61G>C in the NLRP3 gene, encoding cryopyrin, was detected in all 34 tested patients and segregated with the disease. This variant is present in both Finnish and non-Finnish European populations at a frequency of about 0.02% and 0.01%, respectively.

**CONCLUSION:** Keratoendotheliitis fugax hereditaria is an autoinflammatory

cryopyrin-associated periodic syndrome caused by a missense mutation c.61G>C in exon 1 of NLRP3 in Finnish patients. It is additionally expected to occur in other populations of European descent.

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DOI: 10.1016/j.ajo.2018.01.017

PMID: 29366613 [Indexed for MEDLINE]

451. Amyloid. 2018 Mar;25(1):37-45. doi: 10.1080/13506129.2018.1429391. Epub 2018 Jan 24.

Obesity is a significant susceptibility factor for idiopathic AA amyloidosis.

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**BACKGROUND:** To investigate obesity as susceptibility factor in patients with idiopathic AA amyloidosis.

**METHODS:** Clinical, biochemical and genetic data were obtained from 146 patients with AA amyloidosis. Control groups comprised 40 patients with long-standing inflammatory diseases without AA amyloidosis and 56 controls without any inflammatory disease.

**FINDINGS:** Patients with AA amyloidosis had either familial Mediterranean fever (FMF) or long-standing rheumatic diseases as underlying inflammatory disease (n = 111, median age 46 years). However, in a significant proportion of patients with AA amyloidosis no primary disease was identified (idiopathic AA; n = 37, median age 60 years). Patients with idiopathic AA amyloidosis were more obese and older than patients with AA amyloidosis secondary to FMF or rheumatic diseases.

Serum leptin levels correlated with the body mass index (BMI) in all types of AA amyloidosis. Elevated leptin levels of more than 30 µg/l were detected in 18% of FMF/rheumatic + AA amyloidosis and in 40% of patients with idiopathic AA amyloidosis ( $p = .018$ ). Finally, the SAA1 polymorphism was confirmed as a susceptibility factor for AA amyloidosis irrespective of the type of the disease. CONCLUSIONS: Obesity, age and the SAA1 polymorphism are susceptibility factors for idiopathic AA amyloidosis. Recent advances in treatment of FMF and rheumatic disorders will decrease the incidence of AA amyloidosis due to these diseases. Idiopathic AA, however, might be an emerging problem in the ageing and increasingly obese population.

DOI: 10.1080/13506129.2018.1429391

PMID: 29364741 [Indexed for MEDLINE]

452. Sci Signal. 2018 Jan 23;11(514). pii: eaam8104. doi: 10.1126/scisignal.aam8104.

Guanabenz inhibits TLR9 signaling through a pathway that is independent of eIF2 $\alpha$  dephosphorylation by the GADD34/PP1c complex.

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Endoplasmic reticulum (ER) stress triggers or amplifies inflammatory signals and cytokine production in immune cells. Upon the resolution of ER stress, the inducible phosphatase 1 cofactor GADD34 promotes the dephosphorylation of the initiation factor eIF2 $\alpha$ , thereby enabling protein translation to resume. Several aminoguanidine compounds, such as guanabenz, perturb the eIF2 $\alpha$  phosphorylation-dephosphorylation cycle and protect different cell or tissue types from protein misfolding and degeneration. We investigated how pharmacological interference with the eIF2 $\alpha$  pathway could be beneficial to treat autoinflammatory diseases dependent on proinflammatory cytokines and type I interferons (IFNs), the production of which is regulated by GADD34 in dendritic cells (DCs). In mouse and human DCs and B cells, guanabenz prevented the activation of Toll-like receptor 9 (TLR9) by CpG oligodeoxynucleotides or DNA-immunoglobulin complexes in endosomes. In vivo, guanabenz protected mice from CpG oligonucleotide-dependent cytokine shock and decreased autoimmune symptom severity in a chemically induced model of systemic lupus erythematosus. However, we found that guanabenz exerted its inhibitory effect independently of GADD34 activity on eIF2 $\alpha$  and instead decreased the abundance of CH25H, a cholesterol hydroxylase linked to antiviral immunity. Our results therefore suggest that guanabenz and similar compounds could be used to treat type I IFN-dependent pathologies and that CH25H could be a therapeutic target to control these diseases.

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DOI: 10.1126/scisignal.aam8104

PMID: 29363586

453. Ups J Med Sci. 2018 Mar;123(1):57-61. doi: 10.1080/03009734.2017.1423425. Epub 2018 Jan 24.

Increased psoriasis frequency in patients with familial Mediterranean fever.

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**OBJECTIVE:** Familial Mediterranean fever (FMF) is a periodic fever syndrome caused by MEFV mutations. FMF may be associated with psoriasis in some cases. The prevalence of psoriasis in the normal Turkish population is 0.42%. We aimed to investigate the prevalence of psoriasis among FMF patients and their relatives.

**METHODS:** FMF patients followed at Hacettepe University Adult and Pediatric Rheumatology Departments between January and August 2016 were included. FMF patients/their relatives were accepted to have psoriasis if the diagnosis was made by a dermatologist.

**RESULTS:** A total of 351 FMF patients (177 adults; 174 children) were included. The median (min-max) age of adult and pediatric patients was 35 (19-63) and 10 (2-18) years, respectively. Thirteen (3.7%) FMF patients (11 adults, 2 children) had psoriasis. Psoriasis was more common in adult than pediatric patients ( $p = 0.02$ ). Psoriasis was present in 22 (12.4%) of adult and 9 (5.2%) of pediatric patients' relatives ( $p = 0.023$ ). The frequency of psoriasis in  $\geq 1$  relatives of FMF patients was found to be 8.8%. Abdominal pain and fever were significantly higher, and arthralgia, arthritis, pleural chest pain, and pericarditis were significantly less frequent in the pediatric group than in adults ( $p < 0.05$ ).

**CONCLUSION:** Psoriasis was more common in FMF patients than in the normal population. Thus, FMF patients should be questioned and carefully examined for psoriasis lesions and psoriasis family history. Prospective multicenter studies may be important to find the incidence of psoriasis in FMF.

DOI: 10.1080/03009734.2017.1423425

PMCID: PMC5901469

PMID: 29363386 [Indexed for MEDLINE]

Hidradenitis suppurativa, a review of pathogenesis, associations and management.  
Part 2.

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Hidradenitis suppurativa is a chronic, painful, autoinflammatory condition resulting in nodules, abscesses and sinus tracts. We present an evidence-based review providing new understanding of the pathogenesis of hidradenitis suppurativa and associated comorbidities. By the nature of their speciality, dermatologists are uniquely positioned to investigate and treat patients.

© 2018 The Australasian College of Dermatologists.

DOI: 10.1111/ajd.12766

PMID: 29363099

455. Curr Pharm Des. 2018;24(6):675-683. doi: 10.2174/1381612824666180123101313.

Colchicine in Renal Diseases: Present and Future.

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Colchicine is a lipophilic alkaloid drug, which exhibits ant-inflammatory and anti-fibrotic properties. Cardinal mechanisms of action of colchicine are the disruption of the microtubule system and the inhibition of neutrophil adhesion and recruitment. Colchicine is indicated in the prevention and treatment of gouty arthritis and familial Mediterranean fever. In this review, we summarize current and potentially future pharmacologic activities of colchicine in various renal disease entities along with pharmacokinetic and pharmacodynamic properties.

Additionally, we will refer to main interactions of colchicine with medications used in renal medicine, as well as dosing recommendations in patients with reduced glomerular filtration rate.

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DOI: 10.2174/1381612824666180123101313

PMID: 29359660

456. Ann Rheum Dis. 2018 Apr;77(4):612-619. doi: 10.1136/annrheumdis-2017-212401. Epub 2018 Jan 22.

Aberrant tRNA processing causes an autoinflammatory syndrome responsive to TNF inhibitors.

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**OBJECTIVES:** To characterise the clinical features, immune manifestations and molecular mechanisms in a recently described autoinflammatory disease caused by



mutations in TRNT1, a tRNA processing enzyme, and to explore the use of cytokine inhibitors in suppressing the inflammatory phenotype.

**METHODS:** We studied nine patients with biallelic mutations in TRNT1 and the syndrome of congenital sideroblastic anaemia with immunodeficiency, fevers and developmental delay (SIFD). Genetic studies included whole exome sequencing (WES) and candidate gene screening. Patients' primary cells were used for deep RNA and tRNA sequencing, cytokine profiling, immunophenotyping, immunoblotting and electron microscopy (EM).

**RESULTS:** We identified eight mutations in these nine patients, three of which have not been previously associated with SIFD. Three patients died in early childhood. Inflammatory cytokines, mainly interleukin (IL)-6, interferon gamma (IFN- $\gamma$ ) and IFN-induced cytokines were elevated in the serum, whereas tumour necrosis factor (TNF) and IL-1 $\beta$  were present in tissue biopsies of patients with active inflammatory disease. Deep tRNA sequencing of patients' fibroblasts showed significant deficiency of mature cytosolic tRNAs. EM of bone marrow and skin biopsy samples revealed striking abnormalities across all cell types and a mix of necrotic and normal-appearing cells. By immunoprecipitation, we found evidence for dysregulation in protein clearance pathways. In 4/4 patients, treatment with a TNF inhibitor suppressed inflammation, reduced the need for blood transfusions and improved growth.

**CONCLUSIONS:** Mutations of TRNT1 lead to a severe and often fatal syndrome, linking protein homeostasis and autoinflammation. Molecular diagnosis in early life will be crucial for initiating anti-TNF therapy, which might prevent some of the severe disease consequences.

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DOI: 10.1136/annrheumdis-2017-212401

PMCID: PMC5890629

PMID: 29358286

Conflict of interest statement: Competing interests: None declared.

457. J Immunol. 2018 Mar 1;200(5):1607-1617. doi: 10.4049/jimmunol.1700712. Epub 2018 Jan 22.

## Copper Regulates the Canonical NLRP3 Inflammasome.

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Inflammasomes are multimeric protein complexes that are activated through a NOD-like receptor and regulate the proteolytic activation of caspase-1 and cytokines, like IL-1 $\beta$ . The NLRP3 inflammasome is implicated in many human pathologies including infections, autoinflammatory syndromes, chronic inflammation, and metabolic diseases; however, the molecular mechanisms of activation are not fully understood. In this study we show that NLRP3 inflammasome activation requires intracellular copper. A clinically approved copper chelator, tetrathiomolybdate, inhibited the canonical NLRP3 but not the AIM2, NLRC4, and NLRP1 inflammasomes or NF- $\kappa$ B-dependent priming. We demonstrate that NLRP3 inflammasome activation is blocked by removing copper from the active site of superoxide dismutase 1, recapitulating impaired inflammasome function in superoxide dismutase 1-deficient mice. This regulation is specific to macrophages, but not monocytes, both in mice and humans. In vivo, depletion of bioavailable copper resulted in attenuated caspase-1-dependent inflammation and reduced susceptibility to LPS-induced endotoxic shock. Our results indicate that targeting the intracellular copper homeostasis has potential for the treatment of NLRP3-dependent diseases.

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DOI: 10.4049/jimmunol.1700712

PMID: 29358279

## Practice and consensus-based strategies in diagnosing and managing systemic juvenile idiopathic arthritis in Germany.

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**BACKGROUND:** Systemic juvenile idiopathic arthritis (SJIA) is an autoinflammatory disease associated with chronic arthritis. Early diagnosis and effective therapy of SJIA is desirable, so that complications are avoided. The PRO-KIND initiative of the German Society for Pediatric Rheumatology (GKJR) aims to define consensus-based strategies to harmonize diagnostic and therapeutic approaches in Germany.

**METHODS:** We analyzed data on patients diagnosed with SJIA from 3 national registries in Germany. Subsequently, via online surveys and teleconferences among pediatric rheumatologists with a special expertise in the treatment of SJIA, we identified current diagnostic and treatment approaches in Germany. Those were harmonized via the formulation of statements and, supported by findings from a literature search. Finally, an in-person consensus conference using nominal group technique was held to further modify and consent the statements.

**RESULTS:** Up to 50% of patients diagnosed with SJIA in Germany do not fulfill the International League of Associations for Rheumatology (ILAR) classification criteria, mostly due to the absence of chronic arthritis. Our findings suggest that chronic arthritis is not obligatory for the diagnosis and treatment of SJIA, allowing a diagnosis of probable SJIA. Malignant, infectious and hereditary autoinflammatory diseases should be considered before rendering a diagnosis of probable SJIA. There is substantial variability in the initial treatment of SJIA. Based on registry data, most patients initially receive systemic glucocorticoids, however, increasingly substituted or accompanied by biological agents, i.e. interleukin (IL)-1 and IL-6 blockade (up to 27.2% of patients). We identified preferred initial therapies for probable and definitive SJIA, including step-up patterns and treatment targets for the short-term (resolution of fever, decrease in C-reactive protein by 50% within 7 days), the mid-term (improvement in physician global and active joint count by at least 50% or a JADAS-10 score of maximally 5.4 within 4 weeks) and the long-term (glucocorticoid-free clinically inactive disease within 6 to 12 months), and an explicit treat-to-target

strategy.

CONCLUSIONS: We developed consensus-based strategies regarding the diagnosis and treatment of probable or definitive SJA in Germany.

DOI: 10.1186/s12969-018-0224-2

PMCID: PMC5778670

PMID: 29357887 [Indexed for MEDLINE]

459. *Australas J Dermatol*. 2018 Nov;59(4):267-277. doi: 10.1111/ajd.12770. Epub 2018 Jan 21.

Hidradenitis suppurativa, a review of pathogenesis, associations and management. Part 1.

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Hidradenitis suppurativa is a chronic, painful, autoinflammatory condition resulting in nodules, abscesses and sinus tracts. We present an evidence-based review providing new understanding of the pathogenesis of hidradenitis suppurativa and associated comorbidities. By the nature of their speciality, dermatologists are uniquely positioned to investigate and treat patients with this condition. Data collected from a subspecialty hidradenitis suppurativa clinic (N = 106) and experiences thereof are discussed in this review.

© 2018 The Australasian College of Dermatologists.

DOI: 10.1111/ajd.12770

PMID: 29355905

460. *Hemodial Int*. 2018 Apr;22(2):E19-E22. doi: 10.1111/hdi.12628. Epub 2018 Jan 18.

Atypical familial Mediterranean fever developed in a long-term hemodialysis patient.

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Familial Mediterranean Fever (FMF) is usually an autosomal recessive autoinflammatory disease characterized by recurrent attacks of fever and serositis. FMF develops before the age of 20 years in 90% of patients. It has intervals of 1 week to several years between attacks, which leads to renal dysfunction-amyloidosis. We report a case of atypical FMF that developed in a long-term hemodialysis patient. A 65-year-old Japanese female undergoing hemodialysis for 32 years was referred to our hospital with a fever of unknown origin (FUO) following cervical laminoplasty. The fever occurred as recurrent attacks accompanied by oligoarthralgia of the left hip and knee. We suspected FMF because of recurrent self-limited febrile attacks, although the patient showed atypical clinical features such as late-onset and highly frequent attacks. After receiving treatment, she achieved a complete response to colchicine. Therefore, a diagnosis of FMF was made based on the Tel-Hashomer criteria, which was confirmed by genetic testing. The case suggests that FMF may be of note in long-term hemodialysis patients developing FUO.

© 2017 International Society for Hemodialysis.

DOI: 10.1111/hdi.12628

PMID: 29345845

461. Curr Pharm Des. 2018;24(6):654-658. doi: 10.2174/1381612824666180115105850.

Isolating Colchicine in 19th Century: An Old Drug Revisited.

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Colchicine is a tricyclic alkaloid extracted from the herbaceous plant *Colchicum autumnale*. Known since antiquity for its therapeutic efficacy in the treatment of gout, colchicine was reintroduced in 19th century pharmacopeia, thanks to the work of the French chemists and pharmacists Pierre-Joseph Pelletier (1788-1842) and Joseph Bienaimé Caventou (1795-1877) who in 1819, isolated a peculiar substance in the roots of *Colchicum autumnale*. In 1833, the substance was further analyzed by the German pharmacist and chemist Philipp Lorenz Geiger (1785-1836), who coined the name colchicine. In 1884, the French pharmacist Alfred Houde (1854-1919) produced for the first time pure crystallized colchicine in granules of 1milligram which is still sold under this trade name in several countries. In the last two centuries, colchicine's indications were furthermore expanded. From anti-gout drug during antiquity and a diuretic in 19th century, colchicine is currently administered in several affections such as Adamantiades-Behcet's disease, familial Mediterranean fever, pericarditis and atrial fibrillation.

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DOI: 10.2174/1381612824666180115105850

PMID: 29336251

462. Curr Pharm Des. 2018;24(6):690-694. doi: 10.2174/1381612824666180116095658.

The Role of Colchicine in the Treatment of Autoinflammatory Diseases.

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Colchicine has been longstanding and widely used for the treatment of acute gout flares and prevention of gout relapses. Its use has been extended to a series of autoinflammatory diseases, such as familial Mediterranean fever and more recently to periodic fever with aphthous stomatitis, pharyngitis and adenitis, Behcet's disease and idiopathic recurrent acute pericarditis. In this review, we summarize current indications of colchicine use, discuss its pharmacokinetics and mechanism of action and examine its use in the treatment of autoinflammatory diseases. Further understanding of the underlying mechanisms of the latter conditions as well as identification of the therapeutic efficacy and treatment target of colchicine may lead to more effective management of these diseases.

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DOI: 10.2174/1381612824666180116095658

PMID: 29336247

463. J Rheumatol. 2018 Mar;45(3):425-429. doi: 10.3899/jrheum.170684. Epub 2018 Jan 15.

Efficacy of Continuous Interleukin 1 Blockade in Mevalonate Kinase Deficiency: A Multicenter Retrospective Study in 13 Adult Patients and Literature Review.

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**OBJECTIVE:** To report efficacy and tolerance of interleukin 1 blockade in adult patients with mevalonate kinase deficiency (MKD).

**METHODS:** We retrospectively collected data on 13 patients with MKD who had received anakinra (n = 10) and canakinumab (n = 7).

**RESULTS:** Anakinra resulted in complete or partial remission in 3/10 and 5/10 patients, respectively, and no efficacy in 2/10, but a switch to canakinumab led to partial remission. Canakinumab resulted in complete or partial remission in 3/7 and 4/7 patients, respectively.

**CONCLUSION:** These data support frequent partial responses, showing a better response with canakinumab. The genotype and therapeutic outcomes correlation should help in the personalization of treatment.

DOI: 10.3899/jrheum.170684

PMID: 29335349

464. Br J Dermatol. 2018 Mar;178(3):614-618. doi: 10.1111/bjd.16232. Epub 2018 Jan 15.

Pustular psoriasis and related pustular skin diseases.

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Patients with pustular psoriasis or related pustular diseases may have genetic abnormalities impairing the function of key players of the innate skin immune system. Recently, identification of these abnormalities has changed the paradigm of several of these diseases. These include generalized pustular psoriasis, palmoplantar pustular psoriasis and acrodermatitis continua of Hallopeau, and also drug-induced acute exanthematous generalized pustular eruption. Identified mutations in IL36RN, CARD14 and AP1S3 in different groups of patients lead to enhanced inflammatory cascade in several cellular subtypes including keratinocytes, and to the recruitment and activation of neutrophils and macrophages. These insights have unveiled pathophysiological features that shift the existing paradigms and emphasize the autoinflammatory nature of skin pustular disorders. They also highlight the crucial role of the innate immune system across entities belonging to the psoriasis disease spectrum, allowing identification of new appealing therapeutic targets.

© 2018 British Association of Dermatologists.

DOI: 10.1111/bjd.16232

PMID: 29333670

465. Z Rheumatol. 2017 Oct;76(Suppl 2):26-32. doi: 10.1007/s00393-017-0369-2.

[Myelodysplastic syndrome, acute leukemia and stem cell transplantation].

[Article in German]

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Myelodysplastic syndromes (MDS) represent a heterogeneous group of clonal hematopoietic stem cell disorders. They are characterized by inefficient hematopoiesis leading to peripheral cytopenia of one or more lineages and a variable risk of transformation into acute myeloid leukemia. They may either arise de novo as well as following exposition to environmental toxins, previous radiotherapy or chemotherapy or in the context of autoinflammatory diseases and related therapy. Characteristic cytogenetic abnormalities, along with the numbers of hematopoietic lineages affected and bone marrow blasts, enable an assessment of the risk of leukemic transformation. Acute leukemias are characterized by an accumulation of immature myeloid or lymphatic progenitor cells with limited differentiation capacity in the bone marrow. Proliferation of blast cells leads to suppression of normal hematopoiesis resulting in peripheral pancytopenia or leukocytosis associated with anemia and thrombocytopenia. Acute leukemias following MDS are defined as high-risk diseases. Intensive induction therapy followed by allogeneic stem cell transplantation is currently regarded as the only potentially curative treatment strategy. In this article the basic aspects of current diagnostics and treatment strategies for MDS and acute leukemia are outlined. Because of similarities with rheumatic inflammatory diseases, manifestations and treatment of graft versus host disease (GvHD) are also included.

DOI: 10.1007/s00393-017-0369-2

PMID: 29330757

466. Clin Exp Immunol. 2018 Jul;193(1):3-12. doi: 10.1111/cei.13101. Epub 2018 Feb 2.

Genetics of immune-mediated inflammatory diseases.

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Immune-mediated inflammatory diseases (IMIDs) are characterized by dysregulation of the normal immune response, which leads to inflammation. Together, they account for a high disease burden in the population, given that they are usually chronic conditions with associated co-morbidities. Examples include systemic lupus erythematosus, rheumatoid arthritis, Crohn's disease and type 1 diabetes. Since the advent of genome-wide association studies, evidence of considerable genetic overlap in the loci predisposing to a wide range of IMIDs has emerged. Understanding the genetic risk and extent of genetic overlap between IMIDs may help to determine which genes control which aspects of the different diseases; it may identify potential novel therapeutic targets for a number of these conditions, and/or it may facilitate repurposing existing therapies developed originally for different conditions. The findings show that autoantibody-mediated autoimmune diseases cluster more closely with each other than autoantibody-negative diseases such as psoriasis, psoriatic arthritis, Crohn's disease and ankylosing spondylitis which, instead, form a seronegative genetic cluster. The genetic clustering largely mirrors the known response to existing biological therapies, but apparent anomalies in treatment response are discussed.

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DOI: 10.1111/cei.13101

PMCID: PMC6037997 [Available on 2019-07-01]

PMID: 29328507

467. Clin Med Insights Case Rep. 2018 Jan 3;11:1179547617749208. doi: 10.1177/1179547617749208. eCollection 2018.

Very Rare Presentation of Cerebrovascular Accident in 20-Year-Old Man With Familial Mediterranean Fever-Case Report.

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Familial Mediterranean fever (FMF) is characterized by recurrent episodes of fever accompanied by serosal, synovial, or cutaneous inflammation. The central nervous system (CNS) is rarely involved in FMF. The CNS involvement includes demyelinating lesions, posterior reversible encephalopathy syndrome, pseudotumor cerebri, optic neuritis, and cerebral vasculitis. Here, we present a 20-year-old man, a known case of FMF with abrupt left-sided hemiparesis. Brain magnetic resonance imaging revealed right periventricular infarction. Normal echocardiography ruled out cardioembolism, and thrombophilia workup was negative. Therefore, FMF-induced cerebrovascular accident was considered. Although rare, CNS involvement as a result of FMF disease should also be considered when encountering patients with FMF and CNS manifestations.

DOI: 10.1177/1179547617749208

PMCID: PMC5757431

PMID: 29326535

Conflict of interest statement: Declaration Of Conflicting Interests:The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

468. Blood. 2018 Mar 29;131(13):1442-1455. doi: 10.1182/blood-2017-12-820852. Epub 2018 Jan 11.

Interleukin-18 diagnostically distinguishes and pathogenically promotes human and murine macrophage activation syndrome.

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Hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) are life-threatening hyperferritinemic systemic inflammatory disorders. Although profound cytotoxic impairment causes familial HLH (fHLH), the mechanisms driving non-fHLH and MAS are largely unknown. MAS occurs in patients with suspected rheumatic disease, but the mechanistic basis for its distinction is unclear.

Recently, a syndrome of recurrent MAS with infantile enterocolitis caused by NLRC4 inflammasome hyperactivity highlighted the potential importance of interleukin-18 (IL-18). We tested this association in hyperferritinemic and autoinflammatory patients and found a dramatic correlation of MAS risk with chronic (sometimes lifelong) elevation of mature IL-18, particularly with IL-18 unbound by IL-18 binding protein, or free IL-18. In a mouse engineered to carry a disease-causing germ line NLRC4T337S mutation, we observed inflammasome-dependent, chronic IL-18 elevation. Surprisingly, this NLRC4T337S-induced systemic IL-18 elevation derived entirely from intestinal epithelia. NLRC4T337S intestines were histologically normal but showed increased epithelial turnover and upregulation of interferon- $\gamma$ -induced genes. Assessing cellular and tissue expression, classical inflammasome components such as Il1b, Nlrp3, and Mefv predominated in neutrophils, whereas Nlrp4 and Il18 were

distinctly epithelial. Demonstrating the importance of free IL-18, IL18 transgenic mice exhibited free IL-18 elevation and more severe experimental MAS. NLRC4T337S mice, whose free IL-18 levels were normal, did not. Thus, we describe a unique connection between MAS risk and chronic IL-18, identify epithelial inflammasome hyperactivity as a potential source, and demonstrate the pathogenicity of free IL-18. These data suggest an IL-18-driven pathway, complementary to the cytotoxic impairment of fHLH, with potential as a distinguishing biomarker and therapeutic target in MAS.

DOI: 10.1182/blood-2017-12-820852

PMCID: PMC5877443 [Available on 2019-03-29]

PMID: 29326099

469. Mod Rheumatol. 2018 Nov;28(6):1016-1020. doi: 10.1080/14397595.2018.1427459. Epub 2018 Feb 2.

Fatigue in pediatric patients with familial Mediterranean fever.

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**OBJECTIVES:** Familial Mediterranean fever (FMF) is characterized by recurrent, self-limited attacks of fever with serositis involving the peritoneum, pleura and joints. Fatigue is a common problem in many pediatric rheumatic diseases; however, has not been evaluated systematically in FMF patients. Accordingly, the aim of this study was to evaluate fatigue and its possible allied factors in patients with FMF.

**METHODS:** Patients with FMF, aged between 10 and 21 years, were assessed by completed validated fatigue questionnaire (Checklist Individual Strength-20). As a control group, patients with chronic rheumatic diseases and healthy children without any chronic disease were included.



**RESULTS:** The study group comprised 111 patients with FMF, 54 with other chronic rheumatic diseases and 79 healthy subjects. While the CIS-20 total score and subscale scores (including subjective experience of fatigue) were similar between patients with FMF and those with other chronic rheumatic diseases ( $p > .05$ ); both groups had significantly higher scores when compared with healthy subjects ( $p < .05$ ). FMF patients with musculoskeletal complaints had significantly higher scores of subjective experiences of fatigue when compared to those without those complaints.

**CONCLUSIONS:** Fatigue is a common but unrecognized complaint in patients with FMF. Familial Mediterranean fever seems to be a chronic disease with inter attack ongoing complaints.

DOI: 10.1080/14397595.2018.1427459

PMID: 29322855 [Indexed for MEDLINE]

470. Ann Rheum Dis. 2018 May;77(5):728-735. doi: 10.1136/annrheumdis-2017-212403. Epub 2018 Jan 9.

A20 haploinsufficiency (HA20): clinical phenotypes and disease course of patients with a newly recognised NF- $\kappa$ B-mediated autoinflammatory disease.

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**OBJECTIVES:** The association between mutations in TNFAIP3, encoding the NF- $\kappa$ B regulatory protein A20, and a new autoinflammatory disease has recently been recognised. This study aims at describing the clinical phenotypes and disease course of patients with A20 haploinsufficiency (HA20).

**METHODS:** Data for all cases from the initial publication, and additional cases identified through collaborations since, were collected using standardised data collection forms.

**RESULTS:** A total of 16 patients (13 female) from seven families with a genetic diagnosis of HA20 were included. The disease commonly manifested in early childhood (range: first week of life to 29 years of age). The main clinical symptoms were recurrent oral, genital and/or gastrointestinal ulcers (16/16), musculoskeletal (9/16) and gastrointestinal complaints (9/16), cutaneous lesions (8/16), episodic fever (7/16), and recurrent infections (7/16). Clinical phenotypes varied considerably, even within families. Relapsing-remitting disease course was most common, and one patient died. Laboratory abnormalities included elevated acute-phase reactants and fluctuating presence of various autoantibodies such as antinuclear antibodies (4/10 patients tested) and anti-dsDNA (2/5).

Tissue biopsy of different sites revealed non-specific chronic inflammation (6/12 patients tested), findings consistent with class V lupus nephritis in one patient, and pustules and normal results in two patients each. All patients were treated: 4/16 received colchicine and 12/16 various immunosuppressive agents. Cytokine inhibitors effectively suppressed systemic inflammation in 7/9 patients.

**CONCLUSIONS:** Early-onset recurrent oral, genital and/or gastrointestinal ulcers are the hallmark feature of HA20. Frequency and intensity of other clinical manifestations varied highly. Treatment regimens should be based on disease severity, and cytokine inhibitors are often required to control relapses.

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DOI: 10.1136/annrheumdis-2017-212403

PMID: 29317407

Conflict of interest statement: Competing interests: None declared.

471. Arthritis Care Res (Hoboken). 2018 May;70(5):785-790. doi: 10.1002/acr.23506. Epub 2018 Apr 2.

Rash, Fever, and Pulmonary Hypertension in a 6-Year-Old Female.

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DOI: 10.1002/acr.23506

PMCID: PMC5920705 [Available on 2019-05-01]

PMID: 29316368

472. Int J Rheum Dis. 2018 Apr;21(4):880-884. doi: 10.1111/1756-185X.13259. Epub 2018 Jan 5.

Comparison of early versus late onset familial Mediterranean fever.

Yasar Bilge NS(1), Sari I(2), Solmaz D(2), Senel S(3), Emmungil H(4), Kilic L(5), Yilmaz Oner S(6), Yildiz F(7), Yilmaz S(8), Ersozlu Bozkirli D(9), Aydin Tufan M(9), Yilmaz S(10), Yazisiz V(11), Pehlivan Y(12), Bes C(13), Yildirim Cetin G(14), Erten S(15), Gonullu E(1), Sahin F(16), Akar S(2), Aksu K(4), Kalyoncu U(5), Direskeneli H(6), Erken E(7), Sayarlioglu M(14), Cinar M(8), Kasifoglu T(1).

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AIM: Familial Mediterranean fever (FMF) is the most common autoinflammatory disease. One of the common characteristics of this disease is its young age predominance. Nearly 90% of patients experience disease flares during early adult age periods. Currently there are limited data for the comparison of early versus late onset FMF and therefore the primary aim of this study was to investigate these two subsets with regard to their certain demographic, clinical and genetic differences.

METHODS: Early ( $\leq 20$  years, Group 1) and late ( $> 20$  years, Group 2) onset FMF patients were identified from the national FMF registry that involves 2246

patients from 15 adult rheumatology clinics located in different geographical areas of Turkey.

**RESULTS:** Of the 2246 patients, 1633 (72.7%) were aged  $\leq 20$  years old (Group 1) and the remaining 613 were older than 20 years (Group 2). Delay in diagnosis was longer in Group 1 and fever, peritonitis, pleuritis, erysipelas-like erythema (ELE), arthritis, family history of FMF and amyloidosis were more common in Group 1. On the other hand, sex distribution, rates of amyloidosis, vasculitis and kidney failure were not different between the groups. Among patients with available genotypes, homozygous and heterozygous M694V mutations were significantly higher and heterozygous E148Q mutation was significantly lower in Group 1 compared to Group 2.

**CONCLUSION:** Patients with FMF whose symptoms start before 20 years of age seem to have severe symptoms and M694V mutation may be responsible for the early expression of the disease.

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DOI: 10.1111/1756-185X.13259

PMID: 29314707 [Indexed for MEDLINE]

473. Int J Rheum Dis. 2018 Jul;21(7):1452-1457. doi: 10.1111/1756-185X.13258. Epub 2018 Jan 5.

MEFV gene testing may guide physicians for early diagnosis of familial Mediterranean fever.

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**INTRODUCTION:** Familial Mediterranean fever (FMF) is characterized by recurrent attacks of polyserositis. Even though clinical assessment is accepted to be the most important factor in the diagnosis of FMF, some diagnostic procedures may help the physician. In this study, we aimed to compare the number of diagnostic procedures performed and number of physician referrals in early diagnosed and late diagnosed cases. Furthermore, we assessed which diagnostic approaches would affect the decision-making of physicians in the early diagnosed patients.

**MATERIALS AND METHODS:** We enrolled into the study 143 FMF patients who met the Tel-Hashomer Criteria. Demographic variables, MEFV mutations (when available), diagnostic procedures (if performed) and specialist referrals were evaluated.

Early diagnosis was defined as establishment of definite diagnosis within a 5-year period after the appearance of the first symptom.

**RESULTS:** Early diagnosed were referred to physicians less often, and except for genetic testing, had fewer diagnostic procedures. In addition to clinical features, MEFV testing was found to be the only method that might influence the diagnosis by a physician.

**CONCLUSIONS:** MEFV gene assessment, unlike other diagnostic procedures, might support physicians in the early diagnosis of FMF. Especially in atypical cases, MEFV gene assessment might be considered for diagnosis of FMF.

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DOI: 10.1111/1756-185X.13258

PMID: 29314663 [Indexed for MEDLINE]

474. BMJ Case Rep. 2018 Jan 5;2018. pii: bcr-2017-222286. doi: 10.1136/bcr-2017-222286.

Postsurgical pyoderma gangrenosum after an autologous stem cell transplantation for multiple myeloma.

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We report a man who underwent autologous stem cell transplantation (ASCT) for multiple myeloma. Two months after ASCT, he presented with necrotising cholecystitis due to gallbladder stones and was submitted to laparoscopic cholecystectomy. About a week later, he developed progressive skin ulcers at sites where trochanters had been inserted. Progressive enlargement and necrotic aspect of these ulcers took place despite debridement and large spectrum antibiotics. New ulcers developed at the site of enoxaparin injection at the right arm (pathergy phenomenon). A skin biopsy and clinical evaluation favoured the diagnosis of pyoderma gangrenosum (PG). He was treated with daily methylprednisolone and dapsone with improvement of the lesions. This is the first case in the literature of PG after ASCT. Despite the risk factors, the onset of an autoinflammatory disease right after the transplant is intriguing since PG is extremely rare in immunocompromised patients.

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DOI: 10.1136/bcr-2017-222286

PMID: 29305364 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: None declared.

475. Nat Rev Rheumatol. 2018 Feb;14(2):63. doi: 10.1038/nrrheum.2017.217. Epub 2018 Jan 3.

Autoinflammatory diseases: TNF drives cryopyrinopathies in mice.

Onuora S.

DOI: 10.1038/nrrheum.2017.217

PMID: 29296023

476. Rheumatology (Oxford). 2018 Apr 1;57(4):718-726. doi: 10.1093/rheumatology/kex451.

MicroRNA-204-3p inhibits lipopolysaccharide-induced cytokines in familial Mediterranean fever via the phosphoinositide 3-kinase  $\gamma$  pathway.

Koga T(1)(2), Migita K(3), Sato T(1), Sato S(4), Umeda M(1), Nonaka F(1)(5), Fukui S(1), Kawashiri SY(1), Iwamoto N(1), Ichinose K(1), Tamai M(1), Nakamura H(1), Origuchi T(1), Ueki Y(6), Masumoto J(7), Agematsu K(8), Yachie A(9), Yoshiura KI(10), Eguchi K(6), Kawakami A(1).

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**Objective:** We sought to identify the microRNA (miRNA) profile and potential biomarkers in FMF and to clarify their gene targets to elucidate the pathogenesis of FMF.

**Methods:** We performed an miRNA microarray using serum from FMF patients in attack and in remission. We then examined the expression of miRNAs in macrophages derived from THP-1 cells stimulated with toll-like receptor (TLR) ligands.

Macrophages derived from THP-1 cells transfected with pre-miRNA were stimulated with lipopolysaccharides (LPSs) for the quantification of inflammatory cytokine production. To identify the target genes, we overexpressed their miRNA and performed a complementary DNA microarray. Transfection with reporter construct and the precursor miRNA was performed to confirm the suppression of target mRNA.



Results: We found that miR-204-3p was greatly decreased in the serum from FMF patients in attack. The expression of miR-204-3p was suppressed by LPS stimulation in the macrophages derived from THP-1 cells and the inhibition of miR-204-3p significantly induced the production of TLR4-related cytokines. The bioinformatic analysis showed that miR-204-3p is predicted to target genes implicated in the TLR pathway through the regulation of PI3Ky signalling. The reporter assay revealed that miR-204-3p directly suppressed the luciferase activity of 3'-UTR of PIK3CG reporter construct. The inhibition of PI3Ky resulted in decreased amounts of IL-6 and IL-12p40 in monocytes from FMF patients. Conclusion: These data suggest that serum miR-204-3p has potential as a useful biomarker in FMF patients and that miR-204-3p serves as a suppressor of inflammatory cytokine production in FMF by targeting the PI3Ky pathway.

DOI: 10.1093/rheumatology/kex451

PMID: 29294109 [Indexed for MEDLINE]

477. Clin Pract. 2017 Dec 12;7(4):1018. doi: 10.4081/cp.2017.1018. eCollection 2017 Sep 15.

Schnitzler syndrome, a rare autoinflammatory disease. Complete response to IL-1 blockade.

Faggioli P(1), Tamburello A(1), Roncoroni L(2), Mazzone A(1).

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DOI: 10.4081/cp.2017.1018

PMCID: PMC5736995

PMID: 29291047

478. J Invest Dermatol. 2018 Jun;138(6):1338-1347. doi: 10.1016/j.jid.2017.12.024. Epub 2017 Dec 27.

Unopposed IL-36 Activity Promotes Clonal CD4+ T-Cell Responses with IL-17A Production in Generalized Pustular Psoriasis.

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Generalized pustular psoriasis (GPP) is the most severe psoriasis variant. Mutations in the IL-36 antagonist IL36RN, in CARD14 or AP1S3 provide genetic evidence for autoinflammatory etiology but cannot explain its pathogenesis completely. Here we demonstrate that unopposed IL-36 signaling promotes antigen-driven and likely pathogenic T-helper type 17 (Th17) responses in GPP. We observed that CD4<sup>+</sup> T cells in blood and skin lesions of GPP patients were characterized by intense hyperproliferation, production of the GPP key mediator, IL-17A, and highly restricted TCR repertoires with identical T-cell clones in blood and skin lesions, indicating antigen-driven T-cell expansions. The clonally expanded CD4<sup>+</sup> T cells were major producers of IL-17A. IL-36 signaling substantially enhanced TCR-mediated proliferation of CD4<sup>+</sup> T cells. Moreover, GPP patients showed preferences for HLA-DRB1\*14, HLA-DQB1\*05, and HLA-DQB1\*03. We conclude that in GPP unopposed IL-36 signaling and certain HLA-class II alleles may cooperate in promoting antigen-driven Th17 responses, which in the obvious absence of exogenous triggers may reflect autoimmune reactions. This study reveals a pathogenic pathway where innate immune dysregulation promotes T-cell-mediated inflammation in GPP.

479. *Pediatr Rheumatol Online J.* 2017 Dec 29;15(1):87. doi: 10.1186/s12969-017-0216-7.

Dealing with Chronic Non-Bacterial Osteomyelitis: a practical approach.

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**BACKGROUND:** Chronic Non-Bacterial Osteomyelitis (CNO) is an inflammatory disorder that primarily affects children. Although underestimated, its incidence is rare. For these reasons, no diagnostic and no therapeutic guidelines exist. The manuscript wants to give some suggestions on how to deal with these patients in the every-day clinical practice.

**MAIN BODY:** CNO is characterized by insidious onset of bone pain with local swelling. Systemic symptoms such as fever, skin involvement and arthritis may be sometimes present. Radiological findings are suggestive for osteomyelitis, in particular if multiple sites are involved. CNO predominantly affects metaphyses of long bones, but clavicle and mandible, even if rare localizations of the disease, are very consistent with CNO diagnosis. CNO pathogenesis is still unknown, but recent findings highlighted the crucial role of cytokines such as IL-1 $\beta$  and IL-10 in disease pathogenesis. Moreover, the presence of non-bacterial osteomyelitis among autoinflammatory syndromes suggests that CNO could be considered an autoinflammatory disease itself. Differential diagnosis includes infections, malignancies, benign bone tumors, metabolic disorders and other

autoinflammatory disorders. Radiologic findings, either with Magnetic Resonance or with Computer Scan, may be very suggestive. For this reason in patients in good clinical conditions, with multifocal localization and very consistent radiological findings bone biopsy could be avoided. Non-Steroidal Anti-Inflammatory Drugs are the first-choice treatment. Corticosteroids, methotrexate, bisphosphonates, TNF $\alpha$ -inhibitors and IL-1 blockers have also been used with some benefit; but the choice of the second line treatment depends on bone lesions localizations, presence of systemic features and patients' clinical conditions.

CONCLUSION: CNO may be difficult to identify and no consensus exist on diagnosis and treatment. Multifocal bone lesions with characteristic radiological findings are very suggestive of CNO. No data exist on best treatment option after Non-Steroidal Anti-Inflammatory Drugs failure.

DOI: 10.1186/s12969-017-0216-7

PMCID: PMC5747935

PMID: 29287595 [Indexed for MEDLINE]

480. Blood. 2018 Mar 1;131(9):974-981. doi: 10.1182/blood-2017-10-810366. Epub 2017 Dec 28.

Molecular genetic investigation, clinical features, and response to treatment in 21 patients with Schnitzler syndrome.

Rowczenio DM(1), Pathak S(2)(3), Arostegui JI(4), Mensa-Vilaro A(4), Omoyinmi E(5), Brogan P(5), Lipsker D(6)(7), Scambler T(2)(3), Owen R(8), Trojer H(1), Baginska A(1), Gillmore JD(1), Wechalekar AD(1), Lane T(1), Williams R(1), Youngstein T(1), Hawkins PN(1), Savic S(2)(3), Lachmann HJ(1).

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To date, the pathogenic mechanisms underlying Schnitzler syndrome remain obscure, in particular, the interplay between the monoclonal protein and increased interleukin-1 $\beta$  (IL-1 $\beta$ ) production, although interest in the contribution of genetic factors has been fueled by detection of somatic NLRP3 mosaicism in 2 patients with the variant-type Schnitzler syndrome. At 2 specialist UK centers, we have identified 21 patients who fulfilled diagnostic criteria for Schnitzler syndrome with urticarial rash, fever, arthralgia, and bone pain; 47% reported weight loss, 40% fatigue, and 21% lymphadenopathy. An immunoglobulin M (IgM)  $\kappa$  paraprotein was detected in 86%; the remainder had IgM  $\lambda$  or IgG  $\kappa$ . Patients underwent searches for germ line and somatic mutations using next-generation sequencing technology. Moreover, we designed a panel consisting of 32 autoinflammatory genes to explore genetic susceptibility factor(s) to Schnitzler syndrome. Genetic analysis revealed neither germ line nor somatic NLRP3, TNFRSF1A, NLRC4, or NOD2 mutations, apart from 1 patient with a germ line NLRP3 p.V198M substitution. The proinflammatory cytokines and extracellular apoptosis-associated speck-like protein with caspase recruitment domain (ASC) measured in the serum of Schnitzler syndrome patients during active disease were significantly higher than healthy controls. Ninety-five percent of our cohort achieved a complete response to recombinant IL-1 receptor antagonist (anakinra). Our findings do not support a role for somatic NLRP3 mosaicism in disease pathogenesis; although elevated levels of ASC, IL-6, and IL-18 in patients' serum, and the response to anakinra, suggest that Schnitzler syndrome is associated with upregulated inflammasome activation. Despite its rarity, Schnitzler syndrome is an important diagnosis as treatment with IL-1 antagonists dramatically improves quality of life for patients.

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DOI: 10.1182/blood-2017-10-810366

PMCID: PMC5877784

PMID: 29284595

481. J Ultrasound Med. 2018 Jul;37(7):1649-1656. doi: 10.1002/jum.14512. Epub 2017 Dec 23.

## Evaluation of Subclinical Atherosclerosis by Ultrasound Radiofrequency Data Technology in Patients With Familial Mediterranean Fever.

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**OBJECTIVES:** The aim of this study was to noninvasively demonstrate the presence of early risk associated with subclinical inflammatory activity in patients with familial Mediterranean fever (FMF) who had stable disease, using ultrasound (US) radiofrequency data technology.

**METHODS:** A total of 110 participants, including 55 patients with FMF and 55 healthy control participants, were evaluated with Doppler US. The intima-media thickness and arterial stiffness were measured from bilateral common carotid arteries (CCAs) by the radiofrequency method.

**RESULTS:** No statistically significant difference was found between the patients with FMF and controls in terms of the right and left CCA intima-media thickness, distensibility coefficient, compliance coefficient,  $\alpha$  and  $\beta$  stiffness indices, and pulsed wave velocity ( $P > .05$ ). Symptom duration and diagnosis and treatment time of the patients with FMF had a negative correlation with the distensibility and compliance measurements obtained by Doppler US ( $r = -0.324$  and  $-0.303$ ), and a positive ( $r = 0.380$  and  $0.339$ ) and statistically significant relationship was detected between the  $\alpha$  stiffness index,  $\beta$  stiffness index, and pulsed wave velocity ( $P < .05$ ).

**CONCLUSIONS:** Common carotid artery intima-media thickness and arterial stiffness measurements can aid in early prediction of cardiovascular disease development in patients with FMF. Radiofrequency data technology provides a noninvasive method for accurately and quantitatively showing the CCA intima-media thickness elevation and the decrease in vascular elasticity in patients with FMF.

DOI: 10.1002/jum.14512

PMID: 29274074

482. An Bras Dermatol. 2017;92(5 Suppl 1):21-23. doi: 10.1590/abd1806-4841.20176114.

Association of amyloidosis cutis dyschromica and familial Mediterranean fever.

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Amyloidosis cutis dyschromica is a rare type of primary cutaneous amyloidosis characterized by reticulate hyper-pigmentation with discrete hypopigmented macules. Up to date, about 50 cases of amyloidosis cutis dyschromica have been reported and the majority are familial cases of Asian ethnicity. Various diseases, particularly autoimmune diseases such as systemic sclerosis and systemic lupus erythematosus, have been associated with amyloidosis cutis dyschromica. Herein, we report a case of amyloidosis cutis dyschromica accompanying familial Mediterranean fever with a delayed diagnosis of 40 years. To the best of our knowledge, this is the first report of the association of amyloidosis cutis dyschromica and familial mediterranean fever.

DOI: 10.1590/abd1806-4841.20176114

PMCID: PMC5726667

PMID: 29267436 [Indexed for MEDLINE]

483. Brain Pathol. 2018 Jan;28(1):135-136. doi: 10.1111/bpa.12581.

A 44-Year-Old Female with Familial Mediterranean Fever, Cardiomyopathy and End

Stage Renal Disease.

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DOI: 10.1111/bpa.12581

PMCID: PMC6130257

PMID: 29265632 [Indexed for MEDLINE]

484. JCI Insight. 2017 Dec 21;2(24). pii: 97818. doi: 10.1172/jci.insight.97818. [Epub ahead of print]

Therapeutic drug repositioning using personalized proteomics of liquid biopsies.

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**BACKGROUND:** In patients with limited response to conventional therapeutics, repositioning of already approved drugs can bring new, more effective options. Current drug repositioning methods, however, frequently rely on retrospective computational analyses and genetic testing - time consuming methods that delay application of repositioned drugs. Here, we show how proteomic analysis of liquid biopsies successfully guided treatment of neovascular inflammatory vitreoretinopathy (NIV), an inherited autoinflammatory disease with otherwise poor clinical outcomes.

**METHODS:** Vitreous biopsies from NIV patients were profiled by an antibody array for expression of 200 cytokine-signaling proteins. Non-NIV controls were compared with NIV samples from various stages of disease progression. Patterns were identified by 1-way ANOVA, hierarchical clustering, and pathway analysis.

Subjects treated with repositioned therapies were followed longitudinally.

**RESULTS:** Proteomic profiles revealed molecular pathways in NIV pathologies and implicated superior and inferior targets for therapy. Anti-VEGF injections resolved vitreous hemorrhages without the need for vitrectomy surgery.

Methotrexate injections reversed inflammatory cell reactions without the side effects of corticosteroids. Anti-IL-6 therapy prevented recurrent fibrosis and retinal detachment where all prior antiinflammatory interventions had failed. The cytokine array also showed that TNF- $\alpha$  levels were normal and that corticosteroid-sensitive pathways were absent in fibrotic NIV, helping explain prior failure of these conventional therapeutic approaches.

**CONCLUSIONS:** Personalized proteomics can uncover highly personalized therapies for autoinflammatory disease that can be timed with specific pathologic activities. This precision medicine strategy can also help prevent delivery of ineffective drugs. Importantly, proteomic profiling of liquid biopsies offers an endpoint analysis that can directly guide treatment using available drugs.

DOI: 10.1172/jci.insight.97818

PMCID: PMC5752263

PMID: 29263305

485. Ter Arkh. 2017;89(11):111-115. doi: 10.17116/terarkh20178911111-115.

[Schnitzler syndrome: A review of literature, the authors' observation, and experience with the interleukin-1 inhibitor canakinumab].

[Article in Russian; Abstract available in Russian from the publisher]

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The paper reviews the publications dealing with Schnitzler syndrome, a rare autoinflammatory disease, and describes the authors' own clinical observation. It describes the first Russian experience in successfully using the interleukin-1 inhibitor canakinumab to treat this disease.

Publisher: В статье представлен обзор публикаций, посвященных редкому аутовоспалительному синдрому Шнитцлера, приведено описание собственного наблюдения в клинической практике. Отражен первый российский опыт успешного применения ингибитора интерлейкина-1 канакинумаба при этом заболевании.

DOI: 10.17116/terarkh20178911111-115

PMID: 29260755 [Indexed for MEDLINE]

486. Rheumatol Int. 2018 Jan;38(1):97-104. doi: 10.1007/s00296-017-3914-z. Epub 2017 Dec 19.

Does thiol-disulphide balance show oxidative stress in different MEFV mutations?

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Many studies have shown that oxidative stress levels increase in patients with Familial Mediterranean Fever (FMF). Thiols are a class of compounds that include a sulfhydryl group (-SH) and can react with free oxygen radicals to protect tissues. We aimed to investigate thiol-disulphide homeostatic status in FMF patients and examined the effect of different mutations in the MEFV gene on the thiol-disulphide balance. We investigated thiol-disulphide parameters in patients with FMF and healthy controls. To determine the differential effect of MEFV gene mutations on thiol-disulphide balance, subjects were divided into five groups based on homozygous or compound heterozygous exon 10 and nonexon 10 mutations. Tests of thiol-disulphide homeostasis were conducted using the automated spectrophotometric method. Patients with FMF had significantly lower native thiol [433.8  $\mu\text{mol/l}$  (243.3-536.4) vs. 484.1  $\mu\text{mol/L}$  (340.2-612.3),  $p < 0.001$ ], total thiol levels [459.7  $\mu\text{mol/L}$  (281.3-575.4) vs. 529.9  $\mu\text{mol/L}$  (363-669.5),  $p < 0.001$ ], and disulphide levels [14.0  $\mu\text{mol/l}$  (2.7-33.3) vs. 24.4  $\mu\text{mol/l}$  (7.2-36.6),  $p < 0.001$ ] compared to the control group. Moreover, disulphide/native thiol ( $3.4 \pm 1.7$  vs.  $4.7 \pm 1.3$ ,  $p < 0.001$ ) and disulphide/total thiol ( $3.1 \pm 1.4$  vs.  $4.3 \pm 1.0$ ,  $p < 0.001$ ) were also detected lower in the FMF group compared to the control group. But the native thiol/total thiol ratios ( $93.6 \pm 2.9$  vs.  $91.3 \pm 2.1$ ,  $p < 0.001$ ) were higher in the FMF group. There was no significant difference between the native thiol, total thiol, and disulphide levels of individuals with nonexon 10 homozygous or compound heterozygous (Group 1), nonexon 10-exon 10 compound heterozygous (Group 2), exon 10 homozygous or compound heterozygous (Group 3), and heterozygous (Group 4) mutations. However, these parameters significantly differed from those of the healthy control group. Since no differences were found in our study between thiol and disulfide levels of Groups 1, 2 and 3, we believe that this rate cannot be shown as an indicator of oxidative damage in different mutations of FMFs. To the best of our knowledge, this study is the first study that demonstrates the effect of different FMF mutations on the thiol-disulphide balance.

DOI: 10.1007/s00296-017-3914-z

PMID: 29260407 [Indexed for MEDLINE]

487. Inflamm Regen. 2017 May 3;37:9. doi: 10.1186/s41232-017-0040-y. eCollection 2017.

Applications of reconstituted inflammasomes in a cell-free system to drug discovery and elucidation of the pathogenesis of autoinflammatory diseases.

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The inflammasome, typically consisting of a Nod-like receptor, apoptosis-associated speck-like protein, and pro-caspase-1, has recently been identified as a huge intracellular complex, which plays a crucial role in interleukin-1 maturation or specific physiological functions. Two Nod-like receptors, such as nucleotide-binding oligomerization domains-containing protein (Nod)1 and Nod2, interact with the receptor-interacting protein serine-threonine kinase (RIPK)2 accompanied by I $\kappa$ -B kinase (IKK) complexes to construct the nodosome, leading to nuclear factor (NF)- $\kappa$ B activation. The aberrant activation of inflammasomes or nodosomes causes autoinflammatory diseases. Therefore, inflammasomes may be attractive targets to treat autoinflammatory diseases. Our aim is to develop reconstituted inflammasomes in a cell-free system to discover specific molecular-target drugs and elucidate the molecular pathogenesis of autoinflammatory diseases. In this review, we describe reconstituted inflammasomes in a cell-free system.

DOI: 10.1186/s41232-017-0040-y

PMCID: PMC5725934

PMID: 29259708

488. Nat Commun. 2017 Dec 19;8(1):2176. doi: 10.1038/s41467-017-01932-3.

Type I interferon-mediated autoinflammation due to DNase II deficiency.

Rodero MP(1), Tesser A(2), Bartok E(3), Rice GI(4), Della Mina E(1), Depp M(1), Beitz B(5), Bondet V(6)(7), Cagnard N(8), Duffy D(6)(7)(9), Dussiot M(10), Frémond ML(1), Gattorno M(11), Guillem F(10), Kitabayashi N(1), Porcheray F(5),

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Microbial nucleic acid recognition serves as the major stimulus to an antiviral response, implying a requirement to limit the misrepresentation of self nucleic acids as non-self and the induction of autoinflammation. By systematic screening using a panel of interferon-stimulated genes we identify two siblings and a singleton variably demonstrating severe neonatal anemia, membranoproliferative glomerulonephritis, liver fibrosis, deforming arthropathy and increased anti-DNA antibodies. In both families we identify biallelic mutations in DNASE2, associated with a loss of DNase II endonuclease activity. We record increased interferon alpha protein levels using digital ELISA, enhanced interferon signaling by RNA-Seq analysis and constitutive upregulation of phosphorylated STAT1 and STAT3 in patient lymphocytes and monocytes. A hematological disease transcriptomic signature and increased numbers of erythroblasts are recorded in patient peripheral blood, suggesting that interferon might have a particular effect on hematopoiesis. These data define a type I interferonopathy due to DNase II deficiency in humans.

DOI: 10.1038/s41467-017-01932-3

PMCID: PMC5736616

PMID: 29259162 [Indexed for MEDLINE]

489. Mol Med Rep. 2018 Feb;17(2):3364-3371. doi: 10.3892/mmr.2017.8275. Epub 2017 Dec 12.

Human parvovirus B19 nonstructural protein NS1 activates NLRP3 inflammasome signaling in adult-onset Still's disease.

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Dysregulation of inflammasomes serves a pathogenic role in autoinflammatory diseases (AIDs) and adult-onset Still's disease (AOSD) has been categorized as an AID. The present study investigated the expression of NLR family pyrin domain containing proteins (NLRPs) inflammasome in patients with AOSD, the effect of inflammasome inhibitors on NLRP3 signaling and whether human parvovirus B19-associated antigens can activate NLRP3 in patients with AOSD. mRNA expression levels of NLRPs in peripheral blood mononuclear cells (PBMCs) from 34 patients with AOSD and 14 healthy individuals were determined using reverse transcription-quantitative polymerase chain reaction. Protein expression of NLRP3 was evaluated by western blotting. Supernatant cytokine levels were measured by ELISA. Among the NLRPs investigated in the present study, NLRP3 transcripts were markedly elevated and expression of NLRP2, NLRP7 and NLRP12 was decreased in patients with AOSD compared with the controls. Treatment with NLRP3 inhibitors significantly reduced downstream NLRP3 signaling in PBMCs from patients with AOSD. B19-nonstructural protein (NS)1 stimulation of PBMCs from patients with AOSD induced significant upregulation of transcript levels of NLRP3, caspase-1 and interleukin (IL)-1 $\beta$  compared with PBMCs from healthy controls. B19-NS1 stimulation of PBMCs from patients with AOSD induced significant increase in supernatant levels of IL-1 $\beta$  and protein expression of NLRP3, caspase-1, IL-1 $\beta$ , and IL-18 compared with healthy controls. Elevated expression of NLRP3 and its downstream inflammasome signaling components in patients with AOSD indicated a potential pathogenic role of B19-NS1. Thus, B19-NS1 may induce expression of



IL-1 $\beta$  and IL-18 through activation of caspase-1-associated NLRP3-inflammasome in AOSD.

DOI: 10.3892/mmr.2017.8275

PMID: 29257322 [Indexed for MEDLINE]

490. Zhejiang Da Xue Xue Bao Yi Xue Ban. 2017 Jul 25;46(4):449-453.

[Progress on the study of NLRP3 inflammasome in autoinflammatory diseases of children].

[Article in Chinese]

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Autoinflammatory diseases (AID) in childhood is one of refractory diseases, whose pathogenesis is not completely clear. In recent years, a large number of studies have shown that NLRP3 inflammasome plays an important role in the development of AIDs in children. Inflammasome is a cytosolic multiprotein complex that can activate cysteinyl aspartate-specific protease-1 (caspase-1), to further promote the maturation and secretion of proinflammatory cytokines IL-1 $\beta$  and IL-18 as well as pyroptosis and regulate innate immune response. IL-1 receptor antagonist (Anakinra) and IL-1 $\beta$  monoclonal antibody (Canakinumab) have good therapeutic effects in children with AIDs. This article reviews the research progress of NLRP3 inflammasome in the pathogenesis of autoinflammatory diseases.

PMID: 29256237

491. Int Ophthalmol. 2017 Dec 18. doi: 10.1007/s10792-017-0785-y. [Epub ahead of print]

Vision-threatening bilateral panuveitis and TRAPS in a child: an uncommon association.

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**PURPOSE:** To report a childhood case of tumor necrosis factor receptor-associated periodic syndrome (TRAPS) carrying the R92Q variant with a vision-threatening bilateral panuveitis.

**METHODS:** Case report and review of the literature.

**RESULTS:** A 7-year-old boy presented with an active bilateral panuveitis and a macular rash associated with fever. Fundus examination showed two choroidal lesions on the posterior pole of the right eye, and fluorescein angiography revealed early hypofluorescence and late hyperfluorescence of the lesions, which were hyper-autofluorescent. Extensive clinical laboratory analyses ruled out autoimmune diseases and systemic infection. The only remarkable finding was a positive IgG for herpes simplex 1. He underwent two successive diagnostic pars plana vitrectomies as well as cataract and glaucoma surgeries. Genetic analysis revealed a mutation in the TNFRSF1A gene, and the patient was diagnosed with TRAPS-associated bilateral panuveitis. He was treated with adalimumab and has been free of active inflammation since then.

**CONCLUSIONS:** We present here the first case reported of panuveitis in a patient with TRAPS. This finding stresses the increasing importance of genetic analysis in search of autoinflammatory diseases to establish an adequate diagnosis and treatment in cases of uveitis of unknown etiology.

DOI: 10.1007/s10792-017-0785-y

PMID: 29256170

## Serum Interleukin-6 and CCL11/Eotaxin May Be Suitable Biomarkers for the Diagnosis of Chronic Nonbacterial Osteomyelitis.

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**Objectives:** Chronic recurrent multifocal osteomyelitis (CRMO), the most severe form of chronic nonbacterial osteomyelitis (CNO), is an autoinflammatory bone disorder. In the absence of diagnostic criteria or biomarkers, CNO/CRMO remains a diagnosis of exclusion. The aim of this study was to identify biomarkers for diagnosing multifocal disease (CRMO).

**Study design:** Sera from 71 pediatric CRMO patients, 11 patients with osteoarticular infections, 62 patients with juvenile idiopathic arthritis (JIA), 7 patients with para-infectious or reactive arthritis, and 43 patients with acute leukemia or lymphoma, as well as 59 healthy individuals were collected. Multiplex analysis of 18 inflammation- and/or bone remodeling-associated serum proteins was performed. Statistical analysis included univariate ANOVA, discriminant analysis, univariate receiver operating characteristic (ROC) analysis, and logistic regression analyses.

**Results:** For 14 of 18 blood serum proteins, significant differences were determined between CRMO patients, at least one alternative diagnosis, or healthy

controls. Multi-component discriminant analysis delivered five biomarkers (IL-6, CCL11/eotaxin, CCL5/RANTES, collagen I $\alpha$ , sIL-2R) for the diagnosis of CRMO. ROC analysis allowed further reduction to a core set of 2 biomarkers (CCL11/eotaxin, IL-6) that are sufficient to discern between CRMO, healthy controls, and alternative diagnoses.

Conclusion: Serum biomarkers CCL11/eotaxin and IL-6 differentiate between patients with CRMO, healthy controls, and alternative diagnoses (leukemia and lymphoma, osteoarticular infections, para-infectious arthritis, and JIA). Easily accessible biomarkers may aid in diagnosing CRMO. Further studies testing biomarkers in larger unrelated cohorts are warranted.

DOI: 10.3389/fped.2017.00256

PMCID: PMC5716982

PMID: 29250517

493. G Ital Dermatol Venereol. 2018 Apr;153(2):194-207. doi: 10.23736/S0392-0488.17.05845-X. Epub 2017 Dec 15.

Panniculitis in the setting of dermato/rheumatologic diseases.

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Panniculitides represent a heterogeneous group of inflammatory diseases that are traditionally considered one of the most difficult challenge for clinicians and pathologists. They may occur in a variety of dermato/rheumatologic diseases and are of particular relevance for clinicians dealing with such pathologies, including immune-mediated/autoimmune and autoinflammatory disorders. In fact, panniculitides can be the initial sign of presentation of a dermato/rheumatologic disease, thereby providing the physician with important clues to the correct diagnosis. Then, panniculitides may serve as an easy-to-access indicator of both systemic involvement and prognostic outcome in dermato/rheumatologic disorders. This review will focus on clinical and histopathological findings of

panniculitides in the setting of dermato/rheumatologic disorders and discusses the value of skin biopsies and consequent histopathological examination in the diagnosis of these disorders with the help of a logarithmic table.

DOI: 10.23736/S0392-0488.17.05845-X

PMID: 29249125 [Indexed for MEDLINE]

494. G Ital Dermatol Venereol. 2018 Apr;153(2):173-184. doi: 10.23736/S0392-0488.17.05839-4. Epub 2017 Dec 15.

Histopathological aspects of psoriasis and its uncommon variants.

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Psoriasis is a chronic complex multisystem, inflammatory, skin disorder that causes vasodilatation and hyperproliferation of keratinocytes, whose clinical expression includes a thickened, erythematous skin, often covered with silver gray scales. Psoriasis is a unique disease where both autoimmune and autoinflammatory responses coexist and the balance between the two components is essential in determining its clinical and histopathological presentation.

Adaptive immune responses prevail in chronic plaque psoriasis while innate and autoinflammatory responses predominate in pustular psoriasis. The histopathology of psoriasis is easily recognizable when the disease involves the typical sites such as the extensor surfaces. Although a biopsy is rarely required in case of classic psoriasis, in atypical and controversial conditions, histopathological examination remains the main diagnostic tool that can help in differentiating psoriasis from other dermatoses. In this review, we will discuss the histopathological pictures of the different clinical variants of psoriasis giving

some clues to drive the correct diagnosis when the clinical aspects are not enough indicative of the disease.

DOI: 10.23736/S0392-0488.17.05839-4

PMID: 29249124 [Indexed for MEDLINE]

495. Immunol Rev. 2018 Jan;281(1):28-39. doi: 10.1111/imr.12617.

The role of the interleukin-1 family in trained immunity.

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Immunological memory was long considered a trait exclusive to cells of the adaptive immune system. However, recent studies have shown that after activation of the innate immune system, innate immune cells may undergo long-term functional reprogramming characterized by the ability to mount either a stronger or attenuated inflammatory response upon reactivation. This phenomenon, which has been termed trained immunity and is a de facto innate immune memory, is regulated by a network of integrated metabolic and epigenetic rewiring. The endogenous mediators that modulate trained immunity in the host are only partially understood, but increasing evidence supports the concept that the interleukin (IL)-1 family of cytokines plays an important role. In this review, we will highlight key findings from studies that provide insight into the multifaceted roles of members of the IL-1 family for trained immunity. Finally, we will discuss how the recent advances of our understanding on the role of IL-1 cytokines in this field may lead to new therapeutic strategies for treatment of common conditions, such as IL-1-driven autoinflammatory diseases.

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DOI: 10.1111/imr.12617

PMID: 29248003 [Indexed for MEDLINE]

496. Immunol Rev. 2018 Jan;281(1):99-114. doi: 10.1111/imr.12618.

The AIM2 inflammasome: Sensor of pathogens and cellular perturbations.

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Recognition of pathogens and altered self must be efficient and highly specific to orchestrate appropriate responses while limiting excessive inflammation and autoimmune reaction to normal self. AIM2 is a member of innate immune sensors that detects the presence of DNA, arguably the most conserved molecules in living organisms. However, AIM2 achieves specificity by detecting altered or mislocalized DNA molecules. It can detect damaged DNA, and the aberrant presence of DNA within the cytosolic compartment such as genomic DNA released into the cytosol upon loss of nuclear envelope integrity. AIM2 is also a key sensor of pathogens that detects the presence of foreign DNA accumulating in the cytosol during the life cycle of intracellular pathogens including viruses, bacteria, and parasites. AIM2 activation initiates the assembly of the inflammasome, an innate immune complex that leads to the activation of inflammatory caspases. This triggers the maturation and secretion of the cytokines IL-1 $\beta$  and IL-18. It can also initiate pyroptosis, a proinflammatory form of cell death. The AIM2 inflammasome contributes to physiological responses and diseases. It is a key player in host defenses, but its deregulation can contribute immune-linked diseases, such as autoinflammatory and autoimmune pathologies. Moreover, AIM2 may play a role in cancer development. Recent studies have shown that the detection of self-DNA species by AIM2 is an important factor that contributes to diseases associated with perturbation of cellular homeostasis. Thus, in addition of being a sensor of pathogen associated molecular patterns (PAMPs), the AIM2 inflammasome is emerging as a key guardian of cellular integrity.

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DOI: 10.1111/imr.12618

497. Immunol Rev. 2018 Jan;281(1):115-123. doi: 10.1111/imr.12607.

The NLRC4 Inflammasome.

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15 years ago, the fundamental biology of an inflammatory signaling complex eventually dubbed "the inflammasome" began to unravel in chronologic parallel with the discovery that many inflammatory diseases were associated with its hyperactivity. Though the genetic origins of Familial Mediterranean Fever (FMF, caused by mutations in MEFV) were discovered first, it would take nearly two decades before the mechanistic connections to a PYRIN inflammasome were made. In the interim, the intensive study of the NLRP3 inflammasome, and the diseases associated with its hyperactivation, have largely dictated the paradigm of inflammasome composition and function. Despite impressive gains, focusing on NLRP3 left gaps in our understanding of inflammasome biology. Foremost among these gaps were how inflammasomes become activated and the connections between inflammasome structure and function. Fortunately, work in another inflammasome inducer, NLRC4, grew to fill those gaps. The current understanding of the NLRC4 inflammasome is perhaps the most comprehensive illustration of the inflammasome paradigm: trigger (e.g. cytosolic flagellin), sensor (NAIP), nucleator (NLRC4), adaptor (ASC), and effector (CASP1). Detailed work has also identified observations that challenge this paradigm. Simultaneously, the features unique to each inflammasome offer a lesson in contrast, providing perspectives on inflammasome activation, regulation, and function. In this review, we endeavor to highlight recent breakthroughs related to NLRC4 inflammasome structure and activation, important *in vivo* work in infection and systemic inflammation, and the characterization of a spectrum of human NLRC4-associated autoinflammatory diseases.



DOI: 10.1111/imr.12607

PMCID: PMC5897049

PMID: 29247997 [Indexed for MEDLINE]

498. Immunol Rev. 2018 Jan;281(1):124-137. doi: 10.1111/imr.12615.

Function and regulation of IL-1 $\alpha$  in inflammatory diseases and cancer.

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The interleukin (IL)-1 family of cytokines is currently comprised of 11 members that have pleiotropic functions in inflammation and cancer. IL-1 $\alpha$  and IL-1 $\beta$  were the first members of the IL-1 family to be described, and both signal via the same receptor, IL-1R. Over the last decade, much progress has been made in our understanding of biogenesis of IL-1 $\beta$  and its functions in human diseases. Studies from our laboratory and others have highlighted the critical role of nod-like receptors (NLRs) and multi-protein complexes known as inflammasomes in the regulation of IL-1 $\beta$  maturation. Recent studies have increased our appreciation of the role played by IL-1 $\alpha$  in inflammatory diseases and cancer. However, the mechanisms that regulate the production of IL-1 $\alpha$  and its bioavailability are relatively understudied. In this review, we summarize the distinctive roles played by IL-1 $\alpha$  in inflammatory diseases and cancer. We also discuss our current knowledge about the mechanisms that control IL-1 $\alpha$  biogenesis and activity, and the major unanswered questions in its biology.

DOI: 10.1111/imr.12615

PMCID: PMC5739076

PMID: 29247991 [Indexed for MEDLINE]

499. Clin Exp Immunol. 2018 Apr;192(1):129-137. doi: 10.1111/cei.13091. Epub 2018 Jan 8.

New evidence of connections between increased O-GlcNAcylation and inflammasome in the oral mucosa of patients with oral lichen planus.

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Oral lichen planus (OLP) is considered a chronic inflammatory immune-mediated disease of the oral mucosa. Immunopathogenesis of OLP is thought to be associated with cell-mediated immune dysregulation. O-GlcNAcylation is a form of reversible glycosylation. It has been demonstrated that O-GlcNAcylation promoted nuclear factor kappa B (NF- $\kappa$ B) signalling. Activation of NF- $\kappa$ B can induce expression of nucleotide-binding domain-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, which is a large intracellular multi-protein complex involving an immune response. Dysregulated expression of the NLRP3 inflammasome was reported to be associated with autoinflammatory diseases. No integrative studies between O-GlcNAcylation and NLRP3 inflammasome in OLP patients have been reported. The present study aimed to determine the immunohistochemical expression of O-GlcNAcylation, NF- $\kappa$ B signalling molecules and NLRP3 inflammasome in oral mucosae of OLP patients. Oral tissue samples were collected from 30 OLP patients and 30 healthy individuals. Immunohistochemical staining and analyses of immunostaining scores were performed to evaluate expression of O-GlcNAcylation, NF- $\kappa$ B signalling molecules and NLRP3 inflammasome. According to observations in this study, significantly higher levels of O-GlcNAcylation, NF- $\kappa$ B signalling molecules and NLRP3 inflammasome were demonstrated in OLP patients compared with control subjects ( $P < 0.001$ ). Positive correlations among O-GlcNAcylation, NF- $\kappa$ B

signalling molecules and NLRP3 inflammasome were also observed in OLP samples ( $P < 0.01$ ). In conclusion, the present study provides supportive evidence that increased O-GlcNAcylation is associated with increased expression of NLRP3 inflammasome via the NF- $\kappa$ B signalling pathway. These findings provide a new perspective on immunopathogenesis of OLP in relation to autoinflammation.

© 2017 British Society for Immunology.

DOI: 10.1111/cei.13091

PMCID: PMC5842414 [Available on 2019-04-01]

PMID: 29247492

500. J Inherit Metab Dis. 2018 Jan;41(1):19-27. doi: 10.1007/s10545-017-0120-9. Epub 2017 Dec 15.

Understanding childhood diabetes mellitus: new pathophysiological aspects.

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Diabetes mellitus (DM) is not a single disease, but several pathophysiological conditions where synthesis, release, and/or action of insulin are disturbed. A progressive autoimmune/autoinflammatory destruction of islet cells is still considered the main pathophysiological event in the development of T1DM, but there is evidence that T1DM itself is a heterogeneous disease. More than 50 gene regions are closely associated with T1DM and a variety of epigenetic factors and metabolic patterns have been characterized, which may play a role in the development of T1DM. The pathogenesis and genetics of type 2 DM (T2DM) are distinct from T1DM. Genes associated with T2DM are distinct from those in T1DM. Characteristic metabolic patterns, different from those in T1DM were reported in T2DM, and some children with T2DM also express islet-antibodies. Huge progress has been made in the characterization of other specific types of DM, which had been considered very rare before. The molecular clarification of maturity-onset

diabetes of the young (MODY) has greatly improved our understanding of the pathophysiology of DM. There are genetic overlaps between T2DM and monogenetic DM. Neonatal DM has been shown to be monogenetic in most cases, and genetic elucidation leads to more precise and individualized therapies. Cystic fibrosis related DM (CFRDM) should be considered a genuine part of cystic fibrosis, and not a complication, since pancreatic fibrosis does not sufficiently explain the pathophysiology of CFRDM. Disturbances of cystic fibrosis transmembrane conductance regulator (CFTR) as well as autoimmunity are involved in the pathogenesis of CFRDM.

DOI: 10.1007/s10545-017-0120-9

PMID: 29247329 [Indexed for MEDLINE]

501. J Pediatr. 2018 Feb;193:265-274.e3. doi: 10.1016/j.jpeds.2017.10.034. Epub 2017 Dec 12.

The First International Conference on Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis Syndrome.

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DOI: 10.1016/j.jpeds.2017.10.034

PMID: 29246466

502. J Allergy Clin Immunol. 2018 Apr;141(4):1485-1488.e11. doi: 10.1016/j.jaci.2017.10.039. Epub 2017 Dec 11.

Haploinsufficiency of A20 causes autoinflammatory and autoimmune disorders.

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DOI: 10.1016/j.jaci.2017.10.039

PMID: 29241730

503. J Pediatr Hematol Oncol. 2018 Mar;40(2):e111-e112. doi:  
10.1097/MPH.0000000000001055.

A Case of Familial Mediterranean Fever Having Intermittent Leukopenia.

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Familial Mediterranean fever (FMF) is a genetically inherited autoinflammatory disorder characterized by inflammatory attacks and may result in amyloidosis as a severe complication. Elevation of acute phase reactants, including leukocytosis, is seen during attack periods. Here we describe a 13-year-old female patient with a very rare clinical presentation of FMF, who would experience FMF attacks when she did not regularly take her colchicine. During these attacks she had leukopenia and neutropenia instead of leukocytosis. The leukocyte count returned to normal when she continued the medication and avoided attacks. Ethnicity and clinical signs are important in leukopenic patients and should be investigated for FMF to avoid unnecessary procedures and complications.

DOI: 10.1097/MPH.0000000000001055

PMID: 29240030

504. Int J Rheum Dis. 2018 Feb;21(2):552-559. doi: 10.1111/1756-185X.13250. Epub 2017  
Dec 13.

Efficacy of anakinra in a patient with systemic amyloidosis presenting as

amyloidoma.

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Amyloidosis is a heterogeneous group of disorders characterized by extracellular deposition of unique protein fibrils. The least common presentation of an amyloid deposition is as a discrete mass called amyloidoma or amyloid tumor. We report a case of a soft tissue amyloidoma in the abdomen of a 16-year-old girl who was diagnosed as having systemic amyloidosis. A girl aged 16 years was referred to our hospital with a pre-diagnosis of a retroperitoneal mass documented with abdominal ultrasonography and tomography. A laboratory examination revealed nephrotic syndrome. She underwent surgery for a complete resection of the lesion. A histopathologic examination with Congo red and crystal violet dyes verified the diagnosis of amyloidoma. An immunohistochemical study for amyloid A protein was positive. A renal biopsy was also compatible with AA amyloidosis. A detailed search for the etiology of systemic amyloidosis revealed heterozygous mutation in the Mediterranean fever gene. Treatment with colchicine and anakinra were started with the diagnosis of familial Mediterranean fever because the other causes of secondary amyloidosis were ruled out. After 3 months of anakinra treatment, the laboratory findings returned to normal and excessive proteinuria disappeared. In countries where FMF and other autoinflammatory diseases are prevalent, systemic amyloidosis should be kept in mind in the differential diagnosis of children who present with nephrotic syndrome and abdominal mass. Taking previously reported cases and our case together, it appears that anti-interleukin-1 treatment represents a promising new approach in a subset of patients with systemic amyloidosis secondary to autoinflammatory diseases.

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DOI: 10.1111/1756-185X.13250

PMID: 29239128 [Indexed for MEDLINE]

505. J Cancer Res Ther. 2017 Oct-Dec;13(6):1047-1049. doi: 10.4103/jcrt.JCRT\_125\_16.

Multiple pelvic cysts in a patient with familial Mediterranean fever: Benign cystic mesothelioma.

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Benign cystic mesothelioma (BCM) is a rare tumor arising from endothelial cells of the pelvic visceral or parietal peritoneum. It is a clinically and histopathologically benign disease. Etiology and pathogenesis of BCM remain unclear. Familial Mediterranean fever (FMF) is an inherited disorder characterized by episodes of fever, and abdominal, chest and/or joint inflammation. Association between malignant mesothelioma and FMF has been reported previously; however, co-existence of FMF and BCM is rare. Here, we report a case of BCM in a 43-year-old male patient with FMF.

DOI: 10.4103/jcrt.JCRT\_125\_16

PMID: 29237974 [Indexed for MEDLINE]



506. Reumatol Clin. 2017 Dec 8. pii: S1699-258X(17)30274-7. doi: 10.1016/j.reuma.2017.10.015. [Epub ahead of print]

Characteristics and Disease Course in a Cohort of Children With PFAPA Syndrome in the Community of Madrid, Spain.

[Article in English, Spanish]

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**INTRODUCTION:** PFAPA syndrome is an autoinflammatory disease whose diagnosis is mainly clinical. Several treatments have been proposed; among them, tonsillectomy could be an effective one.

**MATERIAL AND METHODS:** Retrospective multicenter study. Patients included were diagnosed with PFAPA syndrome, according to the Thomas criteria, in 3 hospitals in Madrid between 2009-2013.

**RESULTS:** Thirty-two cases were included. Median age at onset and at diagnosis were 32 months (IQR 24-44) and 47.5 months (IQR 37-60), respectively. There were increases in leukocytes (13,580/ $\mu$ L [IQR 8,200-16,600] vs. 8,300/ $\mu$ L [IQR 7,130-9,650],  $P=.005$ ), neutrophils (9,340/ $\mu$ L [IQR 5,900-11,620] vs. 3,660/ $\mu$ L [IQR 2,950-4,580],  $P=.002$ ) and C-reactive protein (11.0mg/dL [IQR 6.6-12.7] vs. 0.2mg/dL [IQR 0.1-0.6],  $P=.003$ ) during febrile episodes. In all, 80.8% of patients reported remission of symptoms within 24h after oral corticosteroid therapy. Fourteen patients were tonsillectomized. In 11, the febrile episodes stopped while, in 3, the frequency was reduced; there were 2 cases of postoperative bleeding. The disease was resolved in 56.3% of the patients, at a median age of 60 months (IQR 47-95), with similar duration in patients who were tonsillectomized and those who were not.

CONCLUSIONS: We present a large cohort of children with PFAPA syndrome, with clinical and analytical features similar to those described in the literature, and a good response to corticosteroids and a high resolution rate of symptoms after tonsillectomy.

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DOI: 10.1016/j.reuma.2017.10.015

PMID: 29229448

507. Rheumatology (Oxford). 2018 Mar 1;57(3):582-583. doi: 10.1093/rheumatology/kex427.

Adult-onset tumour necrosis factor receptor-associated periodic syndrome presenting as transfusion-dependent refractory haemophagocytosis.

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DOI: 10.1093/rheumatology/kex427

PMID: 29228362 [Indexed for MEDLINE]

508. J Clin Immunol. 2018 Jan;38(1):96-128. doi: 10.1007/s10875-017-0464-9. Epub 2017 Dec 11.

International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity.

Picard C(1)(2), Bobby Gaspar H(3), Al-Herz W(4), Bousfiha A(5), Casanova JL(6)(7)(8)(9), Chatila T(10), Crow YJ(11)(12), Cunningham-Rundles C(13), Etzioni A(14), Franco JL(15), Holland SM(16), Klein C(17), Morio T(18), Ochs HD(19), Oksenhendler E(20), Puck J(21), Tang MLK(22)(23)(24), Tangye SG(25)(26), Torgerson TR(19), Sullivan KE(27).

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Beginning in 1970, a committee was constituted under the auspices of the World Health Organization (WHO) to catalog primary immunodeficiencies. Twenty years later, the International Union of Immunological Societies (IUIS) took the remit of this committee. The current report details the categorization and listing of 354 (as of February 2017) inborn errors of immunity. The growth and increasing complexity of the field have been impressive, encompassing an increasing variety of conditions, and the classification described here will serve as a critical reference for immunologists and researchers worldwide.

DOI: 10.1007/s10875-017-0464-9

PMCID: PMC5742601

PMID: 29226302

509. Clin Exp Rheumatol. 2017 Nov-Dec;35 Suppl 108(6):90-94. Epub 2017 Nov 27.

Alteration of the microRNA expression profile in familial Mediterranean fever patients.

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**OBJECTIVES:** Phenotypic heterogeneity in familial Mediterranean fever (FMF) disease indicated that FMF is not a simple monogenic disease. Therefore it has been suggested that epigenetic factors can be one of the reason for the variations. We undertook this study to test potential involvement of miRNAs in the pathogenesis of FMF.

**METHODS:** miRNA array was performed on whole blood RNA samples from 6 healthy controls (-/-), 6 FMF patients (M694V/M694V), 6 carriers who displayed the disease phenotype (M694V/-) and 6 healthy carriers (M694V/-). The raw data was analysed by Multi Experiment Viewer (MeV) and candidate miRNAs were determined according to fold change (more than 2.0 or less than -2.0). The validation of differentially expressed miRNAs was done by qRT-PCR. Then we performed pathway analyses with using bioinformatics tools.

**RESULTS:** 14 miRNAs were found to be significant among groups through the analysis with MeV. miR-20a-5p, miR-197-3p, let-7d-3p and miR-574-3p were found to be associated with inflammatory pathway related genes according to DAVID analysis.

MiR-20a-5p (FDR: 0,00, FCH: 5.55) was significantly up regulated whereas miR-197-3p (FDR: 0,00, FCH: -2.27) was down regulated in homozygotes patients.

Both let-7d-3p (FDR: 0.00, FCH: 28.75) and miR-574-3p (FDR: 0.00, FCH: 3.95) were up regulated in heterozygote patients group.

**CONCLUSIONS:** We showed that there are several differentially expressed miRNAs both in homozygote and heterozygote FMF patients compared to controls and healthy carriers. Thus we suggest that these miRNAs, related with inflammatory pathways

may be responsible for the expression of the disease in FMF.

PMID: 29224588 [Indexed for MEDLINE]

510. Maedica (Buchar). 2017 Sep;12(3):169-173.

Analysis of the Most Common Three MEFV Mutations in 630 Patients with Familial Mediterranean Fever in Iranian Azeri Turkish Population.

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**Introduction:** The aim of the present study was to determine the frequency of M694V, M680I and V726A mutations of the MEFV gene in 630 Azeri Turkish patients with family Mediterranean fever.

**Material and Methods:** The MEFV gene mutations were detected using allele-specific oligonucleotide polymerase chain reaction.

**Outcomes:** 630 cases with a mean age  $\pm$  SD of  $28.54 \pm 16.54$  ranging from 2.5 to 76 years old including 268 (42.54%) males and 362 (57.46%) females, were tested.

Nineteen patients were homozygote for one mutation (3.02%), 127 were heterozygote for one mutation (20.2%) and 18 were compound heterozygote for two mutations (2.86%). Mutation analysis confirmed that the most common mutation was M694V 109 (8.65%). V726A and M680I mutations accounted for 4.44% of the alleles; V726A 32 (2.54%) and M680I 24 (1.9%). In this study, compound heterozygote for M694V and V726A, M694V and M680I, and V726A and M680I mutations were found in 1.43%, 0.79%, and 0.63% from West Azerbaijan province in exon 10. Mutation was found in 164 (26.03%) of cases regarding analysis of the three most common MEFV mutations, but in 466 (73.97%) of cases, no mutation was detected. Among our samples, the frequencies of mutant genotypes were 15 (2.38%), 1 (0.15%), 3 (0.47%), 9 (1.42%), 4 (0.63%) and 5 (0.79%), regarding M694V/M694V, M680I/M680I, V726A/V726A, M694V/V726A, M680I/V726A and M680I/M694V, respectively. In our samples, 79 (12.53%), 26 (4.12%), and 22 (3.49%) cases had M694V/normal, V726A/normal, and M680I/normal genotypes regarding M694V, V726A, and M680I mutations, respectively.

**Conclusions:** The M694V mutation is the most common risk factor for family

Mediterranean fever in our group.

PMCID: PMC5706755

PMID: 29218063

511. Yonsei Med J. 2018 Jan;59(1):154-157. doi: 10.3349/ymj.2018.59.1.154.

A Case of Schnitzler's Syndrome without Monoclonal Gammopathy-Associated Chronic Urticaria Treated with Anakinra.

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Chronic urticaria may often be associated with interleukin (IL)-1-mediated autoinflammatory disease, which should be suspected if systemic inflammation signs are present. Here, we report a case of Schnitzler's syndrome without monoclonal gammopathy treated successfully with the IL-1 receptor antagonist anakinra. A 69-year-old man suffered from a pruritic urticarial rash for 12 years. It became aggravated episodically and was accompanied by high fever, arthralgia, leukocytosis, and an elevated C-reactive protein and erythrocyte sedimentation rate. The episodes each lasted for over one week. Neutrophilic and eosinophilic inflammation was found on skin biopsy. However, serum and urine electrophoresis showed no evidence of monoclonal gammopathy. The cutaneous lesions were unresponsive to various kinds of anti-histamines, systemic glucocorticoids, colchicine, cyclosporine, dapsone, and methotrexate, which were administered over a span of 3 years immediately preceding successful treatment. A dramatic response, however, was observed after a daily administration of anakinra. This observation suggests that the correct diagnosis of this case is Schnitzler's syndrome without monoclonal gammopathy. For an adult patient with refractory chronic urticaria and systemic inflammation, Schnitzler's syndrome could be considered as a possible differential diagnosis. Although the typical form of Schnitzler's syndrome exhibits the presence of monoclonal gammopathy as a

diagnostic criterion, monoclonal gammopathy may be absent in an atypical form. In such a situation, an IL-1 antagonist should be effective for the management of chronic urticaria.

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DOI: 10.3349/ymj.2018.59.1.154

PMCID: PMC5725354

PMID: 29214791 [Indexed for MEDLINE]

512. Adv Exp Med Biol. 2017;1031:497-509. doi: 10.1007/978-3-319-67144-4\_26.

Immunological Rare Diseases.

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The immune system is delegated to defend the body from attacks from outside or inside. Many diseases can affect immune system reducing its ability to defend self or inducing an abnormal response against external or internal antigens. Rare diseases affecting immune system present some issue in common with other rare diseases and some peculiarities due to the huge variability in the disease's expression. However, a correct estimation of the epidemiology of rare disorders is necessary for evaluating the prognosis and the responses to new therapies, for planning proper public health services, and finally to establish fair and sustainable prices for innovative medicines. Due to the enormous number of



different rare immunological diseases, in this chapter we are going to analyse some of them that can be considered paradigmatic of the various expressions of disease.

DOI: 10.1007/978-3-319-67144-4\_26

PMID: 29214588 [Indexed for MEDLINE]

513. Retin Cases Brief Rep. 2018 Jan 16. doi: 10.1097/ICB.0000000000000681. [Epub ahead of print]

#### ACUTE FROSTED RETINAL PERIPHLEBITIS IN A PATIENT WITH MEDITERRANEAN FEVER.

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**PURPOSE:** To present a case of frosted branch periphlebitis in a young Armenian patient with familial Mediterranean fever.

**METHODS:** Case report.

**RESULTS:** A 37-year-old man presented with a unilateral decreased visual acuity and floaters for 4 days on the left eye (LE). Visual acuity was 20/20 in the right eye (RE) and 20/28 in the LE. Anterior segment and fundus examinations of the RE were normal. Slit-lamp examination of LE revealed a mild nongranulomatous anterior uveitis and vitritis. Intraocular pressure was 19 mmHg in the RE and 12 mmHg in the LE. Fundoscopy of the LE showed typical appearance of frosted branch periphlebitis with perivascular sheathing of the retinal veins and scattered retinal hemorrhages. Fluorescein angiography of the RE was normal. The LE showed optic disk and segmented vascular staining without macular leakage. Optical coherence tomography of the RE was normal; LE demonstrated a localized macular thickening and few intraretinal cysts. The detailed ophthalmologic history was negative. The general history and workup were significant for familial

Mediterranean fever and a positive lupus anticoagulant. One week later, the fundus findings worsened with a severe decrease of visual acuity of the LE to 20/200. A single intravitreal (IVT) injection of bevacizumab was performed. Three weeks after injection, fundus findings progressively improved with a decrease of the macular thickening and an improvement of the visual acuity to 20/25. Clinical improvement continued up to the last visit (19 weeks after the injection) with a visual acuity that reached back 20/20 with no signs of active inflammation. CONCLUSION: This case demonstrates a possible association between unilateral frosted branch periphlebitis and familial Mediterranean fever.

DOI: 10.1097/ICB.0000000000000681

PMID: 29210959

514. Gastroenterology. 2018 Mar;154(4):948-964.e8. doi: 10.1053/j.gastro.2017.11.276. Epub 2017 Dec 2.

Pyrin Inflammasome Regulates Tight Junction Integrity to Restrict Colitis and Tumorigenesis.

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BACKGROUND & AIMS: Inflammatory bowel diseases (IBD) increase risk for colorectal cancer. Mutations in the Mediterranean fever gene (MEFV or pyrin) are associated with hereditary autoinflammatory disease and severe IBD. Expression of MEFV, a sensor protein that initiates assembly of the inflammasome complex, is increased in colon biopsies from patients with IBD. We investigated the role of pyrin in intestinal homeostasis in mice.

METHODS: Mefv<sup>-/-</sup> mice and C57/BL6 mice (controls) were given azoxymethane followed by multiple rounds of dextran sodium sulfate (DSS) to induce colitis and tumorigenesis. In some experiments, Mefv<sup>-/-</sup> mice were given injections of

recombinant interleukin 18 (rIL18) or saline (control) during DSS administration. Colon tissues were collected at different time points during colitis development and analyzed by histology, immunohistochemistry, immunoblots, or ELISAs (to measure cytokines). Spleen and mesenteric lymph node were collected, processed, and analyzed by flow cytometry. Colon epithelial permeability was measured in mice with colitis by gavage of fluorescent dextran and quantification of serum levels.

**RESULTS:** MEFV was expressed in colons of control mice and expression increased during chronic and acute inflammation; high levels were detected in colon tumor and adjacent non-tumor tissues. *Mefv*<sup>-/-</sup> mice developed more severe colitis than control mice, with a greater extent of epithelial hyperplasia and a larger tumor burden. Levels of inflammatory cytokines (IL6) and chemokines were significantly higher in colons of *Mefv*<sup>-/-</sup> mice than control mice following colitis induction, whereas the level IL18, which depends on the inflammasome for maturation and release, was significantly lower in colons of *Mefv*<sup>-/-</sup> mice. *Mefv*<sup>-/-</sup> mice had increased epithelial permeability following administration of DSS than control mice, and loss of the tight junction proteins occludin and claudin-2 from intercellular junctions. STAT3 was activated (phosphorylated) in inflamed colon tissues from *Mefv*<sup>-/-</sup>, which also had increased expression of stem cell markers (OLFM4, BMI1, and MSI1) compared with colons from control mice. Administration of rIL18 to *Mefv*<sup>-/-</sup> mice reduced epithelial permeability, intestinal inflammation, the severity of colitis, and colon tumorigenesis.

**CONCLUSIONS:** In studies with DSS-induced colitis, we found that pyrin (MEFV) is required for inflammasome activation and IL18 maturation, which promote intestinal barrier integrity and prevent colon inflammation and tumorigenesis. Strategies to increase activity of MEFV or IL18 might be developed for the treatment of IBD and prevention of colitis-associated tumorigenesis.

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DOI: 10.1053/j.gastro.2017.11.276

PMCID: PMC5847456 [Available on 2019-03-01]

PMID: 29203393 [Indexed for MEDLINE]

515. J Autoimmun. 2018 Feb;87:26-37. doi: 10.1016/j.jaut.2017.11.006. Epub 2017 Dec 6.

Innately versatile:  $\gamma\delta$ 17 T cells in inflammatory and autoimmune diseases.

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IL-17-producing  $\gamma\delta$  ( $\gamma\delta 17$ ) T cells form a versatile subset of cells that respond rapidly to innate stimuli and support the pro-inflammatory functions of different myeloid and lymphoid lineages, being particularly critical in the early stages of inflammatory and autoimmune responses. In mice, under homeostatic conditions, these innate-like lymphocytes are pre-programmed in the fetal thymus, through an intricate process involving both T cell receptor-dependent and -independent signals, which allows them to readily produce IL-17 upon stimulation. However, given their transcriptional and epigenetic wiring,  $\gamma\delta 17$  T cells are permissive to different environmental instructions, and can readily acquire the ability to co-produce multiple cytokines, such as IFN- $\gamma$ , IL-22 and GM-CSF, that further propagate inflammation. Moreover, strong IL-23 signals, which are abundantly found in autoinflammatory conditions, are able to induce de novo differentiation of  $\gamma\delta 17$  T cells from uncommitted precursors, both in mice and humans. This notwithstanding, the exact mechanisms responsible for  $\gamma\delta 17$  T cell pathogenicity and multifunctionality are still poorly understood, especially in humans. The pathogenic roles attributed to  $\gamma\delta 17$  T cells in autoimmune diseases stem mainly from their ability to recruit different inflammatory myeloid populations to the target tissue, and to modulate  $\alpha\beta$  T cell function, either by enhancing inflammatory TH17 responses, or by restraining regulatory Treg cell activity. Given their capacity to link key inflammatory axes of innate and adaptive immunity, a better understanding of the molecular basis underpinning  $\gamma\delta 17$  T cell plasticity, and how much this feature accounts for their pathophysiological roles, may be critical for developing novel therapeutic approaches. In this review, we discuss the importance of  $\gamma\delta 17$  T cells in breaking tolerance and enhancing inflammation in various autoimmune diseases, such as multiple sclerosis, psoriasis and rheumatoid arthritis under the light of their basic biological traits, e.g. development, activation, effector functions and plasticity.

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DOI: 10.1016/j.jaut.2017.11.006

PMID: 29203226

516. J Clin Rheumatol. 2018 Mar;24(2):104-106. doi: 10.1097/RHU.0000000000000636.

Familial Mediterranean Fever Imitating Lupus Flare: A Rare Coexistence of an Autoimmune Disease With an Autoinflammatory Disease.

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DOI: 10.1097/RHU.0000000000000636

PMID: 29200027

517. Immunol Lett. 2018 Jan;193:67-76. doi: 10.1016/j.imlet.2017.11.013. Epub 2017 Dec 1.

New mosaic tiles in childhood hereditary autoinflammatory disorders.

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The protean clinical phenotypes of hereditary autoinflammatory disorders (HAID) are caused by abnormal activation of innate immunity and consist of seemingly unprovoked inflammatory flares localized to multiple organs, such as the skin, joints, serosal membranes, gut, and central nervous system. Different mutations

in genes implied in activation of the interleukin-1 (IL-1)-structured inflammasome, cytoskeletal signaling and apoptosis contribute to the pathogenesis of different HAID, which mostly start in childhood with self-limited flares unrelated to infectious agents, autoantibody production or autoreactive cells. Though IL-1 remains pivotal in many inflammasome-mediated diseases, other cytokinopathies involving IL-18, nuclear factor- $\kappa$ B, interferons, and tumor necrosis factor have provided new horizons in the definition of HAID of children: the list of HAID has expanded as a consequence of a better understanding of their pathogenetic molecular mechanisms and also application of new genetic technologies. However, diagnosis of most HAID is clinical and focused on several evidence-based criteria sets: their discrimination remains challenging for unexperienced pediatricians as there are no universally accepted algorithms, and a still relevant number of patients may linger without any clarifying genetic analysis, whose interpretation combined with processing of treatment options should be discussed on a multidisciplinary basis.

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DOI: 10.1016/j.imlet.2017.11.013

PMID: 29198619 [Indexed for MEDLINE]

518. Clin Dermatol. 2017 Nov - Dec;35(6):541-554. doi: 10.1016/j.clindermatol.2017.08.005. Epub 2017 Aug 3.

Neutrophilic dermatoses: Kids are not just little people.

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Neutrophilic dermatoses are a group of inflammatory skin disorders characterized by an overactive innate immune system with dysregulation of neutrophils without underlying infectious etiology. The major representative conditions discussed are

Sweet syndrome; pyoderma gangrenosum; neutrophilic eccrine hidradenitis; palmoplantar eccrine hidradenitis; subcorneal pustular dermatoses; bowel-associated dermatosis arthritis syndrome; and synovitis, acne, pustulosis, hyperostosis, and osteitis. We will also discuss other neutrophilic conditions present almost exclusively in the pediatric population, including congenital erosive and vesicular dermatosis with reticulated supple scarring and the recently described group of autoinflammatory diseases. The clinical characteristics, diagnostic approach, and treatment management in the pediatric and adult population are discussed.

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DOI: 10.1016/j.clindermatol.2017.08.005

PMID: 29191346 [Indexed for MEDLINE]

519. Mol Genet Genomic Med. 2017 Nov;5(6):742-750. doi: 10.1002/mgg3.336. Epub 2017 Oct 9.

Comprehensive analysis of mutations in the MEFV gene reveal that the location and not the substitution type determines symptom severity in FMF.

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**BACKGROUND:** Familial Mediterranean Fever (FMF) is an autoinflammatory disorder caused by mutations in the MEFV gene. These mutations appear in different populations with different frequencies and their caused symptom severities vary from mild to moderate to severe depending on the mutation type.

**METHODS:** In this study, we analyzed the mutations that have been reported in the MEFV gene from symptomatic FMF patients and compared their frequencies in

different populations from the 1000 Genome and the Exome databases, using statistical clustering. We also analyzed the nucleotide and amino acid substitution patterns across the MEFV gene.

**RESULTS:** We found 16 (8%) nonsynonymous mutations outside exon 10 that did not cluster with known disease-causing mutations (DCMs), due to their high frequencies in other populations. We also studied the substitution patterns for nucleotides and amino acids to determine the conserved and variable regions in the MEFV gene. In general more nonsynonymous substitutions were reported in exons 2, 3, and 10 from the FMF database (symptomatic FMF patients) compared to the 1000 Genome and the Exome databases. The same was true for amino acid (AA) substitutions where there were 1.5 times more radical (RAD) to conservative (CON) changes. However, when it came to AA substitutions exon 10 was quite conserved with a RAD/CON ratio of 0.9. In fact, we report that the most severe FMF symptoms are caused by conservative mutations in two highly conserved exon 10 regions.

**CONCLUSION:** We found presumptive FMF-causing mutations that did not cluster with DCMs based on their allele frequencies. We also observed that the type of mutation is less likely to determine the severity of the FMF symptoms; rather it was the location of the mutations that was the determining factor.

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DOI: 10.1002/mgg3.336

PMCID: PMC5702578

PMID: 29178647 [Indexed for MEDLINE]

520. RMD Open. 2017 Nov 1;3(2):e000550. doi: 10.1136/rmdopen-2017-000550. eCollection 2017.

Autoimmune-autoinflammatory rheumatoid arthritis overlaps: a rare but potentially important subgroup of diseases.

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At the population level, rheumatoid arthritis (RA) is generally viewed as autoimmune in nature with a small subgroup of cases having a palindromic form or systemic autoinflammatory disorder (SAID) phenotype. Herein, we describe resistant cases of classical autoantibody associated RA that had clinical, genetic and therapeutic responses indicative of coexistent autoinflammatory disease. Five patients with clinically overlapping features between RA and SAID including polysynovitis and autoantibody/shared epitope positivity, and who had abrupt severe self-limiting attacks including fevers and serositis, are described. Mutations or single nucleotide polymorphisms in recognised autoinflammatory pathways were evident. Generally, these cases responded poorly to conventional Disease-modifying anti-rheumatic drugs (DMARD) treatment with some excellent responses to colchicine or interleukin 1 pathway blockade. A subgroup of RA cases have a mixed autoimmune-autoinflammatory phenotype and genotype with therapeutic implications.

DOI: 10.1136/rmdopen-2017-000550

PMCID: PMC5687541

PMID: 29177082

Conflict of interest statement: Competing interests: SS and DM have received honoraria from Sobi and Novartis for participation in advisory board meetings and for participating in pharma sponsored symposia.

521. Bull Cancer. 2017 Dec;104(12S):S169-S180. doi: 10.1016/j.bulcan.2017.06.019. Epub 2017 Nov 22.

[Indications and follow-up for autologous hematopoietic stem cell transplantation

in autoimmune and autoinflammatory diseases: Guidelines from the Francophone Society of Bone Marrow Transplantation and Cellular Therapy (SFGM-TC)].

[Article in French]

Pugnet G(1), Castilla-Llorente C(2), Puyade M(3), Terriou L(4), Badoglio M(5), Deligny C(6), Guillaume-Jugnot P(7), Labeyrie C(8), Benzidia I(9), Faivre H(9), Lansiaux P(9), Marjanovic Z(10), Bourhis JH(2), Faucher C(11), Furst S(11), Huynh A(12), Martin T(13), Vermersch P(14), Yakoub-Agha I(15), Farge D(16).

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The Francophone Society of Bone Marrow Transplantation and Cellular Therapy (SFGM-TC) organized the 7th allogeneic hematopoietic stem cell transplantation clinical practices harmonization workshop series in September 2017 in Lille, France and updated recommendations for indications and follow-up in autologous hematopoietic stem cell transplantation in autoimmune and autoinflammatory diseases, previously published under the auspices of SFGM-TC.

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DOI: 10.1016/j.bulcan.2017.06.019

PMID: 29173974 [Indexed for MEDLINE]

522. Rev Bras Reumatol Engl Ed. 2017 Nov - Dec;57(6):535-544. doi: 10.1016/j.rbre.2017.02.002. Epub 2017 Mar 23.

Clinical outcomes and survival in AA amyloidosis patients.

[Article in English, Portuguese]

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**AIM:** Amyloid A amyloidosis is a rare complication of chronic inflammatory conditions. Most patients with amyloid A amyloidosis present with nephropathy and it leads to renal failure and death. We studied clinical characteristics and survival in patients with amyloid A amyloidosis.

**METHODS:** A total of 81 patients (51 males, 30 females) with renal biopsy proven amyloid A amyloidosis were analyzed retrospectively. The patients were divided into good and poor outcomes groups according to survival results.

**RESULTS:** Most of the patients (55.6%) had nephrotic range proteinuria at diagnosis. Most frequent underlying disorders were familial Mediterranean fever (21.2%) and rheumatoid arthritis (10.6%) in the good outcome group and malignancy (20%) in the poor outcome group. Only diastolic blood pressure in the good outcome group and phosphorus level in the poor outcome group was higher. Serum creatinine levels increased after treatment in both groups, while proteinuria in the good outcome group decreased. Increase in serum creatinine and decrease in estimated glomerular filtration rate of the poor outcome group were more significant in the good outcome group. At the time of diagnosis 18.5% and 27.2% of all patients had advanced chronic kidney disease (stage 4 and 5, respectively). Median duration of renal survival was  $65 \pm 3.54$  months. Among all patients, 27.1% were started dialysis treatment during the follow-up period and 7.4% of all patients underwent kidney transplantation. Higher levels of systolic blood pressure [hazard ratios 1.03, 95% confidence interval: 1-1.06,  $p=0.036$ ], serum creatinine (hazard ratios 1.25, 95% confidence interval: 1.07-1.46,  $p=0.006$ ) and urinary protein excretion (hazard ratios 1.08, 95% confidence interval: 1.01-1.16,  $p=0.027$ ) were predictors of end-stage renal disease. Median survival of patients with organ involvement was  $50.3 \pm 16$  months.

**CONCLUSION:** Our study indicated that familial Mediterranean fever constituted a large proportion of cases and increased number of patients with idiopathic amyloid A amyloidosis. Additionally, it was observed that patient survival was not affected by different etiological causes in amyloid A amyloidosis.

523. Rev Bras Reumatol Engl Ed. 2017 Nov - Dec;57(6):501-506. doi: 10.1016/j.rbre.2016.02.004. Epub 2016 Mar 10.

Investigation of MEFV gene polymorphisms (G138G and A165A) in adult patients with familial Mediterranean fever.

[Article in English, Portuguese]

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**AIM:** Various mutations have been identified in the Mediterranean fever (MEFV) gene which is reported to be responsible from Familial Mediterranean fever (FMF). In our study, we aimed to determine the frequency of the MEFV mutations in our region and to investigate the impact of G138G (rs224224, c.414A>G) and A165A (rs224223, c.495C>A) gene polymorphisms on the clinical findings of the disease.

**METHODS:** One hundred and sixteen patients diagnosed with FMF and 95 control subjects were included in this study. We used the DNA sequence analysis method to identify the most prevailing 10 mutations located in exon 2 and 10 of MEFV gene.

**RESULTS:** As a result of the MEFV mutation analysis, the most common mutation was the M694V mutation allele with a frequency rate of 41.8%. When the patients group and control group were compared in terms of frequency of both polymorphic alleles (G polymorphic allele, observed in G138G and the A polymorphic allele, observed in A165A), the variation was observed to be statistically significant ( $p<0.001$ ). It was found that the MEFV mutation types have no relation with clinical findings and amyloidosis ( $p>0.05$ ).

**CONCLUSIONS:** To our knowledge, our study is the first study in the Southern Marmara region that reports the frequency of MEFV mutations. Our findings imply that the polymorphisms of G138G and A165A may have an impact on progress of the disease. We think that more studies, having higher number of cases and investigating the polymorphisms of MEFV gene, are needed.

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DOI: 10.1016/j.rbre.2016.02.004

PMID: 29173686

524. An Bras Dermatol. 2017 Sep-Oct;92(5):655-660. doi: 10.1590/abd1806-4841.20175899.

Outcomes of long term treatments of type I hereditary angioedema in a Turkish family.

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**BACKGROUND:** Hereditary angioedema is a rare autosomal dominantly inherited immunodeficiency disorder characterized by potentially life-threatening angioedema attacks.

**OBJECTIVE:** We aimed to investigate the clinical and genetic features of a family with angioedema attacks.

**METHODS:** The medical history, clinical features and C1-INH gene mutation of a

Turkish family were investigated and outcomes of long-term treatments were described.

**RESULTS:** Five members had experienced recurrent swellings on the face and extremities triggered by trauma. They were all misdiagnosed as familial Mediterranean fever (FMF) depending on frequent abdominal pain and were on colchicine therapy for a long time. They had low C4 and C1-INH protein concentrations and functions. A mutation (c.1247T>A) in C1-INH gene was detected. They were diagnosed as having hereditary angioedema with C1-INH deficiency (C1-INH hereditary angioedema) for the first time. Three of them benefited from danazol treatment without any significant adverse events and one received weekly C1 esterase replacement treatment instead of danazol since she had a medical history of thromboembolic stroke.

**STUDY LIMITATIONS:** Small sample size of participants.

**CONCLUSION:** Patients with C1-INH hereditary angioedema may be misdiagnosed as having familial Mediterranean fever in regions where the disorder is endemic. Medical history, suspicion of hereditary angioedema and laboratory evaluations of patients and their family members lead the correct diagnoses of hereditary angioedema. Danazol and C1 replacement treatments provide significant reduction in hereditary angioedema attacks.

DOI: 10.1590/abd1806-4841.20175899

PMCID: PMC5674698

PMID: 29166502 [Indexed for MEDLINE]

525. Eur J Rheumatol. 2017 Sep;4(3):184-188. doi: 10.5152/eurjrheum.2017.16113. Epub 2017 Sep 1.

Late ventricular potentials in familial Mediterranean fever with and without AA amyloidosis.

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**Objective:** Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by episodic and chronic inflammation that may lead to both accelerated coronary atherosclerosis and cardiac AA amyloidosis. We hypothesized that late ventricular potentials (LPs), an established electrocardiographic susceptibility marker of ventricular arrhythmias, will be more common in FMF than in the adjusted normal population due to these two types of inflammation-associated cardiac effects. Therefore, we aimed to evaluate the occurrence of LPs in FMF patients with and without amyloidosis.

**Material and Methods:** Signal-averaged electrocardiography was performed in consecutive patients with FMF using the Frank corrected orthogonal lead system. At least 200 consecutive beats were digitally recorded and averaged, and the presence of LPs was determined according to acceptable thresholds.

**Results:** There were 54 patients with colchicine-treated FMF, of whom 14 had biopsy-proven AA amyloidosis. None of the uncomplicated FMF patients and 2 of the 14 FMF amyloidosis patients had abnormal or borderline LPs.

**Conclusion:** Based on LPs as a susceptibility marker for arrhythmia, FMF patients, including the large majority of FMF patients with amyloidosis, are seemingly not at an increased risk to develop arrhythmias.

DOI: 10.5152/eurjrheum.2017.16113

PMCID: PMC5685277

PMID: 29164000

**Conflict of interest statement:** Conflict of Interest: No conflict of interest was declared by the author.

526. Front Immunol. 2017 Nov 6;8:1485. doi: 10.3389/fimmu.2017.01485. eCollection 2017.

Glucose-6-Phosphatase Catalytic Subunit 3 (G6PC3) Deficiency Associated With Autoinflammatory Complications.

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G6PC3 deficiency typically causes severe congenital neutropenia, associated with susceptibility to infections, cardiac and urogenital abnormalities. However, here we describe two boys of Pakistani origin who were found to have G6PC3 deficiency due to c.130 C>T mutation, but who have clinical phenotypes that are typical for a systemic autoinflammatory syndrome. The index case presented with combination of unexplained fevers, severe mucosal ulcers, abdominal symptoms, and inflammatory arthritis. He eventually fully responded to anti-TNF therapy. In this study, we show that compared with healthy controls, neutrophils and monocytes from patients have reduced glycolytic reserve. Considering that healthy myeloid cells have been shown to switch their metabolic pathways to glycolysis in response to inflammatory cues, we studied what impact this might have on production of the inflammatory cytokines. We have demonstrated that patients' monocytes, in response to lipopolysaccharide, show significantly increased production of IL-1 $\beta$  and IL-18, which is NLRP3 inflammasome dependent. Furthermore, additional whole blood assays have also shown an enhanced production of IL-6 and TNF from the patients' cells. These cases provide further proof that autoinflammatory complications are also seen within the spectrum of primary immune deficiencies, and resulting from a wider dysregulation of the immune responses.

DOI: 10.3389/fimmu.2017.01485

PMCID: PMC5681747

PMID: 29163546

Evidence for genetic overlap between adult onset Still's disease and hereditary periodic fever syndromes.

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**OBJECTIVE:** Adult onset Still's disease (AOSD) is a severe, autoimmune disease that can be challenging to treat with conventional therapeutics and biologicals in a considerable number of cases. Therefore, there is a high need to understand its pathogenesis better. As major clinical symptoms overlap between AOSD and hereditary periodic fever syndromes (HPFS), we analysed four known HPFS genes in AOSD.

**METHODS:** We performed Sanger sequencing and quantitative analysis of all coding regions of MEFV, TNFRSF1A, MVK and NLRP3 in 40 AOSD patients. All rare coding variants ( $n = 6$ ) were evaluated for several aspects to classify them as benign to pathogenic variants. Statistical analysis was performed to analyse whether variants classified as (likely) pathogenic were associated with AOSD.

**RESULTS:** We identified three rare variants in MEFV, one previously not described. Association to the three likely pathogenic MEFV variants was significant ( $p = 2.34 \times 10^{-3}$ ), and two of the three carriers had a severe course of disease. We observed strong evidence for significant association to mutations in TNFRSF1A ( $p = 2.40 \times 10^{-4}$ ), as 5% of patients (2/40) carried a (likely) pathogenic variant in this gene. Both of them received a biological for treatment.

**CONCLUSION:** Our results indicate TNFRSF1A as a relevant gene in AOSD, especially in patients with a more challenging course of disease, while causal variants

remain to be identified in the majority of patients.

DOI: 10.1007/s00296-017-3885-0

PMID: 29159471 [Indexed for MEDLINE]

528. Rheumatol Int. 2018 Jan;38(1):105-110. doi: 10.1007/s00296-017-3886-z. Epub 2017 Nov 18.

One novel and two uncommon MEFV mutations in Japanese patients with familial Mediterranean fever: a clinicogenetic study.

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Familial Mediterranean fever (FMF) is an autoinflammatory disease caused by mutations in the MEFV gene and characterized by recurrent episodes of fever and polyserositis. To date, over 317 MEFV mutations have been reported, only nine of which account for almost all Japanese patients with FMF. Therefore, the prevalence of rare MEFV variants and their clinical characteristics remains unclear. This study identified MEFV mutations previously unreported in the Japanese population and described their clinical features. We performed MEFV genetic testing in 488 Japanese patients with clinically suspected FMF. Of these

patients, we retrospectively analyzed three patients with novel or very uncommon MEFV mutations. In all patients, the clinical diagnosis of FMF was made according to Tel-Hashomer's criteria. One novel missense mutation (N679H) and two rare mutations (T681I and R410H) were identified in the MEFV gene. These mutations were found in compound heterozygous or complex genotypes with other known mutations in exons 1 or 2. According to clinical images, all three patients exhibited typical FMF symptoms. A number of patients with FMF caused by novel or uncommon MEFV variants might exist in the Japanese population; therefore, careful genetic testing is required for accurate diagnosis of this curable genetic disorder.

DOI: 10.1007/s00296-017-3886-z

PMID: 29151129 [Indexed for MEDLINE]

529. Clin Exp Rheumatol. 2017 Nov-Dec;35 Suppl 108(6):135. Epub 2017 Oct 31.

Recurrent pleural effusion is an important diagnostic clue to distinguish familial Mediterranean fever from Behçet's disease.

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PMID: 29148417 [Indexed for MEDLINE]

530. Clin Exp Rheumatol. 2017 Nov-Dec;35 Suppl 108(6):95-99. Epub 2017 Oct 24.

Exacerbation of Behçet's syndrome and familial Mediterranean fever with menstruation.

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**OBJECTIVES:** Menstruation triggers several conditions such as migraine, recurrent aphthous stomatitis and acne vulgaris in healthy individuals. There is evidence that Behçet's syndrome (BS) and familial Mediterranean fever (FMF) may exacerbate during menstruation. The aim is to assess whether BS and FMF patients experience menstrual flares.

**METHODS:** Females of reproductive age with BS and FMF seen consecutively at the outpatient clinic of Cerrahpasa Medical Faculty at Istanbul, as well as apparently healthy hospital workers were studied using a standardised questionnaire. BS patients were asked whether they experienced increased skin-mucosa lesions during the menstrual period. A similar questionnaire assessing this time the frequency of abdominal pain, chest pain and fever attacks was given to the patients with FMF. The healthy controls received both questionnaires.

**RESULTS:** A total of 200 BS patients, 240 FMF patients and 250 healthy controls were studied. The most commonly reported symptom among both BS patients (51%) and healthy controls (62%) was the acneiform lesion. At least 79% patients with FMF reported attacks with menstruation, notably abdominal pain which, majority thought, could be differentiated from dysmenorrhea. Additionally, 76% of healthy controls reported having abdominal pain consistent most probably with dysmenorrhea.

**CONCLUSIONS:** This survey showed that, in 68% of the patients with BS at least one skin mucosa lesion was exacerbated with menstruation, this was most commonly acneiform lesion. Menstruation had a slightly stronger effect on FMF, triggering at least one symptom in 79%. The main limitation of the study was the self-reported assessment methodology.

PMID: 29148415 [Indexed for MEDLINE]

531. Clin Exp Rheumatol. 2017 Nov-Dec;35 Suppl 108(6):82-85. Epub 2017 Oct 6.

A high and equal prevalence of the Q703K variant in NLRP3 patients with autoinflammatory symptoms and ethnically matched controls.

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**OBJECTIVES:** Cryopyrin associated periodic syndromes (CAPS) comprise a spectrum of autoinflammatory disorders of varying severity caused by mutations in the NLRP3 gene. The NLRP3-Q703K allele has been reported both as a functional polymorphism and as a low penetrance mutation.

**METHODS:** To describe the clinical phenotype of subjects with the Q703K allele and to report the frequency of this allele among patients with autoinflammatory symptoms and healthy controls. To this end, a cohort of 10 ethnically-matched controls per each Q703K-carrying patient, was composed.

**RESULTS:** Ninety patients suspected of harboring a systemic autoinflammatory disease (SAID), exclusive of FMF, were referred to our center for genotyping between 2012 and 2015. Fourteen of them (15.5%) were found to carry the Q703K allele, compared to 22 of 130 (16.9%) healthy, ethnically matched controls.

**CONCLUSIONS:** The similar carrier rate of the NLRP3-Q703K allele among patients with manifestations of a SAID and an ethnically matched control group suggest that this variant, does not determine the clinical phenotype. This reiterates the importance of testing a control group to avoid erroneously attributing a causative role to a gene polymorphism.

532. Clin Exp Rheumatol. 2017 Nov-Dec;35 Suppl 108(6):75-81. Epub 2017 Oct 27.

Other autoinflammatory disease genes in an FMF-prevalent population: a homozygous MVK mutation and a novel heterozygous TNFRSF1A mutation in two different Turkish families with clinical FMF.

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**OBJECTIVES:** No MEFV mutations are detected in approximately 10% of the patients with clinical FMF in populations where the disease is highly prevalent. Causative mutations were searched in other genes in two such families with "MEFV negative clinical FMF".

**METHODS:** Father and daughter of family A had attacks of fever, abdominal pain and AA amyloidosis. The two sibs of family B complained of febrile episodes with abdominal pain and arthritis. The patients were clinically investigated. Exome analysis in the daughter in family A and linkage analysis and candidate gene sequencing for the members of family B were performed. All patients were re-evaluated in the light of the genetic findings.

**RESULTS:** In the daughter in family A, filtering of the exome file for variants in 25 autoimmune/inflammatory disease-related genes revealed two heterozygous missense variants in TNFRSF1A, novel p.Cys72Phe and frequent p.Arg121Gln. In

family B, novel, homozygous missense p.Cys161Arg in MVK was identified. A clinical re-evaluation of the patients revealed a phenotype consistent with FMF rather than TRAPS in family A and an overlap of FMF with HIDS in family B.

CONCLUSIONS: In high risk populations of FMF a proportion of patients without MEFV mutations may carry causative mutations in other genes, and the clinical findings may not be fully consistent with the phenotype expected of the mutation identified but rather resemble FMF or an overlap syndrome.

PMID: 29148404 [Indexed for MEDLINE]

533. Eur J Immunol. 2018 Feb;48(2):230-238. doi: 10.1002/eji.201746947. Epub 2017 Dec 6.

Function and mechanism of the pyrin inflammasome.

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Pyrin, encoded by the MEFV gene, is an intracellular pattern recognition receptor that assembles inflammasome complexes in response to pathogen infections. Mutations in the MEFV gene have been linked to autoinflammatory diseases such as familial Mediterranean fever (FMF) or pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND). Recent insights have now revealed how pyrin is activated during infection, providing a molecular basis for the understanding of such disease-causing mutations in pyrin. Interestingly, pyrin does not directly recognize molecular patterns (pathogen- or host-derived danger molecules), but rather responds to disturbances in cytoplasmic homeostasis caused by the infection. In the case of pyrin, these perturbations, recently defined as 'homeostasis-altering molecular processes' (HAMPs), are processes leading to the inactivation of the RhoA GTPase. This review attempts to combine early observation and findings with the most recent discoveries on how pyrin detects inactivation of RhoA to shed light on the function and mechanism of pyrin activation.



DOI: 10.1002/eji.201746947

PMID: 29148036 [Indexed for MEDLINE]

534. Nat Commun. 2017 Nov 17;8(1):1576. doi: 10.1038/s41467-017-01676-0.

Wiskott-Aldrich syndrome protein regulates autophagy and inflammasome activity in innate immune cells.

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Dysregulation of autophagy and inflammasome activity contributes to the development of auto-inflammatory diseases. Emerging evidence highlights the importance of the actin cytoskeleton in modulating inflammatory responses. Here we show that deficiency of Wiskott-Aldrich syndrome protein (WASp), which signals to the actin cytoskeleton, modulates autophagy and inflammasome function. In a model of sterile inflammation utilizing TLR4 ligation followed by ATP or nigericin treatment, inflammasome activation is enhanced in monocytes from WAS patients and in WAS-knockout mouse dendritic cells. In ex vivo models of enteropathogenic *Escherichia coli* and *Shigella flexneri* infection, WASp deficiency causes defective bacterial clearance, excessive inflammasome activation and host cell death that are associated with dysregulated septin cage-like formation, impaired autophagic p62/LC3 recruitment and defective formation of canonical autophagosomes. Taken together, we propose that dysregulation of autophagy and inflammasome activities contribute to the autoinflammatory manifestations of WAS, thereby identifying potential targets for therapeutic intervention.

DOI: 10.1038/s41467-017-01676-0

PMCID: PMC5691069

PMID: 29146903 [Indexed for MEDLINE]

535. Rheumatol Int. 2018 Jan;38(1):83-87. doi: 10.1007/s00296-017-3883-2. Epub 2017 Nov 15.

Decreased serum vitamin B12 and vitamin D levels affect sleep quality in children with familial Mediterranean fever.

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Familial Mediterranean fever is an autoinflammatory disorder characterized by recurrent fever and serositis. We aimed to describe serum vitamin B12 and vitamin D levels and their correlation with self-reported sleep quality of pediatric FMF patients. Sixty-three children with FMF were enrolled to the study. Information on sleep quality was obtained using self-administration of Pittsburg Sleep Quality Index (PSQI). The patients were divided into subgroups depending on vitamin D serum concentrations:  $\geq 20$  and  $< 20$  ng/ml. We also grouped patients according to their serum B12 concentration:  $\geq 200$ ,  $< 200$  pg/ml. B12 levels were not correlated with PSQI scores, whereas significant correlation was found between vitamin D and total PSQI scores and daytime sleepiness. Total PSQI score, sleep disorders and daytime sleepiness sub-scores were statistically high in patients with serum D vitamin levels below 20 ng/ml. Sleep efficiency was found lower in patients with serum B12 levels below 200 pg/ml. B12 may have a positive role on effective sleep. More importantly, we suggest that vitamin D is protective against sleep disorders and poor sleep, it may also improve daytime activities.

DOI: 10.1007/s00296-017-3883-2

PMID: 29143127 [Indexed for MEDLINE]

536. Hepatology. 2018 May;67(5):1903-1919. doi: 10.1002/hep.29652. Epub 2018 Mar 25.

$\beta$ -Catenin and interleukin-1 $\beta$ -dependent chemokine (C-X-C motif) ligand 10 production drives progression of disease in a mouse model of congenital hepatic fibrosis.

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Congenital hepatic fibrosis (CHF), a genetic disease caused by mutations in the polycystic kidney and hepatic disease 1 (PKHD1) gene, encoding for the protein fibrocystin/polyductin complex, is characterized by biliary dysgenesis, progressive portal fibrosis, and a protein kinase A-mediated activating phosphorylation of  $\beta$ -catenin at Ser675. Biliary structures of *Pkhd1del4/del4* mice, a mouse model of CHF, secrete chemokine (C-X-C motif) ligand 10 (CXCL10), a chemokine able to recruit macrophages. The aim of this study was to clarify whether CXCL10 plays a pathogenetic role in disease progression in CHF/Caroli disease and to understand the mechanisms leading to increased CXCL10 secretion. We demonstrate that treatment of *Pkhd1del4/del4* mice for 3 months with AMG-487, an inhibitor of CXC chemokine receptor family 3, the cognate receptor of CXCL10, reduces the peribiliary recruitment of alternative activated macrophages (cluster of differentiation 45+ F4/80+ cells), spleen size, liver fibrosis (sirius red), and cyst growth (cytokeratin 19-positive area), consistent with a pathogenetic role of CXCL10. Furthermore, we show that in fibrocystin/polyductin complex-defective cholangiocytes, isolated from *Pkhd1del4/del4* mice, CXCL10 production is mediated by Janus kinase/signal transducer and activator of transcription 3 in response to interleukin 1 $\beta$  (IL-1 $\beta$ ) and  $\beta$ -catenin. Specifically, IL-1 $\beta$  promotes signal transducer and activator of transcription 3 phosphorylation, whereas  $\beta$ -catenin promotes its nuclear translocation. Increased pro-IL-1 $\beta$  was regulated by nuclear factor kappa-light-chain-enhancer of activated B cells, and increased secretion of active IL-1 $\beta$  was mediated by the activation of Nod-like receptors, pyrin domain containing 3 inflammasome (increased expression of caspase 1 and Nod-like receptors, pyrin domain containing 3). **CONCLUSION:** In fibrocystin/polyductin complex-defective cholangiocytes,  $\beta$ -catenin and IL-1 $\beta$  are responsible for signal transducer and activator of transcription 3-dependent secretion of CXCL10; in vivo experiments show that the CXCL10/CXC chemokine receptor family 3 axis prevents the recruitment of macrophages, reduces inflammation, and halts the progression of the disease; the increased production of IL-1 $\beta$  highlights the autoinflammatory nature of CHF and may open novel therapeutic avenues. (Hepatology 2018;67:1903-1919).

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DOI: 10.1002/hep.29652

PMCID: PMC5906178 [Available on 2019-05-01]

PMID: 29140564 [Indexed for MEDLINE]

537. Rheumatol Int. 2018 Jan;38(1):75-81. doi: 10.1007/s00296-017-3882-3. Epub 2017 Nov 14.

Fatigue in familial Mediterranean fever and its relations with other clinical parameters.

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Fatigue is a common problem in patients with rheumatic disease. It may cause disability and poor quality of life. The aim of this study is to investigate fatigue in FMF patients as a disabling symptom and its associations with clinical and demographic variables. FMF patients were recruited into the study according to FMF Tel Hashomer criteria. Control group is composed of healthy individuals. Demographic and clinical features of the patients including PRAS scores were noted. Visual analogue score of pain (VAS-pain) and VAS-fatigue were used as clinical parameters. Pittsburgh Sleep Quality Index (PSQI), Multidimensional Assessment of Fatigue (MAF), Nottingham Health Profile (NHP), Fatigue Severity Scale (FSS), Fatigue Impact Scale (FIS) and Hospital Anxiety and Depression Scale (HADS) were filled out by both control and study group. Sixty-one FMF patients and 61 age and gender (44 female, 17 male in each group)-matched controls were enrolled into the study. Mean age of FMF and control group were  $35.5 \pm 11.8$  and  $35.8 \pm 11.7$  years, respectively. The mean disease duration was  $82.5 \pm 81.7$  months. Difference between mean of VAS-pain, VAS-fatigue, PSQI total score, MAF, all subsets of NHP, FSS, FIS, and HADS scores of FMF patients was significantly higher than of control group ( $p = 0.0001$ ). This study has shown that fatigue in FMF is associated with a number of psychological, sleep, quality of life and disease-related factors. FMF group had increased pain, fatigue, sleep disturbance and decreased quality of life compared to control group. FMF patients with fatigue may benefit from pharmacological and psychological interventions which target these factors.

DOI: 10.1007/s00296-017-3882-3

PMID: 29138905 [Indexed for MEDLINE]

538. Clin Pharmacol Ther. 2018 Aug;104(2):364-373. doi: 10.1002/cpt.936. Epub 2017 Dec 8.

Pharmacokinetics, Pharmacodynamics, and Proposed Dosing of the Oral JAK1 and JAK2 Inhibitor Baricitinib in Pediatric and Young Adult CANDLE and SAVI Patients.

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Population pharmacokinetic (popPK) modeling was used to characterize the PK profile of the oral Janus kinase (JAK)1/JAK2 inhibitor, baricitinib, in 18 patients with Mendelian interferonopathies who are enrolled in a compassionate use program. Patients received doses between 0.1 to 17 mg per day. Covariates of weight and renal function significantly influenced volume-of-distribution and clearance, respectively. The half-life of baricitinib in patients less than 40 kg was substantially shorter than in adult populations, requiring the need for

dosing up to 4 times daily. On therapeutic doses, the mean area-under-the-concentration-vs.-time curve was 2,388 nM\*hr, which is 1.83-fold higher than mean baricitinib exposures in adult patients with rheumatoid arthritis receiving doses of 4 mg once-daily. Dose-dependent decreases in interferon (IFN) biomarkers confirmed an in vivo effect of baricitinib on type-1 IFN signaling. PopPK and pharmacodynamic data support a proposal for a weight- and estimated glomerular filtration rate-based dosing regimen in guiding baricitinib dosing in patients with rare interferonopathies.

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DOI: 10.1002/cpt.936

PMCID: PMC6089664 [Available on 2019-08-01]

PMID: 29134648

539. J Allergy Clin Immunol. 2018 Mar;141(3):1135-1138. doi: 10.1016/j.jaci.2017.10.019. Epub 2017 Nov 11.

Autoinflammatory phenotypes in Aicardi-Goutières syndrome with interferon upregulation and serological autoimmune features.

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DOI: 10.1016/j.jaci.2017.10.019

PMID: 29132962

540. J Clin Invest. 2017 Dec 1;127(12):4235-4237. doi: 10.1172/JCI98322. Epub 2017 Nov 13.

Confounding role of tumor necrosis factor in cryopyrin-associated periodic syndromes.

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The NLRP3 inflammasome is a critical component of the innate immune system and can be activated in response to microbial and endogenous danger signals. Activation of the NLRP3 inflammasome results in caspase-1-dependent secretion of the proinflammatory cytokines IL-1 $\beta$  and IL-18. Gain-of-function missense mutations in NLRP3 result in a group of autoinflammatory diseases collectively known as the cryopyrin-associated periodic syndromes (CAPS). CAPS patients have traditionally been successfully treated with therapeutics targeting the IL-1 pathway; however, there are a number of identified CAPS patients who show only a partial response to IL-1 blockade. In this issue of the JCI, McGeough et al. demonstrated that TNF- $\alpha$ , in addition to IL-1 $\beta$ , plays an important role in promoting NLRP3 inflammasomopathies.

DOI: 10.1172/JCI98322

PMCID: PMC5707140

PMID: 29130931

541. Semin Arthritis Rheum. 2018 Jun;47(6):897-899. doi: 10.1016/j.semarthrit.2017.10.008. Epub 2017 Oct 12.

Protracted febrile myalgia syndrome treated with pulse of corticosteroids.

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**OBJECTIVE:** This study describes our 5-year experience treating protracted febrile myalgia syndrome (PFMS) with pulsed doses of corticosteroids.

**METHODS:** Eight patients with PFMS who received pulse corticosteroid therapy were identified from the electronic database of a tertiary pediatric medical center (2011-2016). Their clinical and laboratory data were collected. Differences in continuous variables between hospital admission and discharge were analyzed using Wilcoxon's matched pairs test.

**RESULTS:** There were 6 female and 2 male patients of median age 10.45 years (range 6.2-17.1) Six patients were found to be homozygous for the M694V mutation. In 4 patients, PFMS was the first-ever manifestation of familial Mediterranean fever. Pulse corticosteroid therapy was administered at a dose of 10mg/kg for 3 days. Pain was alleviated (visual analog scale score, 0) within hours of initiation of therapy, although pain flare-ups lasting for minutes to hours were still observed during hospitalization. At discharge, all patients were prescribed continuous oral corticosteroids (1-2mg/kg) with gradual tapering down over 6 weeks.

**CONCLUSION:** Pulse corticosteroid therapy is effective in alleviating PFMS pain; however, it does not completely abort a PFMS episode.

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DOI: 10.1016/j.semarthrit.2017.10.008

PMID: 29129325 [Indexed for MEDLINE]

542. Pediatrics. 2017 Dec;140(6). pii: e20162089. doi: 10.1542/peds.2016-2089. Epub 2017 Nov 9.

Eating Disorders, Autoimmune, and Autoinflammatory Disease.

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Comment in

Pediatrics. 2017 Dec;140(6):.

**OBJECTIVES:** Identifying factors associated with risk for eating disorders is important for clarifying etiology and for enhancing early detection of eating disorders in primary care. We hypothesized that autoimmune and autoinflammatory diseases would be associated with eating disorders in children and adolescents and that family history of these illnesses would be associated with eating disorders in probands.

**METHODS:** In this large, nationwide, population-based cohort study of all children and adolescents born in Denmark between 1989 and 2006 and managed until 2012, Danish medical registers captured all inpatient and outpatient diagnoses of eating disorders and autoimmune and autoinflammatory diseases. The study population included 930 977 individuals (48.7% girls). Cox proportional hazards regression models and logistic regression were applied to evaluate associations.

**RESULTS:** We found significantly higher hazards of eating disorders for children and adolescents with autoimmune or autoinflammatory diseases: 36% higher hazard for anorexia nervosa, 73% for bulimia nervosa, and 72% for an eating disorder not otherwise specified. The association was particularly strong in boys. Parental autoimmune or autoinflammatory disease history was associated with significantly increased odds for anorexia nervosa (odds ratio [OR] = 1.13, confidence interval

[CI] = 1.01-1.25), bulimia nervosa (OR = 1.29; CI = 1.08-1.55) and for an eating disorder not otherwise specified (OR = 1.27; CI = 1.13-1.44).

CONCLUSIONS: Autoimmune and autoinflammatory diseases are associated with increased risk for eating disorders. Ultimately, understanding the role of immune system disturbance for the etiology and pathogenesis of eating disorders could point toward novel treatment targets.

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DOI: 10.1542/peds.2016-2089

PMCID: PMC5703777

PMID: 29122972 [Indexed for MEDLINE]

Conflict of interest statement: POTENTIAL CONFLICT OF INTEREST: Dr Bulik is a grant recipient and consultant for Shire. Dr Zerwas has consulted for L.E.K. consulting. Dr Pisetsky is a grant recipient from Pfizer and is a member of a Data and Safety Monitoring Board for Celgene. Dr Thornton is an investigator on a grant from Shire; the other authors have indicated they have no potential conflicts of interest to disclose.

543. Avicenna J Med. 2017 Oct-Dec;7(4):158-163. doi: 10.4103/ajm.AJM\_78\_17.

Cardiac manifestations of Familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is autoinflammatory disorder characterized by sporadic attacks of fever, peritonitis, pleuritis, and arthritis. It is mainly seen in patients from Mediterranean origins, but it is now reported more frequently in Europe and North America due to immigration. To analyze the data on the cardiovascular manifestations in FMF patients, we searched PubMed using the terms "Familial Mediterranean Fever" or "FMF" in combination with other key words

including "cardiovascular diseases" "pericardial diseases" "atherosclerosis" "coronary artery diseases" "cardiomyopathy" "pulmonary hypertension" or "valvular diseases." suggested several mechanisms to explain the cardiac involvements in FMF including the ongoing inflammation and the amyloid deposits in the heart and vessels' walls at the advanced stages of FMF. The course of these manifestations varies widely, but it can associate with poor prognosis in some cases such as with pulmonary hypertension. Interestingly, Colchicine, which is the cornerstone therapy of FMF, plays a vital role in treating and preventing some of these disorders. In this article, In this article, we will discuss the incidence, pathophysiology, and prognosis of the various cardiac manifestations affecting FMF patients.

DOI: 10.4103/ajm.AJM\_78\_17

PMCID: PMC5655646

PMID: 29119082

Conflict of interest statement: There are no conflicts of interest.

544. Int J Rheum Dis. 2018 Jan;21(1):208-213. doi: 10.1111/1756-185X.13228. Epub 2017 Nov 8.

Monogenic interferonopathies: Phenotypic and genotypic findings of CANDLE syndrome and its overlap with C1q deficient SLE.

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OBJECTIVE: To report the clinical and genetic features of the first cases of

chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome in an Arab population and to compare them with patients of C1q deficient systemic lupus erythematosus (SLE).

**MATERIALS AND METHODS:** This is a retrospective case series of patients with CANDLE syndrome and C1q deficient SLE seen at a single tertiary hospital. Medical records were reviewed for demographic data, clinical and laboratory features, histopathology and imaging findings, and response to therapeutic intervention. Descriptive data were summarized.

**RESULTS:** Three patients from unrelated families fulfilled the clinical manifestations of CANDLE syndrome. The disease onset was within the first 4 months of age. Two patients had uncommon features including uveitis, pulmonary involvement, aseptic meningitis and global delay. Skin biopsy showed heterogeneous findings. Genomic DNA screening was homozygous for mutation in PSMB8, (NM\_004159.4:c.212C>T, p.T71M) in one patient and inconclusive for the other two patients. The comparison group was three patients with familial C1q deficient SLE from three unrelated families, who were born to consanguineous parents with at least one affected sibling. They presented with extensive mucocutaneous lesions, discoid rash and scarring alopecia. They required frequent admissions due to infections.

**CONCLUSION:** This is the first report of CANDLE syndrome in an Arab population; our patients had heterogeneous phenotypic and genetic features with overlap manifestations with C1q deficient SLE. Both are monogenic interferonopathies. However, C1q deficient SLE had more systemic inflammatory disease.

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DOI: 10.1111/1756-185X.13228

PMID: 29115062 [Indexed for MEDLINE]

545. Arthritis Care Res (Hoboken). 2018 Aug;70(8):1228-1237. doi: 10.1002/acr.23462. Epub 2018 Jul 12.

Consensus Treatment Plans for Chronic Nonbacterial Osteomyelitis Refractory to Nonsteroidal Antiinflammatory Drugs and/or With Active Spinal Lesions.

Zhao Y(1), Wu EY(2), Oliver MS(3), Cooper AM(4), Basiaga ML(1), Vora SS(5), Lee TC(3), Fox E(4), Amarilyo G(6), Stern SM(7), Dvergsten JA(8), Haines KA(9),

Rouster-Stevens KA(10), Onel KB(11), Cherian J(12), Hausmann JS(13), Miettunen P(14), Cellucci T(15), Nuruzzaman F(12), Taneja A(10), Barron KS(16), Hollander MC(17), Lapidus SK(18), Li SC(9), Ozen S(19), Girschick H(20), Laxer RM(21), Dedeoglu F(22), Hedrich CM(23), Ferguson PJ(24); Chronic Nonbacterial Osteomyelitis/Chronic Recurrent Multifocal Osteomyelitis Study Group and the Childhood Arthritis and Rheumatology Research Alliance Scleroderma, Vasculitis, Autoinflammatory and Rare Diseases Subcommittee.

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**OBJECTIVE:** To develop standardized treatment regimens for chronic nonbacterial osteomyelitis (CNO), also known as chronic recurrent multifocal osteomyelitis (CRMO), to enable comparative effectiveness treatment studies.

**METHODS:** Virtual and face-to-face discussions and meetings were held within the CNO/CRMO subgroup of the Childhood Arthritis and Rheumatology Research Alliance (CARRA). A literature search was conducted, and CARRA membership was surveyed to evaluate available treatment data and identify current treatment practices.

Nominal group technique was used to achieve consensus on treatment plans for CNO refractory to nonsteroidal antiinflammatory drug (NSAID) monotherapy and/or with active spinal lesions.

**RESULTS:** Three consensus treatment plans (CTPs) were developed for the first 12 months of therapy for CNO patients refractory to NSAID monotherapy and/or with active spinal lesions. The 3 CTPs are methotrexate or sulfasalazine, tumor necrosis factor inhibitors with optional methotrexate, and bisphosphonates. Short courses of glucocorticoids and continuation of NSAIDs are permitted for all regimens. Consensus was achieved on these CTPs among CARRA members. Consensus was also reached on subject eligibility criteria, initial evaluations that should be conducted prior to the initiation of CTPs, and data items to collect to assess treatment response.

**CONCLUSION:** Three consensus treatment plans were developed for pediatric patients with CNO refractory to NSAIDs and/or with active spinal lesions. Use of these CTPs will provide additional information on efficacy and will generate meaningful data for comparative effectiveness research in CNO.

© 2017, American College of Rheumatology.

DOI: 10.1002/acr.23462

PMCID: PMC5938153 [Available on 2019-08-01]

PMID: 29112802

546. Pol Arch Intern Med. 2017 Dec 22;127(12):815-822. doi: 10.20452/pamw.4137. Epub 2017 Nov 3.

Differential expression of programmed death 1 (PD-1) on CD4+ and CD8+ T cells in rheumatoid arthritis and psoriatic arthritis.

Bartosińska J, Zakrzewska E, Król A, Raczkiewicz D, Purkot J, Majdan M, Krasowska D, Chodorowska G, Giannopoulos K.

Comment in

Pol Arch Intern Med. 2017 Dec 22;127(12 ):813-814.

**INTRODUCTION** Rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are characterized by chronic inflammatory processes mediated by proinflammatory cytokines that affect the synovial lining. Programmed death 1 (PD-1) is a critical regulator of T-cell activation by downregulating immune responses.

**OBJECTIVES** The aim of the study was to investigate whether the expression of PD-1 on CD4+ and CD8+ T cells differs between patients with RA and those with PsA. **PATIENTS AND METHODS** The study included 100 patients with RA, 31 patients with PsA, and 52 healthy controls. The percentages, absolute numbers, and mean fluorescence intensity (MFI) of CD4+PD-1+ and CD8+PD-1+ T cells from peripheral blood were analyzed using flow cytometry. **RESULTS** The percentages and absolute numbers of CD4+ and CD8+ T cells with PD-1 expression were significantly higher in patients with RA than in controls. In patients with PsA, the percentages of CD4+PD-1+ and CD8+PD-1+ T cells were significantly lower than in controls. Because of the high frequency of PD-1-positive T cells in RA and their low frequency in PsA, we analyzed the expression level by analyzing the MFI. The median MFI of PD-1 on CD4+ and CD8+ T cells was significantly higher in patients with RA (median, 421 and 437, respectively) in comparison with patients with PsA (median, 222 and 198, respectively) and controls (median, 205 and 187, respectively). **CONCLUSIONS** The differential expression of PD-1 in RA and PsA suggests that PD-1 might be involved in autoimmune mechanisms in RA and autoinflammatory mechanisms in PsA in a different manner.

DOI: 10.20452/pamw.4137

PMID: 29112182

547. Rev Med Interne. 2018 Apr;39(4):287-296. doi: 10.1016/j.revmed.2017.09.002. Epub 2017 Oct 27.

[Cryopyrin-associated periodic syndromes].

[Article in French]



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Cryopyrin-associated periodic syndromes (CAPS) are linked to one single gene mutations, however they are associated with 3 syndromes, which are, from the mildest to the most severe phenotype familial cold urticaria, Muckle-Wells syndrome and chronic, infantile, neurologic, cutaneous, articular (CINCA) syndrome also called neonatal-onset multisystem inflammatory disease (NOMID). Autosomic dominant inheritance is present in most cases but in CINCA/NOMID syndrome where neomutations are more common. Mutations in the gene encoding cryopyrin, NLRP3, are associated with deregulation of caspase-1 activity, excessive interleukin-1 production and an autoinflammatory syndrome, which in familial cold urticaria and Muckle-Wells syndrome may be triggered or worsened by exposure to coldness. More and more mutations are described and even somatic mutations that can explain some clinical signs beginning in adulthood. Patients disclose a pseudo-urticarial rash, arthralgia, headaches, sometimes fever, biological inflammation but also, in severe forms of the disease, neurologic inflammation with central deafness, ophthalmologic inflammation, chronic meningitis. Some CINCA/NOMID patients also develop growth cartilage pseudo-tumoral hypertrophy. Natural disease history is usually benign in familial cold urticarial but severe in the other forms, particularly regarding neuro-sensorial involvement. In addition, secondary AA amyloidosis may develop in all forms in the absence of control of chronic inflammation. Anti-interleukin-1 treatment with anakinra, riloncept or canakinumab induces in most cases complete remission, however sequelae may be present, particularly if central deafness or cartilage bone hypertrophy have already developed. This treatment is also important to prevent secondary amyloidosis or stabilize and even sometimes allow

improvement of amyloidosis lesions.

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DOI: 10.1016/j.revmed.2017.09.002

PMID: 29111302 [Indexed for MEDLINE]

548. J Autoimmun. 2018 Mar;88:11-20. doi: 10.1016/j.jaut.2017.10.012. Epub 2017 Nov 3.

Autophagy dysfunction in autoinflammatory diseases.

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Autoinflammatory diseases (AUIDs) are a genetically heterogeneous group of rheumatic diseases characterized by episodic inflammation linked with dysregulated innate immune responses. In this review, we summarize the molecular mechanisms altered by disease-associated variants in several AUIDs, including NOD2-associated diseases, TNF receptor-associated periodic syndrome (TRAPS), familial Mediterranean fever (FMF) and hyperimmunoglobulinemia D and periodic fever syndrome (HIDS), and highlight the roles dysregulated autophagy plays in disease pathogenesis. Autophagy is a conserved eukaryotic pathway for the elimination of cellular stressors, such as misfolded proteins, damaged

organelles, or intracellular microorganisms. It is now recognized that autophagy also functions to control inflammation through regulatory interactions with innate immune signaling pathways. AUID-associated genetic variants are known to directly activate inflammatory signaling pathways. Recent evidence also indicates that these variants may also cause impairment of autophagy, thus augmenting inflammatory responses indirectly. Intriguingly, these variants can impair autophagy by different mechanisms, further implicating the autophagic response pathway in AUIDs. These discoveries provide evidence that autophagy could be investigated as a new therapeutic target for AUIDs.

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DOI: 10.1016/j.jaut.2017.10.012

PMCID: PMC6034178

PMID: 29108670

549. Nat Med. 2017 Dec;23(12):1481-1487. doi: 10.1038/nm.4428. Epub 2017 Nov 6.

IRF3 and type I interferons fuel a fatal response to myocardial infarction.

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Interferon regulatory factor 3 (IRF3) and type I interferons (IFNs) protect against infections and cancer, but excessive IRF3 activation and type I IFN production cause autoinflammatory conditions such as Aicardi-Goutières syndrome and STING-associated vasculopathy of infancy (SAVI). Myocardial infarction (MI) elicits inflammation, but the dominant molecular drivers of MI-associated inflammation remain unclear. Here we show that ischemic cell death and uptake of cell debris by macrophages in the heart fuel a fatal response to MI by activating IRF3 and type I IFN production. In mice, single-cell RNA-seq analysis of 4,215 leukocytes isolated from infarcted and non-infarcted hearts showed that MI provokes activation of an IRF3-interferon axis in a distinct population of interferon-inducible cells (IFNICs) that were classified as cardiac macrophages. Mice genetically deficient in cyclic GMP-AMP synthase (cGAS), its adaptor STING, IRF3, or the type I IFN receptor IFNAR exhibited impaired interferon-stimulated gene (ISG) expression and, in the case of mice deficient in IRF3 or IFNAR, improved survival after MI as compared to controls. Interruption of IRF3-dependent signaling resulted in decreased cardiac expression of inflammatory cytokines and chemokines and decreased inflammatory cell infiltration of the heart, as well as in attenuated ventricular dilation and improved cardiac function. Similarly, treatment of mice with an IFNAR-neutralizing antibody after MI ablated the interferon response and improved left ventricular dysfunction and survival. These results identify IRF3 and the type I IFN response as a potential therapeutic target for post-MI cardioprotection.

550. Clin Rheumatol. 2018 Jun;37(6):1683-1687. doi: 10.1007/s10067-017-3883-3. Epub 2017 Nov 3.

Long-term follow-up of paediatric MEFV carriers.

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Although familial Mediterranean fever (FMF) is inherited autosomal recessively, some heterozygotes may express disease phenotype and require therapy. To date, there is no study in the literature about how to follow-up Mediterranean fever (MEFV) heterozygotes who do not fulfil FMF criteria in the paediatric age group. This study aims to share a single-centre experience of the long-term clinical and laboratory follow-up of paediatric MEFV carriers. We reviewed the charts of 69 children who were heterozygous for MEFV variants. All children were followed-up with their routine analysis and serum amyloid A levels every 6 months. Thirty-nine children had pathogenic mutations and 30 children had variants of unknown significance. The mean follow-up was  $3.2 \pm 1.6$  years (min 2 years, max 6 years). The children with pathogenic mutations had significantly higher mean SAA levels than the children with variants of unknown significance ( $p = 0.018$ ); however, the mean CRP and ESR were similar. Besides, the children with pathogenic mutations complained of fever episodes significantly more than the children with variants of unknown significance ( $p = 0.04$ ). None of the children had persistent proteinuria in the follow-up. We started colchicine in only two patients who were M694V heterozygous. Both patients had family history for FMF and fulfilled the disease criteria after 2 years of follow-up. Neither of these patients had persistently elevated acute phase reactants in their routine follow-up. This study suggested that routine clinical follow-up is useful; however, routine periodic laboratory workup is not necessary among MEFV carriers.

551. PLoS One. 2017 Nov 3;12(11):e0187572. doi: 10.1371/journal.pone.0187572.  
eCollection 2017.

Autoimmunity and autoinflammation: A systems view on signaling pathway  
dysregulation profiles.

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**INTRODUCTION:** Autoinflammatory and autoimmune disorders are characterized by  
aberrant changes in innate and adaptive immunity that may lead from an initial  
inflammatory state to an organ specific damage. These disorders possess  
heterogeneity in terms of affected organs and clinical phenotypes. However,  
despite the differences in etiology and phenotypic variations, they share genetic  
associations, treatment responses and clinical manifestations. The mechanisms  
involved in their initiation and development remain poorly understood, however  
the existence of some clear similarities between autoimmune and autoinflammatory  
disorders indicates variable degrees of interaction between immune-related  
mechanisms.

**METHODS:** Our study aims at contributing to a holistic, pathway-centered view on  
the inflammatory condition of autoimmune and autoinflammatory diseases. We have

evaluated similarities and specificities of pathway activity changes in twelve autoimmune and autoinflammatory disorders by performing meta-analysis of publicly available gene expression datasets generated from peripheral blood mononuclear cells, using a bioinformatics pipeline that integrates Self Organizing Maps and Pathway Signal Flow algorithms along with KEGG pathway topologies.

**RESULTS AND CONCLUSIONS:** The results reveal that clinically divergent disease groups share common pathway perturbation profiles. We identified pathways, similarly perturbed in all the studied diseases, such as PI3K-Akt, Toll-like receptor, and NF-kappa B signaling, that serve as integrators of signals guiding immune cell polarization, migration, growth, survival and differentiation.

Further, two clusters of diseases were identified based on specifically dysregulated pathways: one gathering mostly autoimmune and the other mainly autoinflammatory diseases. Cluster separation was driven not only by apparent involvement of pathways implicated in adaptive immunity in one case, and inflammation in the other, but also by processes not explicitly related to immune response, but rather representing various events related to the formation of specific pathophysiological environment. Thus, our data suggest that while all of the studied diseases are affected by activation of common inflammatory processes, disease-specific variations in their relative balance are also identified.

DOI: 10.1371/journal.pone.0187572

PMCID: PMC5669448

PMID: 29099860 [Indexed for MEDLINE]

552. Ocul Immunol Inflamm. 2017 Nov 3:1-6. doi: 10.1080/09273948.2017.1391297. [Epub ahead of print]

Ten-Year Retention Rate of Infliximab in Patients with Behçet's Disease-Related Uveitis.

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**PURPOSE:** To evaluate the 10-year drug retention rate of infliximab (IFX) in Behçet's disease (BD)-related uveitis, the effect of a concomitant use of disease modifying anti-rheumatic drugs (DMARDs) on drug survival and differences according to the lines of biologic treatment.

**METHODS:** Cumulative survival rates were studied using the Kaplan-Meier plot, while the Log-rank (Mantel-Cox) test was used to compare survival curves.

**RESULTS:** Forty patients (70 eyes) were eligible for analysis. The drug retention rates at 12-, 24-, 60- and 120-month follow-up were 89.03%, 86.16%, 75.66% and 47.11% respectively. No differences were identified according to the use of concomitant DMARDs ( $p = 0.20$ ), while a statistically significant difference was observed in relation to the different lines of IFX treatment ( $p = 0.014$ ). Visual acuity improved from baseline to the last follow-up visit ( $p = 0.047$ ) and a corticosteroid-sparing effect was observed ( $p < 0.0001$ ).

**CONCLUSIONS:** IFX retention rate in BD-uveitis is excellent and is not affected by concomitant DMARDs.

DOI: 10.1080/09273948.2017.1391297

PMID: 29099660

553. Rheumatol Int. 2018 Jan;38(1):37-50. doi: 10.1007/s00296-017-3854-7. Epub 2017 Nov 1.

Cardiovascular disease in patients with autoinflammatory syndromes.



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Autoinflammatory syndromes (AIS) are characterized by recurring events of inflammation, leading to a variety of organ manifestations and fever attacks. A subgroup of AIS is commonly referred to as hereditary periodic fever syndromes (HPFS). There is substantial evidence that autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus are strongly associated with cardiovascular morbidity and mortality. The link between AIS and cardiovascular disease is not that clear, even if the concept of continuous inflammation as a risk factor for cardiovascular disease is widely accepted. Research on the association of AIS and cardiovascular disease is increasing within the last years. In this review, we will discuss the association of several AIS with cardiovascular disease. Based on the rarity of some entities, lack of data, however, led to exclusion of some rare AIS. Especially, for Behcet's disease (BD), adult-onset Still's disease (AOSD), and Familial Mediterranean fever (FMF), there is an association with a number of cardiovascular abnormalities. BD is the AIS, which is most strongly associated with manifestation in the arterial and venous system. AOSD is strongly associated with cardiac inflammation (peri-/myocarditis). FMF patients are likely to suffer from serositis. Of note, there seems to be a link between variants of AOSD as well as FMF and idiopathic recurrent acute pericarditis.

DOI: 10.1007/s00296-017-3854-7

PMID: 29094181 [Indexed for MEDLINE]

554. Sci Rep. 2017 Nov 1;7(1):14818. doi: 10.1038/s41598-017-13858-3.

Trisomy 21 causes changes in the circulating proteome indicative of chronic

autoinflammation.

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Trisomy 21 (T21) causes Down syndrome (DS), but the mechanisms by which T21 produces the different disease spectrum observed in people with DS are unknown. We recently identified an activated interferon response associated with T21 in human cells of different origins, consistent with overexpression of the four interferon receptors encoded on chromosome 21, and proposed that DS could be understood partially as an interferonopathy. However, the impact of T21 on systemic signaling cascades in living individuals with DS is undefined. To address this knowledge gap, we employed proteomics approaches to analyze blood samples from 263 individuals, 165 of them with DS, leading to the identification of dozens of proteins that are consistently deregulated by T21. Most prominent

among these proteins are numerous factors involved in immune control, the complement cascade, and growth factor signaling. Importantly, people with DS display higher levels of many pro-inflammatory cytokines (e.g. IL-6, MCP-1, IL-22, TNF- $\alpha$ ) and pronounced complement consumption, resembling changes seen in type I interferonopathies and other autoinflammatory conditions. Therefore, these results are consistent with the hypothesis that increased interferon signaling caused by T21 leads to chronic immune dysregulation, and justify investigations to define the therapeutic value of immune-modulatory strategies in DS.

DOI: 10.1038/s41598-017-13858-3

PMCID: PMC5665944

PMID: 29093484

555. Gene. 2018 Jan 30;641:279-286. doi: 10.1016/j.gene.2017.10.068. Epub 2017 Nov 6.

Genotype-phenotype correlation in FMF patients: A "non classic" recessive autosomal or "atypical" dominant autosomal inheritance?

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**BACKGROUND:** Uncertainty remains on the pathogenetic mechanisms, model of inheritance as well as genotype-phenotype correlation of FMF disease.

**OBJECTIVE:** To investigate the impact of genetic factors on the FMF phenotype and the disease inheritance model.

**METHODS:** A total of 107 FMF patients were enrolled. Patients were diagnosed clinically. All patients underwent genetic analysis of the FMF locus on 16p13.3.

**RESULTS:** 9 distinct mutations were detected. Specifically, the 85.98% of patients showed a heterozygous genotype. The most common genotypes were p.Met680Ile/wt and p.Met694Val/wt. The most frequent clinical findings were fever, abdominal pain,

joint pain, thoracic pain, and erysipelas-like erythema. Analysis of clinical data did not detect any significant difference in clinical phenotype among heterozygous, homozygous as well as compound homozygous subjects, further supporting the evidence that, contrary to the recessive autosomal inheritance, heterozygous patients fulfilled the criteria of clinical FMF. Moreover, subjects with p.Met694Val/wt and p.Met680Ile/wt genotype reported the most severe clinical phenotype. p.Ala744Ser/wt, p.Glu148Gln/Met680Ile, p.Met680Ile/Met680Ile, p.Met680Ile/Met694Val, p.Pro369Ser/wt, p.Met694Ile/wt, p.Glu148Gln/Glu148Gln, p.Lys695Arg/wt resulted in 100% pathogenicity.

CONCLUSIONS: The existence of a "non classic" autosomal recessive inheritance as well as of an "atypical" dominant autosomal inheritance with incomplete penetrance and variable expressivity cannot be excluded in FMF.

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DOI: 10.1016/j.gene.2017.10.068

PMID: 29080837 [Indexed for MEDLINE]

556. Curr Osteoporos Rep. 2017 Dec;15(6):542-554. doi: 10.1007/s11914-017-0405-9.

Chronic Recurrent Multifocal Osteomyelitis (CRMO): Presentation, Pathogenesis, and Treatment.

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**PURPOSE OF REVIEW:** Chronic non-bacterial osteomyelitis (CNO) with its most severe form chronic recurrent multifocal osteomyelitis (CRMO) is an autoinflammatory bone disorder. We summarize the clinical presentation, diagnostic approaches, most recent advances in understanding the pathophysiology, and available treatment options and outcomes in CNO/CRMO.

**RECENT FINDINGS:** Though the exact molecular pathophysiology of CNO/CRMO remains somewhat elusive, it appears likely that variable defects in the TLR4/MAPK/inflammasome signaling cascade result in an imbalance between pro- and anti-inflammatory cytokine expressions in monocytes from CNO/CRMO patients. In this context, we present previously unpublished data on cytokine and chemokine expression in monocytes and tissues. CNO/CRMO is an autoinflammatory bone disorder resulting from imbalanced cytokine expression from innate immune cells. Though the exact molecular pathophysiology remains unclear, variable molecular defects appear to result in inflammasome activation and pro-inflammatory cytokine expression in monocytes from CNO/CRMO patients. Recent advances suggest signaling pathways and single molecules as biomarkers for CNO/CRMO as well as future treatment targets.

DOI: 10.1007/s11914-017-0405-9

PMCID: PMC5705736

PMID: 29080202 [Indexed for MEDLINE]

557. Pediatrics. 2017 Nov;140(5). pii: e20163148. doi: 10.1542/peds.2016-3148.

Tocilizumab for the Treatment of SLC29A3 Mutation Positive PHID Syndrome.

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Pigmentary hypertrichosis and non-autoimmune insulin-dependent diabetes mellitus (PHID) is associated with recessive mutations in SLC29A3, encoding the equilibrative nucleoside transporter hENT3 expressed in mitochondria, causing PHID and H syndromes, familial Rosai-Dorfman disease, and histiocytosis-lymphadenopathy-plus syndrome. Autoinflammation is increasingly recognized in these syndromes. We previously reported a 16-year-old girl with PHID syndrome associated with severe autoinflammation that was recalcitrant to interleukin-1 and tumor necrosis factor- $\alpha$  blockade. Tocilizumab is a humanized, monoclonal, anti-human interleukin-6 receptor antibody routinely used to treat arthritis in children and adults. Herein we report the first case of successful treatment of PHID syndrome using tocilizumab. Before commencing tocilizumab, there was evidence of significant systemic inflammation, and progressive sclerodermatous changes (physician global assessment [PGA] 7/10). Twelve weeks after starting tocilizumab (8 mg/kg every 2 weeks, intravenously) systemic inflammatory symptoms improved, and acute phase response markers normalized; serum amyloid A reduced from 178 to 8.4 mg/L. After a dose increase to 12 mg/kg every 2 weeks her energy levels, appetite, fevers, and night sweats further improved. Less skin tightness (PGA 5/10) was documented 12 months later. This excellent clinical and serological response was sustained over 48 months, and cutaneous sclerosis had improved further (PGA 3/10). Her height remained well below the 0.4th centile, and tocilizumab also had no impact on her diabetes or exocrine pancreatic insufficiency. Although the mechanism of autoinflammation of PHID remains uncertain, we suggest that tocilizumab should be the first choice when considering treatment of the autoinflammatory or cutaneous manifestations of this genetic disease.

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DOI: 10.1542/peds.2016-3148

PMID: 29079714 [Indexed for MEDLINE]

Conflict of interest statement: POTENTIAL CONFLICT OF INTEREST: Dr Brogan has

received institutional grant funding and consultancy fees from Roche; Drs Rafiq and Hussain have indicated they have no potential conflicts of interest to disclose.

558. Clin Calcium. 2017;27(11):1551-1559. doi: CliCa171115511559.

[Update on recent progress in vitamin D research. The effects of vitamin D in autoinflammatory diseases.]

[Article in Japanese]

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Various kinds of immune cells -including dendritic cells, macrophages, T cells and B cells- express the vitamin D receptor and 1 $\alpha$ -hydroxylase(CYP27B1). In vitro studies have shown the anti-inflammatory effect of 1,25-dihydroxyvitamin D:the active form of vitamin D. As vitamin D deficiency spread in our society, epidemiological studies have established the association between vitamin D deficiency and incidence or progression of several inflammatory diseases, including rheumatoid arthritis(RA), systemic lupus erythematosus(SLE), and multiple sclerosis(MS). In addition, recently the property of vitamin D for treatment or prevention is debated. Here, we review the recent epidemiological evidence associated with vitamin D and inflammatory diseases, and describe the immunomodulatory effect of vitamin D underlying it.

DOI: CliCa171115511559

PMID: 29074827 [Indexed for MEDLINE]

559. Arthritis Rheumatol. 2018 Feb;70(2):298-307. doi: 10.1002/art.40352. Epub 2018 Jan 18.

Accumulation of Antigen-Driven Lymphoproliferations in Complement Receptor 2/CD21-/low B Cells From Patients With Sjögren's Syndrome.

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**OBJECTIVE:** Patients with Sjögren's syndrome (SS) are prone to develop malignant lymphomas, and a correlation has been established between the lymphoproliferations occurring in these disorders and the presence in patients' blood of an unusual B cell population that down-regulates complement receptor 2/CD21. This study was undertaken to identify the B cell compartment from which these lymphoproliferations emerge and determine the mechanisms that promote clonal B cell expansion in patients with SS.

**METHODS:** The reactivity of antibodies expressed by CD19+CD10-CD27-IgM+CD21-/low cells isolated from the blood of patients with SS was tested using a polymerase chain reaction-based approach that allows us to clone and express, in vitro, recombinant antibodies produced by single B cells.

**RESULTS:** Clonal expansions were identified in CD21-/low B cells isolated from the peripheral blood of 3 patients with SS. These lymphoproliferations expressed B cell receptors (BCRs) that displayed somatic hypermutation lineage trees characteristic of a strong selection by antigens; one of these antigens was identified as a ribosomal self antigen. When the mutated BCR sequences expressed by the expanded CD21-/low B cell clones from patients with SS were reverted in vitro to their germline counterparts, one clone remained autoreactive.

**CONCLUSION:** Clonal lymphoproliferations in patients with SS preferentially accumulate in the autoreactive CD21-/low B cell compartment often expanded in these subjects, and recognition of self antigens may drive the clonal B cell expansion while further refining BCR self-reactivity.



DOI: 10.1002/art.40352

PMCID: PMC5788702 [Available on 2019-02-01]

PMID: 29073352

560. J Am Acad Dermatol. 2018 Jun;78(6):1164-1170. doi: 10.1016/j.jaad.2017.10.023. Epub 2017 Oct 21.

Self-healing juvenile cutaneous mucinosis: Clinical and histopathologic findings of 9 patients: The relevance of long-term follow-up.

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**BACKGROUND:** Self-healing juvenile cutaneous mucinosis (SHJCM) is a rare disorder, and its pathogenesis and long-term prognosis are unknown.

**OBJECTIVE:** To elucidate the clinical and histopathologic characteristics, pathogenesis, and outcome in patients with SHJCM.

**METHODS:** Retrospective study of 9 patients with SHJCM. To complement initial findings, data collection forms were sent to the referring physicians.

**RESULTS:** All patients had an acute onset of firm nodules. Of the 9 patients, 6 presented initially with waxy papules on the dorsum of the hands; 5 suffered from periorbital edema, and 6 had a febrile prodrome. Histopathologic assessment of the papules revealed dermal mucin deposition, whereas the nodules showed proliferative fasciitis-like features or nonspecific chronic lobular panniculitis. Laboratory studies elicited evidence of active viral infection in 2 patients (human herpes virus 6 and rotavirus). Seven cases had spontaneous resolution within 6 months, and 2 patients with incomplete resolution showed subsequent transition to fibroblastic rheumatism and an autoinflammatory rheumatologic disease, respectively.

**LIMITATIONS:** This was a retrospective study with incomplete data from referring physicians.

**CONCLUSIONS:** Although spontaneous complete regression is expected, patients with SHJCM need long-term follow-up because of the possible development of dematorheumatologic conditions. The pathogenetic role of microbial agents deserves further investigation.

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DOI: 10.1016/j.jaad.2017.10.023

PMID: 29066274 [Indexed for MEDLINE]

561. Turk Pediatri Ars. 2017 Sep 1;52(3):113-121. doi: 10.5152/TurkPediatriArs.2017.4953. eCollection 2017 Sep.

Role of genetics in pediatric rheumatology.

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Pediatric rheumatology includes autoinflammatory monogenic diseases, autoinflammatory multifactorial diseases with complex inheritance, and diseases with uncertain clinical diagnosis or undefined conditions, even though they show signs of autoinflammation. Most of these diseases are systemic; it is important to diagnose patients promptly and definitively and to select proper treatment options based on the diagnoses. Clinical observation and acute-phase responses are usually sufficient for diagnosis; however, genetic analyses can provide supportive data for definite diagnosis and treatment, especially for rare monogenic diseases. As for multifactorial autoinflammatory diseases, susceptibility genes, and factors involved in the etiopathogenesis have not been fully identified. It is possible to identify disease genes and novel diseases, and lead to new treatment options by gene mapping studies and high-throughput screening strategies for multifactorial diseases and conditions with uncertain clinical characteristics. In this review, we discuss the three groups of autoinflammatory diseases and role of genetics in their diagnosis.

DOI: 10.5152/TurkPediatriArs.2017.4953

PMCID: PMC5644577

PMID: 29062244

Conflict of interest statement: Conflict of Interest: No conflict of interest was declared by the authors.

562. ACS Med Chem Lett. 2017 Sep 27;8(10):1048-1053. doi: 10.1021/acsmchemlett.7b00258. eCollection 2017 Oct 12.

## Identification of Potent and Selective RIPK2 Inhibitors for the Treatment of Inflammatory Diseases.

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NOD2 (nucleotide-binding oligomerization domain-containing protein 2) is an internal pattern recognition receptor that recognizes bacterial peptidoglycan and stimulates host immune responses. Dysfunction of NOD2 pathway has been associated with a number of autoinflammatory disorders. To date, direct inhibitors of NOD2 have not been described due to technical challenges of targeting the oligomeric protein complex. Receptor interacting protein kinase 2 (RIPK2) is an intracellular serine/threonine/tyrosine kinase, a key signaling partner, and an obligate kinase for NOD2. As such, RIPK2 represents an attractive target to probe the pathological roles of NOD2 pathway. To search for selective RIPK2 inhibitors, we employed virtual library screening (VLS) and structure based design that eventually led to a potent and selective RIPK2 inhibitor 8 with excellent oral bioavailability, which was used to evaluate the effects of inhibition of RIPK2 in various in vitro assays and ex vivo and in vivo pharmacodynamic models.

DOI: 10.1021/acsmchemlett.7b00258

PMCID: PMC5641954

PMID: 29057049

563. Rheumatol Int. 2018 Jan;38(1):51-58. doi: 10.1007/s00296-017-3853-8. Epub 2017 Oct 20.

Cardiac disease in familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is an autoinflammatory disease manifested by inflammatory attacks of peritonitis, pleuritis, pericarditis accompanied by fever and arthritis. Mutations of MEFV gene results in pyrin dysfunction, which causes uncontrolled interleukin-1 beta production and triggers the inflammatory attacks. Inflammation persists even during attack-free periods in one-third of the FMF patients. Findings of elevated proinflammatory cytokine patterns during remission as well as inflammatory attacks indicate the continuous subclinical disease activity and inflammation. Chronic inflammation was thought to be related to the cardiovascular risk in FMF patients. Main cardiac manifestations reported in FMF are pericarditis, idiopathic recurrent pericarditis, pericardiac tamponade, coronary heart disease and abnormal cardiovascular reactivity. Cardiac involvement in FMF may often be related to secondary AA amyloidosis. Deposition of amyloid may lead to cardiovascular morbidity and mortality in FMF patients. Associations of several vasculitic disorders such as Immunoglobulin A-associated vasculitis, polyarteritis nodosa and Behcet's disease are common in FMF. Appropriate prophylactic treatment with colchicine is recommended to prevent from cardiovascular risks. For those resistant to colchicine, IL-1 inhibitor agents can be used. Associated vasculitis should be treated with immunosuppressive agents. This review article aims to compile information about cardiac disease in FMF and refer to recent studies on the topic.

DOI: 10.1007/s00296-017-3853-8

PMID: 29051974 [Indexed for MEDLINE]

564. Orphanet J Rare Dis. 2017 Oct 18;12(1):167. doi: 10.1186/s13023-017-0720-3.

A web-based collection of genotype-phenotype associations in hereditary recurrent fevers from the Eurofever registry.

Papa R(1), Doglio M(2), Lachmann HJ(3), Ozen S(4), Frenkel J(5), Simon A(6), Neven B(7), Kuemmerle-Deschner J(8), Ozgocan H(9), Caorsi R(2), Federici S(2), Finetti M(2), Trachana M(10), Brunner J(11), Bezrodnik L(12), Pinedo Gago MC(13), Maggio MC(14), Tsitsami E(15), Al Suwairi W(16), Espada G(17), Shcherbina A(18), Aksu G(19), Ruperto N(2), Martini A(20), Ceccherini I(21), Gattorno M(2); Paediatric Rheumatology International Trials Organisation (PRINTO) and the Eurofever Project.

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**BACKGROUND:** Hereditary recurrent fevers (HRF) are a group of rare monogenic diseases leading to recurrent inflammatory flares. A large number of variants has been described for the four genes associated with the best known HRF, namely MEFV, NLRP3, MVK, TNFRSF1A. The Infevers database (<http://fmf.igh.cnrs.fr/ISSAID/infevers>) is a large international registry collecting variants reported in these genes. However, no genotype-phenotype associations are provided, but only the clinical phenotype of the first patient(s) described for each mutation. The aim of this study is to develop a registry of genotype-phenotype associations observed in patients with HRF, enrolled and validated in the Eurofever registry.

**RESULTS:** Genotype-phenotype associations observed in all the patients with HRF enrolled in the Eurofever registry were retrospectively analyzed. For autosomal dominant diseases (CAPS and TRAPS), all mutations were individually analyzed. For autosomal recessive diseases (FMF and MKD), homozygous and heterozygous combinations were described. Mean age of onset, disease course (recurrent or chronic), mean duration of fever episodes, clinical manifestations associated with fever episodes, atypical manifestations, complications and response to treatment were also studied. Data observed in 751 patients (346 FMF, 133 CAPS, 114 MKD, 158 TRAPS) included in the Eurofever registry and validated by experts were summarized in Tables. A total of 149 variants were described: 46 TNFRSF1A and 27 NLRP3 variants, as well as various combinations of 48 MVK and 28 MEFV variants were available.

**CONCLUSIONS:** We provide a potentially useful tool for physicians dealing with HRF, namely a registry of genotype-phenotype associations for patients enrolled in the Eurofever registry. This tool is complementary to the Infevers database and will be available at the Eurofever and Infevers websites.

PMID: 29047407 [Indexed for MEDLINE]

565. Infect Disord Drug Targets. 2018;18(2):105-121. doi: 10.2174/1871526517666171017114901.

Colchicine: A Review on Chemical Structure and Clinical Usage.

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For many years, colchicine has been used for therapeutic purposes and has been given considerable attention because of its association with tubulin and inhibition of small tubular polymerization. Colchicine is an alkaloid extracted from the colchicum autumnale plant, having molecular formula C<sub>22</sub>H<sub>25</sub>NO<sub>6</sub>, and consists of three rings. Many studies are concerned with structural changes in order to increase their pharmacological effectiveness and reduce the side effects of toxicity arising from it. The therapeutic use of colchicine has been mainly documented in Gout, Familial Mediterranean Fever, and many other diseases such as atrial fibrillation. This review summarizes the history of chemical structure of colchicine and presents some of its analogues. Furthermore, it shows binding mechanism with target protein when colchicine is used as a therapeutic drug, and gives a light spot on some studies that discuss the safe use of colchicine.

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DOI: 10.2174/1871526517666171017114901

PMID: 29046164 [Indexed for MEDLINE]

566. Nat Immunol. 2017 Oct 18;18(11):1271. doi: 10.1038/ni1117-1271a.

Corrigendum: The monogenic autoinflammatory diseases define new pathways in human



innate immunity and inflammation.

Manthiram K, Zhou Q, Aksentijevich I, Kastner DL.

Erratum for

Nat Immunol. 2017 Jul 19;18(8):832-842.

This corrects the article DOI: 10.1038/ni.3777.

DOI: 10.1038/ni1117-1271a

PMID: 29044244

567. Pediatr Rheumatol Online J. 2017 Oct 17;15(1):76. doi: 10.1186/s12969-017-0204-y.

H syndrome: 5 new cases from the United States with novel features and responses to therapy.

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**BACKGROUND:** H Syndrome is an autosomal recessive disorder characterized by cutaneous hyperpigmentation, hypertrichosis, and induration with numerous systemic manifestations. The syndrome is caused by mutations in SLC29A3, a gene located on chromosome 10q23, which encodes the human equilibrative transporter 3 (hENT3). Less than 100 patients with H syndrome have been described in the literature, with the majority being of Arab descent, and only a few from North

America.

**CASE PRESENTATION:** Here we report five pediatric patients from three medical centers in the United States who were identified to have H syndrome by whole exome sequencing. These five patients, all of whom presented to pediatric rheumatologists prior to diagnosis, include two of Northern European descent, bringing the total number of Caucasian patients described to three. The patients share many of the characteristics previously reported with H syndrome, including hyperpigmentation, hypertrichosis, short stature, insulin-dependent diabetes, arthritis and systemic inflammation, as well as some novel features, including selective IgG subclass deficiency and autoimmune hepatitis. They share genetic mutations previously described in patients of the same ethnic background, as well as a novel mutation. In two patients, treatment with prednisone improved inflammation, however both patients flared once prednisone was tapered. In one of these patients, treatment with tocilizumab alone resulted in marked improvement in systemic inflammation and growth. The other had partial response to prednisone, azathioprine, and TNF inhibition; thus, his anti-TNF biologic was recently switched to tocilizumab due to persistent polyarthritis. Another patient improved on Methotrexate, with further improvement after the addition of tocilizumab.

**CONCLUSION:** H syndrome is a rare autoinflammatory syndrome with pleiotropic manifestations that affect multiple organ systems and is often mistaken for other conditions. Rheumatologists should be aware of this syndrome and its association with arthritis. It should be considered in patients with short stature and systemic inflammation, particularly with cutaneous findings. Some patients respond to treatment with biologics alone or in combination with other immune suppressants; in particular, treatment of systemic inflammation with IL-6 blockade appears to be promising. Overall, better identification and understanding of the pathophysiology may help devise earlier diagnosis and better treatment strategies.

DOI: 10.1186/s12969-017-0204-y

PMCID: PMC5645937

PMID: 29041934 [Indexed for MEDLINE]

568. Rheumatology (Oxford). 2018 Jan 1;57(1):100-111. doi: 10.1093/rheumatology/kex373.

Familial Mediterranean fever mutations are hypermorphic mutations that

specifically decrease the activation threshold of the Pyrin inflammasome.

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**Objectives:** FMF is the most frequent autoinflammatory disease and is associated in most patients with bi-allelic MEFV mutations. MEFV encodes Pyrin, an inflammasome sensor activated following RhoGTPase inhibition. The functional consequences of MEFV mutations on the ability of Pyrin variants to act as inflammasome sensors are largely unknown. The aim of this study was to assess whether MEFV mutations affect the ability of Pyrin to detect RhoGTPase inhibition and other inflammasome stimuli.

**Methods:** IL-1 $\beta$  and IL-18 released by monocytes from healthy donors (HDs) and FMF patients were measured upon specific engagement of the Pyrin, NLRP3 and NLRC4 inflammasomes. Cell death kinetics following Pyrin activation was monitored in real time.

**Results:** Monocytes from FMF patients secreted significantly more IL-1 $\beta$  and IL-18 and died significantly faster than HD monocytes in response to low concentrations

of Clostridium difficile toxin B (TcdB), a Pyrin-activating stimulus. Monocytes from patients bearing two MEFV exon 10 pathogenic variants displayed an increased Pyrin inflammasome response compared with monocytes from patients with a single exon 10 pathogenic variant indicating a gene-dosage effect. Using a short priming step, the response of monocytes from FMF patients to NLRP3- and NLRC4-activating stimuli was normal indicating that MEFV mutations trigger a specific hypersensitivity of monocytes to low doses of a Pyrin-engaging stimulus.

Conclusion: Contrary to the NLRP3 mutations described in cryopyrin-associated periodic syndrome, FMF-associated MEFV mutations do not lead to a constitutive activation of Pyrin. Rather, FMF-associated mutations are hypermorphic mutations that specifically decrease the activation threshold of the Pyrin inflammasome without affecting other canonical inflammasomes.

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DOI: 10.1093/rheumatology/kex373

PMID: 29040788 [Indexed for MEDLINE]

569. Iran J Kidney Dis. 2017 Oct;11(5):388-391.

Multiple Myeloma in a Patient With Familial Mediterranean Fever.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent episodes of painful inflammation in the abdomen, chest, or joints. The coexistence of multiple myeloma (MM) and FMF is an extremely rare event. Here, we report a case of FMF with concurrent MM. A 63-year-old woman was diagnosed with FMF since 15 years earlier. She was admitted with a complaint of low back pain. Regarding the presence of back pain, anemia, hypercalcemia, and kidney failure, a diagnosis of MM was suspected. A skeletal

survey showed punched-out lesions in the skull. Serum protein electrophoresis demonstrated an immunoglobulin G kappa monoclonal gammopathy, and bone marrow aspiration revealed 30% involvement by abnormally appearing plasma cells, suggestive of MM. Although the association between FMF and MM may be a mere coincidence, further studies are necessary to understand their concurrent development.

PMID: 29038396 [Indexed for MEDLINE]

570. Cold Spring Harb Perspect Biol. 2019 Jan 2;11(1). pii: a028563. doi: 10.1101/cshperspect.a028563.

Inflammasome-Dependent Cytokines at the Crossroads of Health and Autoinflammatory Disease.

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As key regulators of both innate and adaptive immunity, it is unsurprising that the activity of interleukin (IL)-1 cytokine family members is tightly controlled by decoy receptors, antagonists, and a variety of other mechanisms. Additionally, inflammasome-mediated proteolytic maturation is a prominent and distinguishing feature of two important members of this cytokine family, IL-1 $\beta$  and IL-18, because their full-length gene products are biologically inert. Although vital in antimicrobial host defense, deregulated inflammasome signaling is linked with a growing number of autoimmune and autoinflammatory diseases. Here, we focus on introducing the diverse inflammasome types and discussing their causal roles in periodic fever syndromes. Therapies targeting IL-1 or IL-18 show great efficacy in some of these autoinflammatory diseases, although further understanding of the molecular mechanisms leading to unregulated production of these key cytokines is required to benefit more patients.

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571. Br J Dermatol. 2018 Oct;179(4):959-962. doi: 10.1111/bjd.16071. Epub 2018 Mar 14.

Successful treatment of SAPHO syndrome with apremilast.

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SAPHO (synovitis, acne, pustulosis, hyperostosis and osteitis) syndrome is a rare disease with inflammatory osteoarticular and skin involvement. The pathogenesis of SAPHO syndrome remains unclear, but evidence suggests it may be an autoinflammatory disease triggered upon exposure to infectious agents in genetically predisposed individuals. Induction of the interleukin (IL)-23/T helper 17 axis in addition to neutrophil activation seem to play a key role, and therapies targeting these immunological pathways, including tumour necrosis factor (TNF) inhibitors, ustekinumab, secukinumab and the IL-1 inhibitor anakinra, are potential treatment options that need further investigation. Here we report a case of a 24-year-old woman with SAPHO syndrome who presented at our clinic with palmoplantar pustulosis and sternoclavicular joint involvement. Previous treatments with topical steroids and keratolytics combined with nonsteroidal anti-inflammatory drugs, intravenous methylprednisolone, methotrexate and sulfasalazine had all failed to improve symptoms. Therapy with etanercept was not tolerated, and because of a previous demyelinating peripheral neuropathy, further treatment with TNF inhibitors was avoided. We initiated ustekinumab 45 mg, which improved skin manifestations but not joint pain. Dose escalation to 90 mg initially improved joint pain, but the dose had to be reduced to 45 mg again because of increased infections. During subsequent 45-mg ustekinumab treatment, joint pain exacerbated so we switched to adalimumab which caused an exacerbation of the disease, so we switched to secukinumab, which

improved skin and joint symptoms significantly but was associated with a pustular hypersensitivity reaction. Finally, we began treatment with apremilast, a pan-cytokine approach, resulting in stabilization of the skin and joint symptoms without side-effects. To our knowledge, this is the first case report of apremilast as a treatment for SAPHO syndrome.

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DOI: 10.1111/bjd.16071

PMID: 29034454

572. Rheumatol Int. 2018 Jan;38(1):13-24. doi: 10.1007/s00296-017-3839-6. Epub 2017 Oct 14.

Vasculitis and vasculitis-like manifestations in monogenic autoinflammatory syndromes.

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Monogenic autoinflammatory syndromes are a rare group of disorders characterized by periodic episodes of systemic inflammation of endogenous origin. Sometimes, these diseases may present with features akin to vasculitis. We conducted a literature review on such vasculitic manifestations in described monogenic autoinflammatory syndromes utilizing the Online Mendelian Inheritance in Man (OMIM), Medline, and Scopus databases. Our search identified that Familial

Mediterranean fever (FMF) can manifest with features of either small, medium, large, or variable-vessel vasculitis. Stimulator of interferon gene (STING)-associated vasculopathy of infancy (SAVI) is an interferonopathy that can mimic the presentation of medium-vessel or small-vessel vasculitis, whereas deficiency of adenosine deaminase 2 (DADA2) is another such mimic of medium-vessel vasculitis, associated in a significant number of patients with features of immunodeficiency. Occasional reports exist of vasculitic manifestations in tumor necrosis factor (TNF) receptor-associated periodic fever syndrome (TRAPS) and chronic infantile neurologic cutaneous and articular disorder (CINCA), whereas mevalonate kinase deficiency can also mimic the presentation of small- or medium-vessel vasculitis. Clinicians should be aware of the possibility of autoinflammatory disease presenting as vasculitis to diagnose and treat the same appropriately.

DOI: 10.1007/s00296-017-3839-6

PMID: 29032440 [Indexed for MEDLINE]

573. J Pediatr. 2018 Jan;192:253-255. doi: 10.1016/j.jpeds.2017.08.078. Epub 2017 Oct 12.

PFAPA Syndrome in a Population with Endemic Familial Mediterranean Fever.

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We reviewed the medical records of patients with periodic fever, aphthosis, pharyngitis, and adenitis (PFAPA) to investigate the clinical course, treatment response, and association with MEFV gene mutation. Familial Mediterranean fever should be considered in patients with PFAPA who do not respond to adenotonsillectomy.

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DOI: 10.1016/j.jpeds.2017.08.078

PMID: 29031862 [Indexed for MEDLINE]

574. Clin Immunol. 2018 Feb;187:33-36. doi: 10.1016/j.clim.2017.10.001. Epub 2017 Oct 10.

Type I interferon pathway activation in COPA syndrome.

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Mutations of the COPA gene cause an immune dysregulatory disease characterised by polyarticular arthritis and progressive interstitial lung disease with pulmonary haemorrhages. We report the case of a young girl that presented at age 3 with polyarticular arthritis, chronic cough and high titer rheumatoid factor.

Radiologic imaging showed interstitial lung disease with tree-in-a-bud nodules and air-filled cysts. Targeted genetic analysis of COPA gene showed the reported c.698G>A mutation. The patient was lost to follow up for 3years during which therapy was discontinued with the development of joint damage and deformities.

Analysis of peripheral blood showed activation of type 1 interferon pathway, which was also confirmed in 4 previously reported COPA patients. Our observations underline the importance of early treatment in COPA disease to avoid loss of joint function. Furthermore, our results suggest a role for type 1 interferon in disease pathogenesis opening the possibility for targeted therapeutic approaches.

575. Rheumatology (Oxford). 2017 Dec 1;56(12):2229-2236. doi: 10.1093/rheumatology/kex360.

The association between omega-3 fatty acid biomarkers and inflammatory arthritis in an anti-citrullinated protein antibody positive population.

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**Objectives:** Higher circulating omega-3 fatty acids (n-3 FAs) are associated with a lower prevalence of anti-CCP antibodies and RF in subjects without RA. We examined whether, in anti-CCP+ subjects, n-3 FAs also play a role in development of inflammatory arthritis (IA).

**Methods:** At Colorado-based health fairs from 2008 to 2014, participants without a previous diagnosis of RA who were anti-CCP3+ (n = 47) were recruited into a follow-up study; symptom assessments and joint examinations were conducted every 6 months for the determination of IA. We measured n-3 FAs as a percentage of total lipids in red blood cell membranes (n-3 FA%) at each visit.

**Results:** We detected IA in 10 anti-CCP3+ subjects (21%) at the baseline visit. Increased total n-3 FA% in red blood cell membranes [odds ratio (OR) = 0.09, 95% CI: 0.01, 0.76], specifically docosapentaenoic acid (OR = 0.16, 95% CI: 0.03, 0.83) and docosahexaenoic acid (OR = 0.23, 95% CI: 0.06, 0.86), was associated with a lower odds of IA at the baseline visit, adjusting for n-3 FA supplement use, current smoking, RF+, elevated CRP+ and shared epitope. We followed 35 of the anti-CCP3+ subjects who were IA negative at baseline and detected 14 incident IA cases over an average of 2.56 years of follow-up. In a time-varying survival

analysis, increasing docosapentaenoic acid significantly decreased risk of incident IA (hazard ratio = 0.52, 95% CI: 0.27, 0.98), adjusting for age at baseline, n-3 FA supplement use, RF+, CRP+ and shared epitope.  
Conclusion: n-3 FAs may potentially lower the risk of transition from anti-CCP positivity to IA, an observation that warrants further investigation.

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DOI: 10.1093/rheumatology/kex360  
PMCID: PMC5850337  
PMID: 29029330 [Indexed for MEDLINE]

576. Rheumatology (Oxford). 2018 Feb 1;57(2):382-387. doi: 10.1093/rheumatology/kex353.

Use of colchicine in pregnancy: a systematic review and meta-analysis.

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Objectives: Colchicine is an anti-inflammatory agent used in the treatment of several rheumatological conditions. The use of colchicine in pregnancy is controversial. The current study aimed to systematically review and meta-analyse the existing data in the literature regarding the safety of colchicine in pregnancy.

Methods: A systematic review was carried out using six electronic databases, identifying all relevant studies where colchicine was administered to pregnant

women, and where pregnancy-related outcomes were measured. The primary endpoints were miscarriage and major foetal malformation. Secondary endpoints included birthweight and gestational age at birth.

Results: Four studies were included for meta-analysis. Use of colchicine throughout pregnancy was not associated with an increased incidence of miscarriage or major foetal malformations. The incidence of miscarriage was significantly lower in women who took colchicine compared with those that did not. In women with FMF who took colchicine throughout the pregnancy, there was no significant difference in birthweight or gestational age compared with those who did not take colchicine. When not limited to FMF, colchicine use was associated with a significantly lower birthweight and gestational age compared with a control group including healthy women who did not take colchicine.

Conclusions: Colchicine therapy did not significantly increase the incidence of foetal malformations or miscarriage when taken during pregnancy. Colchicine therapy for FMF should not be withheld on this basis during pregnancy.

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DOI: 10.1093/rheumatology/kex353

PMID: 29029311 [Indexed for MEDLINE]

577. Rheumatol Int. 2018 Jan;38(1):137-140. doi: 10.1007/s00296-017-3848-5. Epub 2017 Oct 13.

Neonatal ulcerative colitis associated with Familial Mediterranean fever: a case report.

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Neonatal inflammatory bowel disease (IBD) is a subclass of very early onset IBD that includes children younger than 1 month. It is characterized by more colonic involvement and monogenetic etiology, resistance to classical anti-inflammatory/immunomodulatory treatments and associated with colitis in first-degree family members. Herein we report a 3 month-old girl who was admitted with bloody diarrhea since 10 days of age. Her symptoms persist despite diet elimination. She was diagnosed with neonatal ulcerative colitis (UC) based on clinical, laboratory and histopathological examination. But, she was unresponsive to the immunosuppressive therapy. On the follow-up, she was hospitalized for the high fever two times. Genetic analysis revealed homozygote M694 V mutation. Bloody diarrhea and other clinical findings were improved after colchicine therapy. Neonatal UC associated with Familial Mediterranean fever is an extremely rare condition and to the best of our knowledge our case is the first case in literature. Early diagnosis autoinflammatory disease may prevent complications related to unnecessary immunosuppressive drug usage and the risk of development of amyloidosis associated with autoinflammatory disorders.

DOI: 10.1007/s00296-017-3848-5

PMID: 29027576 [Indexed for MEDLINE]

578. Can Fam Physician. 2017 Oct;63(10):756-762.

Approach to recurrent fever in childhood.

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**OBJECTIVE:** To provide an approach to recurrent fever in childhood, explain when infections, malignancies, and immunodeficiencies can be excluded, and describe the features of periodic fever and other autoinflammatory syndromes.

**SOURCES OF INFORMATION:** PubMed was searched for relevant articles regarding the pathogenesis, clinical findings, diagnosis, prognosis, and treatment of periodic fever and autoinflammatory syndromes.

**MAIN MESSAGE:** Fever is a common sign of illness in children and is most frequently due to infection. However, when acute and chronic infections have been excluded and when the fever pattern becomes recurrent or periodic, the expanding spectrum of autoinflammatory diseases, including periodic fever syndromes, should be considered. Familial Mediterranean fever is the most common inherited monogenic autoinflammatory syndrome, and early recognition and treatment can prevent its life-threatening complication, systemic amyloidosis. Periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome is the most common periodic fever syndrome in childhood; however, its underlying genetic basis remains unknown.

**CONCLUSION:** Periodic fever syndromes and other autoinflammatory diseases are increasingly recognized in children and adults, especially as causes of recurrent fevers. Individually they are rare, but a thorough history and physical examination can lead to their early recognition, diagnosis, and appropriate treatment.

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PMCID: PMC5638471

PMID: 29025800 [Indexed for MEDLINE]

579. J Exp Med. 2017 Nov 6;214(11):3219-3238. doi: 10.1084/jem.20171419. Epub 2017 Oct 11.

Identification of a selective and direct NLRP3 inhibitor to treat inflammatory disorders.

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The NLRP3 inflammasome has been implicated in the pathogenesis of a wide variety of human diseases. A few compounds have been developed to inhibit NLRP3 inflammasome activation, but compounds directly and specifically targeting NLRP3 are still not available, so it is unclear whether NLRP3 itself can be targeted to prevent or treat diseases. Here we show that the compound CY-09 specifically blocks NLRP3 inflammasome activation. CY-09 directly binds to the ATP-binding motif of NLRP3 NACHT domain and inhibits NLRP3 ATPase activity, resulting in the suppression of NLRP3 inflammasome assembly and activation. Importantly, treatment with CY-09 shows remarkable therapeutic effects on mouse models of cryopyrin-associated autoinflammatory syndrome (CAPS) and type 2 diabetes. Furthermore, CY-09 is active ex vivo for monocytes from healthy individuals or

synovial fluid cells from patients with gout. Thus, our results provide a selective and direct small-molecule inhibitor for NLRP3 and indicate that NLRP3 can be targeted in vivo to combat NLRP3-driven diseases.

© 2017 Jiang et al.

DOI: 10.1084/jem.20171419

PMCID: PMC5679172

PMID: 29021150 [Indexed for MEDLINE]

580. Cytokine. 2018 Apr;104:143-146. doi: 10.1016/j.cyto.2017.10.007. Epub 2017 Oct 7.

Longitudinal analysis of serum interleukin-18 in patients with familial Mediterranean fever carrying MEFV mutations in exon 10.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is an autoinflammatory disease caused by mutations in the MEFV gene. Mutations in exon 10 are associated with typical FMF phenotypes, and patients with exon 10 mutations have higher serum levels of interleukin (IL)-18 both during attacks and afebrile phases, compared to those without exon 10 mutations. However, longitudinal changes of serum IL-18 in FMF have not been fully characterized.

**METHODS:** We serially evaluated serum levels of pro-inflammatory cytokines, including IL-18, in 12 patients with FMF carrying exon 10 mutations, all of whom showed typical FMF attacks.

**RESULTS:** Markedly high concentrations of IL-18 were observed in all patients at diagnosis ( $5099 \pm 6084$  pg/mL). Serum IL-18 levels declined progressively after colchicine treatment in 7 patients (group A), whereas 5 patients showed continued elevation of circulating IL-18, despite declines in IL-6 and neopterin (group B).



The mean follow-up times in the two groups were  $4.7 \pm 3.2$  and  $4.8 \pm 1.5$  years, respectively. The mean serum IL-18 level at the last hospital visit in group B was  $4190 \pm 2610$  pg/mL. There were no differences in onset age, initial IL-18 levels, and colchicine doses between the groups. FMF attacks almost disappeared in both groups, but there were trends towards more frequent subtle symptoms such as abdominal discomfort in group B.

**CONCLUSIONS:** Sustained elevation of serum IL-18 may suggest the presence of persistent subclinical inflammation. Therefore, longitudinal examination of serum IL-18 may contribute to better follow-up of FMF patients with exon 10 mutations.

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DOI: 10.1016/j.cyto.2017.10.007

PMID: 29017770

581. Arthritis Care Res (Hoboken). 2018 Jul;70(7):1090-1094. doi: 10.1002/acr.23446. Epub 2018 Apr 24.

Nationwide Experience With Off-Label Use of Interleukin-1 Targeting Treatment in Familial Mediterranean Fever Patients.

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**OBJECTIVE:** Approximately 30-45% of patients with familial Mediterranean fever (FMF) have been reported to have attacks despite colchicine treatment. Currently, data on the treatment of colchicine-unresponsive or colchicine-intolerant FMF patients are limited; the most promising alternatives seem to be anti-interleukin-1 (anti-IL-1) agents. Here we report our experience with the off-label use of anti-IL-1 agents in a large group of FMF patients.

**METHODS:** In all, 21 centers from different geographical regions of Turkey were included in the current study. The medical records of all FMF patients who had used anti-IL-1 treatment for at least 6 months were reviewed.

**RESULTS:** In total, 172 FMF patients (83 [48%] female, mean age 36.2 years [range 18-68]) were included in the analysis; mean age at symptom onset was 12.6 years (range 1-48), and the mean colchicine dose was 1.7 mg/day (range 0.5-4.0). Of these patients, 151 were treated with anakinra and 21 with canakinumab. Anti-IL-1 treatment was used because of colchicine-resistant disease in 84% and amyloidosis in 12% of subjects. During the mean 19.6 months of treatment (range 6-98), the yearly attack frequency was significantly reduced (from 16.8 to 2.4;  $P < 0.001$ ), and 42.1% of colchicine-resistant FMF patients were attack free. Serum levels of C-reactive protein, erythrocyte sedimentation rate, and 24-hour urinary protein excretion (5,458.7 mg/24 hours before and 3,557.3 mg/24 hours after) were significantly reduced.

**CONCLUSION:** Anti-IL-1 treatment is an effective alternative for controlling

attacks and decreasing proteinuria in colchicine-resistant FMF patients.

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DOI: 10.1002/acr.23446

PMID: 28992387

582. Arthritis Rheumatol. 2018 Jan;70(1):127-133. doi: 10.1002/art.40344. Epub 2017 Dec 7.

Familial Mediterranean Fever and Incidence of Cancer: An Analysis of 8,534 Israeli Patients With 258,803 Person-Years.

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**OBJECTIVE:** Familial Mediterranean fever (FMF) is an autoinflammatory disease manifested as recurrent serosal inflammation. An association between FMF and malignancy has not been evaluated. The aim of this study was to estimate cancer risk in a large cohort of FMF patients from a single institution.

**METHODS:** The study cohort consisted of 8,534 FMF patients registered at the National FMF Center in Tel Hashomer, Israel. We linked the study cohort to the database of the Israel National Cancer Registry using the national identity number. Cancer incidence in FMF patients was determined and then stratified by age and sex. Standardized incidence ratios (SIRs) for cancers were calculated.

**RESULTS:** Among 8,534 FMF patients (4,400 men, 4,134 women), 350 developed cancer during the years 1970-2011. The overall cancer risk among patients with FMF was significantly lower than was expected in specific sex and ethnic groups of the

Israeli population: for males of Jewish ethnicity, SIR 0.66 (95% confidence interval [95% CI] 0.55-0.77),  $P < 0.001$ ; for females of Jewish ethnicity, SIR 0.75 (95% CI 0.64-0.86),  $P < 0.001$ ; and for males of Arab ethnicity, SIR 0.34 (95% CI 0.07-0.99),  $P = 0.024$ .

CONCLUSION: FMF patients have a significantly lower incidence of cancer than the general population of Israel. This pattern was demonstrated in 2 ethnic populations: Jewish and Arab. We speculate that the lower cancer incidence could be attributed to a direct physiologic effect of FMF or to its treatment.

© 2017, American College of Rheumatology.

DOI: 10.1002/art.40344

PMID: 28992365

583. Curr Rheumatol Rep. 2017 Oct 5;19(11):70. doi: 10.1007/s11926-017-0699-8.

Deficiency of Adenosine Deaminase 2 (DADA2), an Inherited Cause of Polyarteritis Nodosa and a Mimic of Other Systemic Rheumatologic Disorders.

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PURPOSE OF REVIEW: A new autoinflammatory disease, deficiency of adenosine deaminase 2 (DADA2), caused by mutations in the CECR1 gene, was first reported in 2014. This review aims to update progress in defining, treating, and understanding this multi-faceted disorder.

RECENT FINDINGS: DADA2 was first described in patients with systemic inflammation, mild immune deficiency, and vasculopathy manifested as recurrent stroke or polyarteritis nodosa (PAN). More than 125 patients have now been reported, and the phenotype has expanded to include children and adults presenting primarily with pure red cell aplasia (PRCA), or with antibody

deficiency. Age of onset and clinical severity vary widely, even among related patients, and are not clearly related to CECR1 genotype. Inflammatory features often respond to anti-TNF agents, but marrow failure and severe immune deficiency may require hematopoietic stem cell transplantation. ADA2 is expressed and secreted by monocytes and macrophages, but its biological function and the pathogenesis of DADA2 are uncertain and will remain an important area of research. Pre-clinical investigation of ADA2 replacement therapy and CECR1-directed gene therapy are warranted, but complicated by the absence of a suitable animal model.

DOI: 10.1007/s11926-017-0699-8

PMID: 28983775 [Indexed for MEDLINE]

584. Endocr Metab Immune Disord Drug Targets. 2018 Feb 13;18(2):148-154. doi: 10.2174/1871530317666171003155517.

Ankylosing Spondylitis Among Familial Mediterranean Fever Patients.

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**BACKGROUND:** Familial Mediterranean Fever (FMF) is one of the most common hereditary auto-inflammatory diseases especially among Arabs, Armenians, Jews, and Turks characterized by recurrent attacks of fever, abdominal pain and arthritis. Whether the prevalence of ankylosing spondylitis (AS) is increased in FMF patients is a matter of debate. This review will summarize all the literature data relevant to this topic.

**METHODS:** We searched all the articles through PubMed and Embase databases from 1963 until 2017 addressing the relationship between AS and FMF patients.

**RESULTS:** The prevalence of AS among FMF patients is highly variable. However, a significant relationship was found to exist between MEFV gene mutations and AS. Most patients with coexistent MEFV gene mutations and AS were human leucocyte antigen B27 (HLA-B27) negative. The effect of these mutations on AS severity and prognosis was not significant.

**CONCLUSION:** Large based population studies are needed to further assess the existence of MEFV gene mutations among AS patients and their effect on the clinical course of the disease in addition to assessment of AS prevalence in patients with FMF.

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DOI: 10.2174/1871530317666171003155517

PMID: 28982344 [Indexed for MEDLINE]

585. Ocul Immunol Inflamm. 2017 Oct 5:1-6. doi: 10.1080/09273948.2017.1351573. [Epub ahead of print]

Rapid and Sustained Efficacy of Golimumab in the Treatment of Multirefractory Uveitis Associated with Behçet's Disease.

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**PURPOSE:** To evaluate golimumab (GOL) efficacy in the management of Behçet's disease (BD)-related uveitis.

**METHODS:** We retrospectively collected data from 5 patients (8 eyes) with at least two recent relapses of uveitis, treated with GOL at the standard dose of 50 mg every 4 weeks.

**RESULTS:** A complete control of intraocular inflammation was observed in 7/8 eyes (87.5%) at 12-month follow-up. The number of relapses 12 months before and after GOL initiation was 11 and 1, respectively. At baseline, four eyes had active retinal vasculitis (RV). At 3-month follow-up evaluation RV resolved in all eyes. Mean Best Corrected Visual Acuity was  $6.93 \pm 4.34$  at baseline and  $7.32 \pm 3.87$  at 12-months follow-up.

**CONCLUSION:** We confirm GOL efficacy in reducing intraocular inflammation in BD, both in term of reduction in the number of uveitis relapses and in achieving a prompt resolution of active RV.

DOI: 10.1080/09273948.2017.1351573

PMID: 28981395

586. Clin Exp Rheumatol. 2017 Nov-Dec;35 Suppl 108(6):16-18. Epub 2017 Sep 21.

Can we make a diagnosis of autoinflammatory diseases based upon clinical features only?

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PMID: 28980913

587. Clin Exp Rheumatol. 2017 Nov-Dec;35 Suppl 108(6):130-131. Epub 2017 Sep 7.

Ustekinumab efficacy and safety in mucocutaneous multi-refractory Behçet's disease.

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PMID: 28980903 [Indexed for MEDLINE]

588. Clin Exp Rheumatol. 2017 Nov-Dec;35 Suppl 108(6):124-127. Epub 2017 Sep 26.

Comparison of patients with familial Mediterranean fever accompanied with sacroiliitis and patients with juvenile spondyloarthropathy.

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**OBJECTIVES:** Familial Mediterranean fever (FMF) is the most common autoinflammatory disease manifesting with self-limited recurrent febrile attacks and polyserositis. Acute recurrent monoarthritis is the most common form of musculoskeletal involvement in FMF; however, up to 5% of FMF patients may develop chronic joint diseases including sacroiliitis. It is difficult to distinguish whether sacroiliitis is a musculoskeletal finding of FMF or whether this is the



coexistence of two diseases, FMF and SpA. In this study, we aimed to evaluate FMF patients with sacroiliitis, and compare their features with juvenile spondyloarthropathy (SpA) patients, all of whom had sacroiliitis.

**METHODS:** 15 paediatric FMF patients with sacroiliitis and 30 patients with juvenile SpA followed between 2014-2016 at the Department of Paediatric Rheumatology at Hacettepe University, Ankara, were included in the study.

**RESULTS:** The median (min-max) age at diagnosis of sacroiliitis was 11 (7-15) for FMF+sacroiliitis, and 11.5 (7-16) years for juvenile SpA patients. All patients suffered from hip pain and morning stiffness. Only two FMF+sacroiliitis patients had enthesitis, while nearly half of juvenile SpA patients (46.7%) had enthesitis. Four FMF patients suffered from lower back pain, although none of them had spinal involvement. On the other hand, approximately one third of juvenile SpA patients had spinal involvement. The median white blood cell count, erythrocyte sedimentation rate, and C reactive protein values in FMF+sacroiliitis patients were higher ( $10.1 \times 10^3/\text{mm}^3$  vs  $7.8 \times 10^3/\text{mm}^3$ ,  $p = 0.002$ ; 41 vs 28 mm/h,  $p < 0.001$ ; 4.6 vs 1.3 mg/dl,  $p < 0.001$ ; respectively) than juvenile SpA patients. HLA B27 positivity was more common in juvenile SpA than FMF+sacroiliitis patients (86.6% vs 26.7%, respectively,  $p = 0.001$ ). The most common MEFV (Mediterranean FeVer) mutation was M694V in FMF patients. All juvenile SpA patients but one were negative for MEFV mutations. One juvenile SpA patient was heterozygous for E148Q.

**CONCLUSIONS:** We demonstrated that paediatric patients with FMF+sacroiliitis showed different characteristics (higher inflammatory markers, less frequent spinal and enthesitis involvement and HLA-B27 positivity) from patients with juvenile SpA. Whether FMF is a triggering factor for SpA or sacroiliitis is a feature of FMF, is still a matter of debate.

PMID: 28980897 [Indexed for MEDLINE]

589. Rheumatol Int. 2018 Jan;38(1):141-147. doi: 10.1007/s00296-017-3823-1. Epub 2017 Oct 3.

Colchicine intoxication in familial Mediterranean fever patients using clarithromycin for the treatment of *Helicobacter pylori*: a series of six patients.

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Familial Mediterranean fever is a hereditary disease, characterized by recurrent episodes of inflammation. Colchicine, the mainstay of therapy, is administered continuously to all diagnosed FMF patients. Drug-drug interaction between colchicine and clarithromycin, resulting in colchicine intoxication, has been noted, mainly in association with gout and pneumonia. In FMF, this adverse event has been scarcely described. We present and characterize six patients with clarithromycin-related colchicine intoxication, aiming mainly at characterizing the FMF-specific features of this event. This study is a retrospective analysis, based on clinical and hospital records of all FMF patients admitted to one hospital during 2002-2015, for colchicine intoxication, precipitated by consumption of clarithromycin. All six patients were women who received colchicine for FMF, and clarithromycin for *Helicobacter pylori* (HBP) gastric infection. Their daily dosages of colchicine ranged from 1.5 to 2.5 mg. Two had mild FMF, two moderate and two severe diseases. Colchicine intoxication occurred despite intact kidney function and was characterized by abdominal pain, diarrhea, weakness, rhabdomyolysis, hepatitis, kidney impairment and bone marrow injury. It is concluded that clarithromycin-induced colchicine intoxication is a hazard in FMF. It occurs despite normal kidney function and standard colchicine dose and is associated with female sex and moderate to severe FMF.

DOI: 10.1007/s00296-017-3823-1

PMID: 28975396 [Indexed for MEDLINE]

## Carriage of Mediterranean Fever (MEFV) Mutations in Patients with Postpericardiotomy Syndrome (PPS).

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**BACKGROUND:** Postpericardiotomy syndrome (PPS) is characterized by pleuro-pericardial inflammation, which occurs in patients undergoing surgical procedures involving the pleura, pericardium, or both. The syndrome is considered to be immune mediated. However, its pathogenesis is not fully understood. It has previously been demonstrated that the Mediterranean Fever (MEFV) gene, which is associated with familial Mediterranean fever (FMF), has a role in the activation and expression of several inflammatory diseases.

**OBJECTIVES:** To investigate whether carriage of the MEFV mutation may precipitate PPS or affect its phenotype.

**METHODS:** The study population included 45 patients who underwent cardiac surgery and developed PPS. The control group was comprised of 41 patients who did not develop PPS. Clinical and demographic data was collected. The severity of PPS was evaluated. Genetic analysis to determine the carriage of one the three most common MEFV gene mutations (M694V, V726A, E148Q) was performed. The carriage rate of MEFV mutations in patients with and without PPS was compared. Association between MEFV mutation carriage and severity of PPS was evaluated.

**RESULTS:** The rate of mutation carriage in the MEFV gene was similar in patients with and without PPS (15.6% in the study groups vs. 29.3% in the control group,  $P = 0.1937$ ). The rate of mutation carriage in the MEFV gene was significantly lower among patients with severe PPS as compared to patients with mild-moderate PPS (4.8% vs. 25%,  $P < 0.05$ ).

**CONCLUSIONS:** Carriage of mutations in the MEFV gene is not associated with development of PPS; however, it may affect PPS severity.

591. Front Immunol. 2017 Aug 24;8:1018. doi: 10.3389/fimmu.2017.01018. eCollection 2017.

Diagnostic Criteria for Adult-Onset Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis (PFAPA) Syndrome.

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**OBJECTIVE:** To identify a set of variables that could discriminate patients with adult-onset periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome from subjects with fever of unknown origin (FUO).

**METHODS:** We enrolled 74 adults diagnosed with PFAPA syndrome according to the currently used pediatric diagnostic criteria and 62 additional patients with FUO.

After having collected clinical and laboratory data from both groups, univariate and multivariate analyses were performed to identify the variables associated with PFAPA diagnosis. Odds ratio (OR) values, their statistical significance, and corresponding 95% confidence interval (CI) were evaluated for each diagnostic factor both at the univariate and multivariate analyses. Diagnostic accuracy was evaluated by the area under receiver operating characteristic (ROC) curve, while the leave-one-out cross-validation procedure was used to ensure that the model

maintains the same diagnostic power when applied to new data.

**RESULTS:** According to the multivariate analysis, the clinical variables that discriminated PFAPA patients were: fever episodes associated with cervical lymphadenitis (OR = 92;  $p < 0.0001$ ), fever attacks associated with erythematous pharyngitis (OR = 231;  $p < 0.0001$ ), increased inflammatory markers during fever attacks (OR = 588;  $p = 0.001$ ), and the lack of clinical and laboratory signs of inflammation between flares (OR = 1202;  $p < 0.0001$ ). These variables were considered for a diagnostic model which accounted for their OR values. The diagnostic accuracy of the proposed set of criteria corresponded to an area under ROC curve of 0.978 (95% CI 0.958-0.998), with a model sensitivity and specificity equal to 93.4% (95% CI 87.5-96.5%) and 91.7% (95% CI 82.8-96.7%), respectively.

**CONCLUSION:** we have provided herein a set of clinical diagnostic criteria for adult-onset PFAPA syndrome. Our criteria represent an easy-to-use diagnostic tool aimed at identifying PFAPA patients among subjects with FUO with a high-predictive potential, as shown by its very high sensitivity and specificity.

DOI: 10.3389/fimmu.2017.01018

PMCID: PMC5609591

PMID: 28970828

592. Rheumatology (Oxford). 2018 Apr 1;57(4):606-618. doi: 10.1093/rheumatology/kex306.

Bone involvement in monogenic autoinflammatory syndromes.

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Until recently the most common autoinflammatory diseases (AIDs) associated with bone disease in childhood included a few genetically complex (chronic non-bacterial osteomyelitis, synovitis, acne, pustulosis, hyperostosis and osteitis syndrome) and monogenic (Majeed syndrome, deficiency of IL-1 receptor antagonist, cherubism) AIDs. However, the spectrum of monogenic AIDs associated with bone manifestations has markedly expanded to include both recently identified diseases such as the type I interferonopathies and also newly recognized bone dysplasias in already established AIDs. In addition, we propose that some known bone dysplasia syndromes, especially those presenting with hyperostosis and associated systemic inflammation, be classified as AIDs. Collectively, we provide an overview of the diverse bone manifestations identified in the genetically defined AIDs, discuss the hypotheses of the underlying pathophysiological mechanisms and highlight potential novel therapeutic strategies.

DOI: 10.1093/rheumatology/kex306

PMID: 28968889 [Indexed for MEDLINE]

593. Rheumatology (Oxford). 2017 Dec 1;56(12):2102-2108. doi: 10.1093/rheumatology/kex305.

International multi-centre study of pregnancy outcomes with interleukin-1 inhibitors.

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**Objective:** To provide outcome data concerning pregnancies exposed to the Interleukin-1 (IL-1) inhibitors prior to conception in both men and women, during pregnancy and breast feeding.

**Methods:** Retrospective data were collected from members of the International Society for Systemic Autoinflammatory diseases and collated in a single centre. A uniform data collection sheet was used to obtain standardized data including maternal age and diagnosis, type, duration of and response to IL-1 blockade, pregnancy duration, delivery, mode of feeding and neonatal development.

**Results:** There were 31 maternal-exposed pregnancies from seven countries and we report the first data on paternal exposure: six to anakinra and five to canakinumab, with no negative outcomes. We also report the first data on canakinumab-exposed pregnancies: eight pregnancies that resulted in the delivery of seven healthy infants of normal gestational age and birthweight. There were 23 anakinra-exposed pregnancies resulting in the birth of 21 healthy infants, and one baby with unilateral renal agenesis and ectopic neurohypophysis. There were two first trimester miscarriages affecting a mother with active disease. There were no serious neonatal infections. Fourteen infants were breast fed with no complications. There were no reports of developmental delay, with follow-up of up to 10 years (median 18 months).

**Conclusion:** This series substantially increases the published experience of IL-1 blockade and reproduction including the first data on canakinumab and on paternal exposure to these agents. Data are generally reassuring, although the case of renal agenesis is the second reported in an anakinra-exposed pregnancy.

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DOI: 10.1093/rheumatology/kex305

PMCID: PMC6251516

PMID: 28968868 [Indexed for MEDLINE]

594. Rheumatology (Oxford). 2017 Nov 1;56(11):2035-2036. doi: 10.1093/rheumatology/kex294.

Osteitis as a manifestation of familial Mediterranean fever.

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DOI: 10.1093/rheumatology/kex294

PMID: 28968681 [Indexed for MEDLINE]

595. Joint Bone Spine. 2018 Jul;85(4):435-440. doi: 10.1016/j.jbspin.2017.09.003. Epub 2017 Sep 28.

Building a transitional care checklist in rheumatology: A Delphi-like survey.

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**OBJECTIVES:** To design a transitional care checklist to be used by and facilitate the work of health professionals in providing transitional care for children with a chronic rheumatologic disease and their families.

**METHODS:** A Delphi-like study among an international expert panel was carried out in four steps: (1) a working group of 6 specialists established a draft; (2) a web-survey among a panel of international experts evaluated it; (3) a 2-day consensus conference with an expert panel discussed items not reaching agreement; (4) a web-survey among the panel of international experts with the list of reformulated items.

**RESULTS:** The first draft of the checklist included 38 items in 3 phases of transition and 5 age groups. Thirty-three international experts evaluated the checklist reaching  $\geq 80\%$  agreement for 26 items and  $\leq 80\%$  for 12. The consensus conference of 12 experts discussed and redefined the 12 items. Twenty-five international experts filled out the web-survey and all items reached a minimum of 80% agreement except one. The final checklist was reached.

**CONCLUSIONS:** This Delphi-like study defined what themes should be included and at what age they need to be addressed with patients with a chronic rheumatology disease and their families during transition. This checklist reached a strong

international and interdisciplinary consensus while examining transition in a broad way. It should now be spread widely to health professionals to be used by all those who care for adolescents aged  $\geq 12$  years at times of transition. It could be transposed to most chronic conditions. Recommendations for further research are given.

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DOI: 10.1016/j.jbspin.2017.09.003

PMID: 28965941

596. Front Endocrinol (Lausanne). 2017 Sep 14;8:232. doi: 10.3389/fendo.2017.00232. eCollection 2017.

Type I Interferon Is a Catastrophic Feature of the Diabetic Islet Microenvironment.

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A detailed understanding of the molecular pathways and cellular interactions that result in islet beta cell ( $\beta$  cell) destruction is essential for the development and implementation of effective therapies for prevention or reversal of type 1 diabetes (T1D). However, events that define the pathogenesis of human T1D have remained elusive. This gap in our knowledge results from the complex interaction between genetics, the immune system, and environmental factors that precipitate T1D in humans. A link between genetics, the immune system, and environmental factors are type 1 interferons (T1-IFNs). These cytokines are well known for inducing antiviral factors that limit infection by regulating innate and adaptive immune responses. Further, several T1D genetic risk loci are within genes that link innate and adaptive immune cell responses to T1-IFN. An additional clue that links T1-IFN to T1D is that these cytokines are a known constituent of the autoinflammatory milieu within the pancreas of patients with T1D. The presence of IFN $\alpha/\beta$  is correlated with characteristic MHC class I (MHC-I) hyperexpression

found in the islets of patients with T1D, suggesting that T1-IFNs modulate the cross-talk between autoreactive cytotoxic CD8<sup>+</sup> T lymphocytes and insulin-producing pancreatic  $\beta$  cells. Here, we review the evidence supporting the diabetogenic potential of T1-IFN in the islet microenvironment.

DOI: 10.3389/fendo.2017.00232

PMCID: PMC5604085

PMID: 28959234

597. Curr Opin Allergy Clin Immunol. 2017 Dec;17(6):398-404. doi: 10.1097/ACI.0000000000000396.

NLRC4 inflammasomopathies.

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**PURPOSE OF REVIEW:** The purpose of the review is to highlight developments in autoinflammatory diseases associated with gain-of-function mutations in the gene encoding NLR-family CARD-containing protein 4 (NLRC4), the NLRC4-inflammasomopathies.

**RECENT FINDINGS:** Three years since the identification of the first autoinflammation with infantile enterocolitis (AIFEC) patients, there is an improved understanding of how the NLRC4 inflammasome and interleukin 18 (IL-18) contribute to gut inflammation in myeloid and also intestinal epithelial cells. This information has opened new therapeutic avenues to treat AIFEC patients with targeted agents like recombinant IL-18 binding protein and antiinterferon- $\gamma$  antibodies. Additional phenotypes traditionally associated with NLRP3 mutations like familial cold autoinflammatory syndrome and neonatal onset multisystem inflammatory disease (NOMID), have now also been associated with gain-of-function NLRC4 mutations. Finally, NLRC4 somatic mosaicism has now been identified in a

NOMID and an AIFEC patient, a finding emphasizing nontraditional modes of inheritance in autoinflammatory diseases.

**SUMMARY:** The NLRC4 inflammasomopathies constitute a growing autoinflammatory disease category that spans a broad clinical spectrum from cold urticaria to NOMID and the often fatal disease AIFEC. Rapid case identification with biomarkers like elevated serum IL-18 concentrations and early intervention with targeted immunomodulatory therapies are key strategies to improving outcomes for AIFEC patients.

DOI: 10.1097/ACI.0000000000000396

PMCID: PMC6070355

PMID: 28957823 [Indexed for MEDLINE]

598. *Pediatr Radiol*. 2018 Feb;48(2):279-282. doi: 10.1007/s00247-017-3961-3. Epub 2017 Sep 28.

Imaging findings of Copa syndrome in a 12-year-old boy.

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Copa syndrome is a newly described autosomal dominant autoinflammatory disease that presents as pulmonary hemosiderosis and polyarticular arthritis. Twenty-one cases from five families have been reported to date. We present chest computed tomography (CT) and temporomandibular joint magnetic resonance (MR) findings of a 12-year-old boy presenting with dyspnea on exertion, fatigue and clubbing.

Additional findings included a restrictive pattern of pulmonary involvement and positive inflammatory markers and autoantibodies. Genetic testing revealed a p.W240R variant of the COPA gene confirming the diagnosis of Copa syndrome. CT of

the chest showed a nonspecific interstitial pneumonia pattern distributed mainly in the lower lobes. MR of the temporomandibular joints and follow-up CT three years later are also described.

DOI: 10.1007/s00247-017-3961-3

PMID: 28956095 [Indexed for MEDLINE]

599. Biochem Biophys Rep. 2016 Dec 23;9:146-152. doi: 10.1016/j.bbrep.2016.12.002. eCollection 2017 Mar.

Accurate clinical genetic testing for autoinflammatory diseases using the next-generation sequencing platform MiSeq.

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Autoinflammatory diseases occupy one of a group of primary immunodeficiency diseases that are generally thought to be caused by mutation of genes responsible for innate immunity, rather than by acquired immunity. Mutations related to autoinflammatory diseases occur in 12 genes. For example, low-level somatic mosaic NLRP3 mutations underlie chronic infantile neurologic, cutaneous, articular syndrome (CINCA), also known as neonatal-onset multisystem inflammatory disease (NOMID). In current clinical practice, clinical genetic testing plays an important role in providing patients with quick, definite diagnoses. To increase the availability of such testing, low-cost high-throughput gene-analysis systems are required, ones that not only have the sensitivity to detect even low-level somatic mosaic mutations, but also can operate simply in a clinical setting. To

this end, we developed a simple method that employs two-step tailed PCR and an NGS system, MiSeq platform, to detect mutations in all coding exons of the 12 genes responsible for autoinflammatory diseases. Using this amplicon sequencing system, we amplified a total of 234 amplicons derived from the 12 genes with multiplex PCR. This was done simultaneously and in one test tube. Each sample was distinguished by an index sequence of second PCR primers following PCR amplification. With our procedure and tips for reducing PCR amplification bias, we were able to analyze 12 genes from 25 clinical samples in one MiSeq run. Moreover, with the certified primers designed by our short program-which detects and avoids common SNPs in gene-specific PCR primers-we used this system for routine genetic testing. Our optimized procedure uses a simple protocol, which can easily be followed by virtually any office medical staff. Because of the small PCR amplification bias, we can analyze simultaneously several clinical DNA samples with low cost and can obtain sufficient read numbers to detect a low level of somatic mosaic mutations.

DOI: 10.1016/j.bbrep.2016.12.002

PMCID: PMC5614572

PMID: 28956000

600. Curr Pharm Des. 2017;23(37):5569-5576. doi: 10.2174/1381612823666170926113754.

Inflammation and Epilepsy: Preclinical Findings and Potential Clinical Translation.

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**BACKGROUND:** The lack of treatments which can prevent epilepsy development or improve disease prognosis represents an unmet and urgent clinical need. The development of such drugs requires a deep understanding of the mechanisms underlying disease pathogenesis. In the last decade, preclinical studies in models of acute seizures and of chronic epilepsy highlighted that

neuroinflammation arising in brain areas of seizure onset and generalization is a key contributor to neuronal hyper-excitability underlying seizure generation. Microglia and astrocytes are pivotal cells involved in both the induction and perpetuation of the inflammatory response to epileptogenic injuries or seizures; other cell contributors are neurons, cell components of the blood brain barrier and leukocytes.

**METHODS:** From the clinical standpoint, neuroinflammation is now considered an hallmark of epileptogenic foci in various forms of focal onset pharmacoresistant epilepsies. Moreover, pharmacological studies in animal model with drugs targeting specific inflammatory molecules, and changes in intrinsic seizure susceptibility of transgenic mice with perturbed neuroinflammatory mechanisms, have demonstrated that neuroinflammation is not a bystander phenomenon but has a pathogenic role in seizures, cell loss and neurological co-morbidities.

Understanding the role of neuroinflammation in seizure pathogenesis is instrumental for a mechanism-based discovery of selective therapies targeting the epilepsy causes rather than its symptoms, thereby allowing the development of novel disease-modifying treatments. Notably, clinical translation of laboratory findings may take advantage of anti-inflammatory drugs already in medical use for peripheral autoinflammatory or autoimmune disorders.

**CONCLUSION:** This review reports key preclinical and clinical findings supporting a role for brain inflammation in the pathogenesis of seizures. It also highlights the emerging proof-of-concept studies showing signs of clinical efficacy of target-specific anti-inflammatory interventions in epilepsies of differing etiologies. We will discuss the need for biomarkers and novel clinical trial designs for anti-inflammatory therapies that have a mechanism of action very different than standard antiepileptic drugs.

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DOI: 10.2174/1381612823666170926113754

PMID: 28950818

601. Eur J Med Genet. 2017 Dec;60(12):701-705. doi: 10.1016/j.ejmg.2017.09.007. Epub 2017 Sep 21.

The spectrum of Familial Mediterranean Fever gene (MEFV) mutations and genotypes in Iran, and report of a novel missense variant (R204H).

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**BACKGROUND:** Familial Mediterranean Fever (FMF) is an autosomal recessive disorder, characterized by recurrent and self-limited episodes of fever, abdominal pain, synovitis and pleuritis. FMF as the most common inherited monogenic autoinflammatory disease mainly affects ethnic groups of the Mediterranean basin, Arab, Jewish, Turkish, Armenian North Africans and Arabic descent.

**MATERIALS AND METHODS:** In the present study, we selected 390 unrelated FMF patients according to the Tel-Hashomer criteria, and analyzed all patients for 12 most common mutations of MEFV gene by reverse hybridization assay (FMF strip assay). We also investigated exon 2 and 10 of MEFV gene in 78 patients by Sanger sequencing.

**RESULTS:** According to strip assay results, at least one mutation was found in 234 patients (60%), and no mutation was found in other 156 patients (40%). The five most common mutations and allelic frequencies were M694V (13.6%), E148Q (10.4%), M694I (6.5%), V726A (4.1%), and M680I (3.8%). Moreover, we detected a novel missense variant (R204H, c.611 G > A) (SCV000297822) and following rare mutations among sequenced samples; R202Q, P115T, G304R, and E230K.

**CONCLUSION:** This study describes the MEFV mutations spectrum and distribution in Iranian population, and shows different mutation patterns among Iranian ethnicities. Moreover, M694V is the most common MEFV mutation in Iran.



DOI: 10.1016/j.ejmg.2017.09.007

PMID: 28943464 [Indexed for MEDLINE]

602. Rheumatol Int. 2018 Jan;38(1):3-11. doi: 10.1007/s00296-017-3820-4. Epub 2017 Sep 23.

Tumor necrosis factor-associated periodic syndrome in adults.

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Tumor necrosis factor-associated periodic syndrome is an autoinflammatory disorder classified under hereditary periodic fever syndromes. Mutations in the tumor necrosis factor receptor contribute to tumor necrosis factor-associated periodic syndrome. Decreased shedding of receptors and increased mitochondrial reactive oxygen species production leading to elevated proinflammatory cytokines are documented. Inflammation in various organs is hallmark of tumor necrosis factor-associated periodic syndrome and manifests as spiking fever, abdominal pain, conjunctivitis and polyserositis in adults. The ongoing challenge is to diagnose the disease early in its course to prevent amyloidosis. The treatment options have evolved from use of nonsteroidal anti-inflammatory drugs and corticosteroids to targeted therapy like tumor necrosis factor receptor inhibitors and interleukin-1 blockers. The aim of this review is to give an overview of the pathogenesis, clinical features and the various treatment modalities available for tumor necrosis factor-associated periodic syndrome and aid physicians in recognizing the signs of the disease earlier.

DOI: 10.1007/s00296-017-3820-4

PMID: 28942479 [Indexed for MEDLINE]

603. Am J Med Genet A. 2018 Apr;176(4):784-803. doi: 10.1002/ajmg.a.38480. Epub 2017 Sep 21.

From clinical observations and molecular dissection to novel therapeutic strategies for primary immunodeficiency disorders.

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The field of primary immunodeficiency diseases (PID) is rapidly expanding with more than 300 genetically defined disorders that have been clinically described and molecularly analyzed. The molecular dissection of these entities has led to the discovery of new immunologic pathways and to novel and effective disease-specific therapies. This review provides a summary of these primary immune defects categorized by clinical phenotype and molecular similarity as defined by the International Union of Immunologic Societies (IUIS) Expert Committee for PID. In this synopsis, we discuss the molecular basis of various categories of PIDs including, but not limited to, severe combined immunodeficiencies, primary antibody deficiencies, immune dysregulation syndromes, as well as defects of the innate immune system such as phagocytic abnormalities, autoinflammatory fever syndromes, and complement deficiencies. We have attempted to focus on current strategies to prevent complications, ameliorate symptoms, or cure these disorders by promptly using antimicrobial therapies, immunoglobulin replacement, and hematopoietic stem cell transplantation. In addition, we will explore novel therapies such as molecularly targeted immunosuppression with monoclonal antibodies and specific immunomodulatory agents. Finally, we address experimental therapies targeting specific molecular defects, including gene therapy and gene editing.

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DOI: 10.1002/ajmg.a.38480

PMID: 28941161

604. Clin Exp Dermatol. 2017 Dec;42(8):939-941. doi: 10.1111/ced.13215. Epub 2017 Sep

20.

Fever, lipodystrophy and cutaneous lesions.

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DOI: 10.1111/ced.13215

PMID: 28940565 [Indexed for MEDLINE]

605. J Clin Rheumatol. 2017 Oct;23(7):395-397. doi: 10.1097/RHU.0000000000000533.

Systemic Vasculopathy in a Patient With Tumor Necrosis Factor Receptor-Associated Periodic Syndrome.

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DOI: 10.1097/RHU.0000000000000533

PMID: 28937477

606. J Exp Med. 2017 Nov 6;214(11):3449-3466. doi: 10.1084/jem.20170412. Epub 2017 Sep 21.

A multidimensional blood stimulation assay reveals immune alterations underlying systemic juvenile idiopathic arthritis.

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The etiology of sporadic human chronic inflammatory diseases remains mostly unknown. To fill this gap, we developed a strategy that simultaneously integrates blood leukocyte responses to innate stimuli at the transcriptional, cellular, and secreted protein levels. When applied to systemic juvenile idiopathic arthritis (sJIA), an autoinflammatory disease of unknown etiology, this approach identified gene sets associated with specific cytokine environments and activated leukocyte subsets. During disease remission and off treatment, sJIA patients displayed dysregulated responses to TLR4, TLR8, and TLR7 stimulation. Isolated sJIA monocytes underexpressed the IL-1 inhibitor aryl hydrocarbon receptor (AHR) at baseline and accumulated higher levels of intracellular IL-1 $\beta$  after stimulation. Supporting the demonstration that AHR down-regulation skews monocytes toward macrophage differentiation, sJIA monocytes differentiated in vitro toward macrophages, away from the dendritic cell phenotype. This might contribute to the increased incidence of macrophage activation syndrome in these patients. Integrated analysis of high-dimensional data can thus unravel immune alterations predisposing to complex inflammatory diseases.

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DOI: 10.1084/jem.20170412

PMCID: PMC5679164

PMID: 28935693 [Indexed for MEDLINE]

607. PLoS One. 2017 Sep 21;12(9):e0184843. doi: 10.1371/journal.pone.0184843. eCollection 2017.

Discovery of PF-06928215 as a high affinity inhibitor of cGAS enabled by a novel fluorescence polarization assay.

Hall J(1), Brault A(1), Vincent F(1), Weng S(2), Wang H(1), Dumlao D(1), Aulabaugh A(1), Aivazian D(3), Castro D(3), Chen M(1), Culp J(1), Dower K(4), Gardner J(5), Hawrylik S(1), Golenbock D(6), Hepworth D(7), Horn M(3), Jones L(7), Jones P(7), Latz E(6)(8), Li J(7), Lin LL(4), Lin W(1), Lin D(1), Lovering F(7), Niljanskul N(1), Nistler R(2), Pierce B(1), Plotnikova O(1), Schmitt D(1), Shanker S(1), Smith J(1), Snyder W(3), Subashi T(1), Trujillo J(1), Tyminski E(2), Wang G(2), Wong J(1), Lefker B(7), Dakin L(7), Leach K(2).

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Cyclic GMP-AMP synthase (cGAS) initiates the innate immune system in response to cytosolic dsDNA. After binding and activation from dsDNA, cGAS uses ATP and GTP to synthesize 2', 3' -cGAMP (cGAMP), a cyclic dinucleotide second messenger with mixed 2'-5' and 3'-5' phosphodiester bonds. Inappropriate stimulation of cGAS has been implicated in autoimmune disease such as systemic lupus erythematosus, thus inhibition of cGAS may be of therapeutic benefit in some diseases; however, the size and polarity of the cGAS active site makes it a challenging target for the development of conventional substrate-competitive inhibitors. We report here the development of a high affinity ( $K_D = 200$  nM) inhibitor from a low affinity fragment hit with supporting biochemical and structural data showing these

molecules bind to the cGAS active site. We also report a new high throughput cGAS fluorescence polarization (FP)-based assay to enable the rapid identification and optimization of cGAS inhibitors. This FP assay uses Cy5-labelled cGAMP in combination with a novel high affinity monoclonal antibody that specifically recognizes cGAMP with no cross reactivity to cAMP, cGMP, ATP, or GTP. Given its role in the innate immune response, cGAS is a promising therapeutic target for autoinflammatory disease. Our results demonstrate its druggability, provide a high affinity tool compound, and establish a high throughput assay for the identification of next generation cGAS inhibitors.

DOI: 10.1371/journal.pone.0184843

PMCID: PMC5608272

PMID: 28934246 [Indexed for MEDLINE]

608. Ann Rheum Dis. 2018 Feb;77(2):162-164. doi: 10.1136/annrheumdis-2017-212061. Epub 2017 Sep 19.

The evolving role of the rheumatologist in the management of immune-related adverse events (irAEs) caused by cancer immunotherapy.

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The rapid introduction of immunotherapies for cancer-targeting immunological checkpoints has led to a new class of toxicities that appear to be of autoimmune and or autoinflammatory origin. These disorders are now referred to as immune-related adverse events (irAEs) and pose considerable challenges to patient care in terms of how to optimally manage these formidable toxicities while allowing effective antitumoural therapy to continue. While rheumatologists will naturally be called on to manage those irAEs of rheumatic origin, we believe there is a need and an opportunity for rheumatologists to participate as central figures in this evolving field, in large part because of our familiarity with

multiorgan autoimmune disease and our expertise in crafting and utilising both traditional and biological immune-based therapies. Rheumatologists urgently need education in this evolving field to be best positioned as contributors to care of such patients and investigators of the underlying mechanisms of these complications.

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DOI: 10.1136/annrheumdis-2017-212061

PMID: 28928270

Conflict of interest statement: Competing interests: None declared.

609. Eur J Paediatr Neurol. 2018 Jan;22(1):72-81. doi: 10.1016/j.ejpn.2017.08.007. Epub 2017 Sep 1.

TNFRSF1A and MEFV mutations in childhood onset multiple sclerosis.

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To investigate frequency and phenotype of TNFRSF1A and MEFV mutations in childhood-onset multiple sclerosis (MS). Twenty-nine clinically well characterized patients were investigated for mutations in exons 2, 3, 4, and 6 of the TNFRSF1A gene and in exons 2, 3, 9, 10 of the MEFV gene. Standardized morbidity ratio (SMR) was used to assess whether the number of observed mutations was higher than expected. Eleven out of 29 patients tested positive for mutations. Heterozygosity for the TNFRSF1A R92Q (rs4149584) variant was found in 6/11 mutation-positive patients. The SMR for R92Q in our pediatric MS population was 4.6 (95% CI 1.7-10.0), 7.0 (95% CI 2.6-15.2), and 13.6 (95% CI 5.0-29.7), depending on reference population. Six patients carried at least one heterozygous MEFV mutation with SMRs of 21.4 (95% CI 7.9-46.6) and 14.6 (95% CI 5.4-31.9). Clinical characteristics of childhood MS patients with or without mutations did not differ significantly. Conclusion One third of our childhood MS patients had a heterozygous mutation in the TNFRSF1A and/or MEFV gene. This proportion by far exceeds the number of mutations expected and was higher than in adult MS patients, suggesting that these mutations might contribute to the pathogenesis of childhood MS.

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DOI: 10.1016/j.ejpn.2017.08.007

PMID: 28927886 [Indexed for MEDLINE]



Familial Mediterranean Fever Is Associated With Increased Mortality After Kidney Transplantation-A 19 Years' Single Center Experience.

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**BACKGROUND:** Current data regarding the outcome of kidney transplantation in patients with familial Mediterranean fever (FMF) who reach end-stage renal disease (ESRD) due to reactive amyloidosis A (AA) are scarce and inconclusive.

**METHODS:** The outcomes of 20 patients with FMF and biopsy-proven AA amyloidosis that were transplanted between 1995 and 2014 were compared with 82 control patients (32 with diabetes mellitus and 50 with nondiabetic kidney disease).

Major outcome data included overall patient and graft survivals.

**RESULTS:** During a mean overall follow-up of  $116.6 \pm 67.5$  months 11 patients (55%) with FMF died versus 26 patients (31%) in the control group. Median time of death for patients with FMF was 61 months (range, 16-81) after transplantation.

Estimated 5-year, 10-year, and actuarial 15-year overall patients survival rates were 73%, 45%, and 39%, respectively, for patients with FMF, versus 84%, 68% and 63%, respectively, for the control group ( $P = 0.028$ ). FMF was associated with more than twofold increased risk for death after transplantation, and with a threefold increased risk for hospitalization because of infections during the first year. Infections and cardiovascular disease were the cause of death in the majority of patients with FMF. Overall graft survival was similar between the groups. Recurrence of AA amyloidosis was diagnosed in 2 patients during the first year after transplantation.

**CONCLUSIONS:** FMF is associated with increased risk of mortality after kidney transplantation.

611. Bosn J Basic Med Sci. 2018 Feb 20;18(1):21-28. doi: 10.17305/bjbms.2017.2259.

Vitamin D status, serum lipid concentrations, and vitamin D receptor (VDR) gene polymorphisms in Familial Mediterranean fever.

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Vitamin D (VitD) is critical for the regulation of inflammatory processes, and VitD deficiency has been linked to several chronic inflammatory disorders. We aimed to investigate the concentrations of serum 25(OH)D3, lipid parameters, and three known VDR polymorphisms (BsmI, FokI, and TaqI) in patients with Familial Mediterranean fever (FMF), an autosomal recessive autoinflammatory disease. The study included 123 FMF patients and 105 controls. Seventy patients had no attack (group 1), 30 had 1-2 attacks (group 2), and 23 had 3 or more attacks (group 3) within last three months. Serum 25(OH)D3 concentrations were determined using liquid chromatography-tandem mass spectrometry. BsmI, FokI, and TaqI polymorphisms were analyzed by a competitive allele specific polymerase chain reaction assay (KASPar). Serum lipid parameters were measured with enzymatic colorimetric methods. 25(OH)D3 concentrations were lower in FMF patients compared to controls ( $p < 0.001$ ). No difference was observed in 25(OH)D3 concentration between groups 1, 2, and 3. The distributions of FokI and TaqI genotypes were not significantly different between FMF patients and controls. There was a significant difference in the distribution of AA BsmI genotype between male FMF patients and male controls. Increased concentrations of triglycerides ( $p = 0.012$ ) and decreased concentrations of high-density lipoprotein cholesterol [HDL-C] ( $p = 0.006$ ) were found in FMF patients compared to controls. Although lower 25(OH)D3 concentrations were observed in FMF patients versus controls, no association was determined between FMF attack frequency and 25(OH)D3 concentrations. We showed that the AA genotype of BsmI polymorphism is associated with FMF in males but not in females. The effects of decreased HDL-C and increased triglyceride concentrations on cardiovascular events in FMF patients should be further

investigated.

DOI: 10.17305/bjbms.2017.2259

PMCID: PMC5826670

PMID: 28926322 [Indexed for MEDLINE]

612. Med Clin (Barc). 2018 Jan 23;150(2):67-74. doi: 10.1016/j.medcli.2017.07.012. Epub 2017 Sep 15.

Monogenic autoinflammatory diseases: General concepts and presentation in adult patients.

[Article in English, Spanish]

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Monogenic autoinflammatory diseases (AIFD) are rare disorders characterized by an uncontrolled increase of the systemic inflammatory response, which is caused by mutations in genes involved in inflammatory pathways. Over the last few years, new genes and proteins responsible for new monogenic AIFD have been identified and a substantial improvement in their treatment has been achieved. Monogenic AIFD manifestations typically begin during childhood, but they can also occur in adults. Compared to pediatric patients, adults usually present with a less severe disease and fewer long-term complications. In addition, patients with adult-onset disease carry low-penetrance mutations more often than pathogenic variants. A late-onset of AIFD may be occasionally associated with the presence of somatic mutations. In this study, we review the most frequent monogenic AIFD, and others recently described, which may occur during adulthood.

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DOI: 10.1016/j.medcli.2017.07.012

PMID: 28923673

613. Cell Mol Immunol. 2018 Jan;15(1):12-14. doi: 10.1038/cmi.2017.90. Epub 2017 Sep 18.

Ebosin: a potential therapeutic agent for rheumatoid arthritis and autoinflammatory syndromes.

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DOI: 10.1038/cmi.2017.90

PMCID: PMC5827182

PMID: 28920583

614. Eur J Med Genet. 2017 Dec;60(12):690-694. doi: 10.1016/j.ejmg.2017.09.004. Epub 2017 Sep 13.

A homozygote TREX1 mutation in two siblings with different phenotypes: Chilblains and cerebral vasculitis.

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Three prime repair exonuclease 1 degrades single and double stranded DNA with 3'-5' nuclease activity and its mutations are related to type 1 IFN mediated autoinflammation due to accumulated intracellular nucleic acids. To date, several cases of systemic lupus erythematosus, Aicardi-Goutieres syndrome, familial chilblain lupus, retinal vasculopathy-cerebral leukodystrophy have been reported with TREX1 mutations. Chilblain lupus is a skin disease characterized by blue-reddish coloring, swelling or ulcers on acral regions of body such as fingertips, heels, nose and auricles. Central nervous system vasculitis is a prominent cause of childhood strokes. 10 families with familial chilblain lupus related to TREX1 mutations were reported previously in the literature, in which homozygote D18N variant in TREX1 gene was related to chilblains with cerebral vasculitis. In this report, whole-exome-sequencing revealed a homozygote R114C mutation in TREX1 gene was shown in two siblings with recurrent chilblains whom one of them was the second case accompanied by cerebral vasculitis in the literature. As a result, the approach of WES in clinical use revealed a novel mutation in clinically heterogenous patients to provide genetic counseling.

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DOI: 10.1016/j.ejmg.2017.09.004

PMID: 28919362 [Indexed for MEDLINE]

615. J Plast Reconstr Aesthet Surg. 2018 Jan;71(1):44-52. doi: 10.1016/j.bjps.2017.08.013. Epub 2017 Aug 16.

Reconstructive microsurgical approach for the treatment of pyoderma gangrenosum.

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**INTRODUCTION:** Pyoderma gangrenosum (PG) is a rare type of autoimmune disease that results in progressive ulcers with or without previous trauma. However, PG is not well understood to date, and its treatment therefore remains a challenge. Because of the disease's systemic characteristic and the unpredictability of the clinical course, no gold standard treatment is available, especially concerning the surgical procedures to treat pyodermic lesions. Often, PG is not recognized during routine clinical practice, and standard ulcer treatment (conservative wound care, debridement, skin grafting, and local flap coverage) is initiated; this induces an autoinflammatory response, resulting in disastrous ulcers, thereby making free flap coverage necessary. The purpose of this study was to assess the outcome of microvascular free-tissue transfer as a treatment option for extended soft-tissue defects resulting from PG.

**MATERIALS AND METHODS:** We retrospectively evaluated 8 cases in 5 patients suffering from PG of the lower extremity who received defect closure with a microvascular free-tissue transfer under immunosuppressive and corticosteroid therapy.

**RESULTS:** The average patient age was 60 years; three were male, and two were female. Seven defects were covered with free gracilis muscle flap. One patient received an anterolateral thigh flap. The average defect size was 93 cm<sup>2</sup>. No flap loss was observed during follow-up. All patients received broad-spectrum antibiotic treatment and corticosteroids. Two patients also received infliximab.

**DISCUSSION AND CONCLUSION:** PG once diagnosed is not a contraindication for microvascular free-tissue transfer. Multidisciplinary evaluation of each case is fundamental. All surgical treatments should be performed only with sufficient protective immunosuppression therapy. If the defect requires free flap coverage, it should be considered as a surgical option despite the potential risk of a pathergic response in PG and was a safe treatment option in all our cases. In conclusion, we share our experience regarding preoperative, intraoperative, and

postoperative care of patients with PG receiving free flap surgery.

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DOI: 10.1016/j.bjps.2017.08.013

PMID: 28918934 [Indexed for MEDLINE]

616. Acta Reumatol Port. 2017 Jul-Sep;42(3):232-239.

Reuma.pt contribution to the knowledge of immune-mediated systemic rheumatic diseases.

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Patient registries are key instruments aimed at a better understanding of the natural history of diseases, at assessing the effectiveness of therapeutic interventions, as well as identifying rare events or outcomes that are not captured in clinical trials. However, the potential of registries goes far beyond these aspects. For example, registries promote the standardization of clinical practice, can also provide information on domains that are not routinely collected in clinical practice and can support decision-making. Being aware of the importance of registries, the Portuguese Society of Rheumatology developed the Rheumatic Diseases Portuguese Register- Reuma.pt - which proved to be an innovative instrument essential to a better understanding of systemic immune-mediated rheumatic diseases. **OBJECTIVE:** To describe the contribution of Reuma.pt to the knowledge of systemic immune-mediated rheumatic diseases. **RESULTS:** Reuma.pt is widely implemented, with 77 centres actively contributing to the recruitment and follow-up of patients. Reuma.pt follows in a standardized way

patients with the following systemic inflammatory rheumatic diseases: rheumatoid arthritis (n=6218), psoriatic arthritis (n=1498), spondyloarthritis (n=2529), juvenile idiopathic arthritis (n =1561), autoinflammatory syndromes (n=122), systemic lupus erythematosus (n =1718), systemic sclerosis (n=180) and vasculitis (n=221). This platform is intended for use as an electronic medical record, provides standardized assessment of patients and support to the clinical decision, thereby contributing to a better quality of care of rheumatic patients. The research based on Reuma.pt identified genetic determinants of susceptibility and response to therapy, characterized in detail systemic rheumatic diseases and their long-term impact, critically appraised the performance of instruments for monitoring the disease activity, established the effectiveness and safety of biologic therapies and identified predictors of response, and proactively engaged patients in the management of their disease.

CONCLUSION: Reuma.pt is an innovative tool, widely established in the country that contributes to a clinical practice of excellence and simultaneously to increase the knowledge of systemic immune-mediated rheumatic diseases. Additionally, Reuma.pt fosters patients' participation in the management of the disease.

PMID: 28917219 [Indexed for MEDLINE]

617. Clin Dermatol. 2017 Sep - Oct;35(5):421-434. doi: 10.1016/j.clindermatol.2017.06.004. Epub 2017 Jun 27.

Behçet disease: New aspects.

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Behçet disease is currently considered an "autoinflammatory disease" triggered by infection and environmental factors in genetically predisposed individuals.



Although the disease is characterized by recurrent oral and genital aphthous ulcers and ocular involvement, it can affect multiple organ systems. Complex aphthosis is characterized by recurrent oral and/or genital aphthous ulcers. It is important to evaluate the patient with complex aphthosis for Behçet disease and related systemic disorders. We discuss the etiopathogenesis, clinical features, diagnostic criteria, and treatment approaches for complex aphthosis and Behçet disease in light of the current literature.

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DOI: 10.1016/j.clindermatol.2017.06.004

PMID: 28916023 [Indexed for MEDLINE]

618. Front Immunol. 2017 Aug 31;8:1058. doi: 10.3389/fimmu.2017.01058. eCollection 2017.

Inflammatory Markers for Arterial Stiffness in Cardiovascular Diseases.

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Arterial stiffness predicts an increased risk of cardiovascular events. Inflammation plays a major role in large arteries stiffening, related to atherosclerosis, arteriosclerosis, endothelial dysfunction, smooth muscle cell migration, vascular calcification, increased activity of metalloproteinases, extracellular matrix degradation, oxidative stress, elastolysis, and degradation of collagen. The present paper reviews main mechanisms explaining the crosstalk between inflammation and arterial stiffness and the most common inflammatory markers associated with increased arterial stiffness, considering the most recent clinical and experimental studies. Diverse studies revealed significant correlations between the severity of arterial stiffness and inflammatory markers, such as white blood cell count, neutrophil/lymphocyte ratio, adhesion molecules, fibrinogen, C-reactive protein, cytokines, microRNAs, and cyclooxygenase-2, in patients with a broad variety of diseases, such as metabolic syndrome, diabetes, coronary heart disease, peripheral arterial disease, malignant and rheumatic disorders, polycystic kidney disease, renal transplant, familial Mediterranean fever, and oral infections, and in women with preeclampsia or after menopause. There is strong evidence that inflammation plays an important and, at least, partly reversible role in the development of arterial stiffness, and inflammatory markers may be useful additional tools in the assessment of the cardiovascular risk in clinical practice. Combined assessment of arterial stiffness and inflammatory markers may improve non-invasive assessment of cardiovascular risk, enabling selection of high-risk patients for prophylactic treatment or more regular medical examination. Development of future destiffening therapies may target pro-inflammatory mechanisms.

DOI: 10.3389/fimmu.2017.01058

PMCID: PMC5583158

PMID: 28912780

619. Nature. 2017 Sep 28;549(7673):528-532. doi: 10.1038/nature23910. Epub 2017 Sep 13.

Maternal gut bacteria promote neurodevelopmental abnormalities in mouse offspring.

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Comment in

Nature. 2017 Sep 13;549(7671):131-132.

Nature. 2017 Sep 28;549(7673):466-467.

Maternal immune activation (MIA) contributes to behavioural abnormalities associated with neurodevelopmental disorders in both primate and rodent offspring. In humans, epidemiological studies suggest that exposure of fetuses to maternal inflammation increases the likelihood of developing autism spectrum disorder. In pregnant mice, interleukin-17a (IL-17a) produced by T helper 17 (TH17) cells (CD4<sup>+</sup> T helper effector cells involved in multiple inflammatory conditions) induces behavioural and cortical abnormalities in the offspring exposed to MIA. However, it is unclear whether other maternal factors are required to promote MIA-associated phenotypes. Moreover, the underlying mechanisms by which MIA leads to T cell activation with increased IL-17a in the maternal circulation are not well understood. Here we show that MIA phenotypes in offspring require maternal intestinal bacteria that promote TH17 cell differentiation. Pregnant mice that had been colonized with mouse commensal segmented filamentous bacteria or human commensal bacteria that induce intestinal TH17 cells were more likely to produce offspring with MIA-associated abnormalities. We also show that small intestine dendritic cells from pregnant,

but not from non-pregnant, females secrete IL-1 $\beta$ , IL-23 and IL-6 and stimulate T cells to produce IL-17a upon exposure to MIA. Overall, our data suggest that defined gut commensal bacteria with a propensity to induce TH17 cells may increase the risk of neurodevelopmental disorders in the offspring of pregnant mothers undergoing immune system activation owing to infections or autoinflammatory syndromes.

DOI: 10.1038/nature23910

PMCID: PMC5870873

PMID: 28902840 [Indexed for MEDLINE]

620. Curr Med Chem. 2018;25(24):2797-2810. doi: 10.2174/0929867324666170911162331.

Reappraisal of Antimalarials in Interferonopathies: New Perspectives for Old Drugs.

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The story of antimalarials as antiinflammatory drugs dates back several centuries. Chinin, the extract of the Cinchona bark, has been exploited since the 18th century for its antimalarial and antifebrile properties. Later, during the Second World War, the broad use of antimalarials allowed arguing their antirheumatic effect on soldiers. Since then, these drugs have been broadly used to treat Systemic Lupus Erythematosus, but, only recently, have the molecular mechanisms of action been partly clarified. Inhibitory action on vacuole function and trafficking has been considered for decades the main mechanism of the action of antimalarials, affecting the activation of phagocytes and dendritic cells. In addition, chloroquine is also known as a potent inhibitor of autophagy, providing

another possible explanation of its antiinflammatory action. However, much attention has been recently devoted to the action of antimalarials on the so-called cGAS/STING pathway leading from the sensing of cytoplasmic nucleic acids to the production of type I interferons. This pathway is a fundamental mechanism of host defence, since it is able to detect microbial DNA and induce the type I interferon-mediated immune response. Of note, genetic defects in the degradation of nucleic acids lead to inappropriate cGAS-STING activation and inflammation. These disorders, called type I interferonopathies, represent a valuable model to study the antiinflammatory potential of antimalarials. We will discuss possible development of antimalarials to improve the treatment of type I interferonopathies and likely multifactorial disorders characterised by interferon inflammation, such as Systemic Lupus Erythematosus.

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DOI: 10.2174/0929867324666170911162331

PMID: 28901270 [Indexed for MEDLINE]

621. J Immunol Res. 2017;2017:1514294. doi: 10.1155/2017/1514294. Epub 2017 Aug 16.

SIAE Rare Variants in Juvenile Idiopathic Arthritis and Primary Antibody Deficiencies.

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Sialic acid acetyltransferase (SIAE) deficiency was suggested to lower the levels of

ligands for sialic acid-binding immunoglobulin-like receptors, decreasing the threshold for B-cell activation. In humans, studies of rare heterozygous loss-of-function mutations in SIAE gene in common autoimmune diseases, including juvenile idiopathic arthritis (JIA), yielded inconsistent results. Considering the distinct pathogenesis of the two main subtypes of JIA, autoinflammatory systemic (sJIA) and autoimmune oligo/polyarticular (aJIA), and a predisposition to autoimmunity displayed by patients and families with primary antibody deficiencies (PADs), the aim of our study was to analyze whether SIAE rare variants are associated with both the phenotype of JIA and the autoimmunity risk in families with PADs. A cohort of 69 patients with JIA, 117 healthy children, 54 patients, and family members with PADs were enrolled in the study. Three novel SIAE variants (p.Q343P, p.Y495X, and c.1320+33T>C) were found only in patients with aJIA but interestingly also in their healthy relatives without autoimmunity, while none of PAD patients or their relatives carried SIAE defects. Our results show that SIAE rare variants are not causative of autoimmunity as single defects.

DOI: 10.1155/2017/1514294

PMCID: PMC5576406

PMID: 28900629 [Indexed for MEDLINE]

622. Arthritis Res Ther. 2017 Sep 12;19(1):199. doi: 10.1186/s13075-017-1406-x.

Effects of HLA-DRB1 alleles on susceptibility and clinical manifestations in Japanese patients with adult onset Still's disease.

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BACKGROUND: HLA-DRB1 alleles are major determinants of genetic predisposition to rheumatic diseases. We assessed whether DRB1 alleles are associated with susceptibility to particular clinical features of adult onset Still's disease

(AOSD) in a Japanese population by determining the DRB1 allele distributions.

METHODS: DRB1 genotyping of 96 patients with AOSD and 1,026 healthy controls was performed. Genomic DNA samples from the AOSD patients were also genotyped for

MEFV exons 1, 2, 3, and 10 by direct sequencing.

**RESULTS:** In Japanese patients with AOSD, we observed a predisposing association of DRB1\*15:01 ( $p = 8.60 \times 10^{-6}$ , corrected  $p$  ( $P_c$ ) = 0.0002, odds ratio (OR) = 3.04, 95% confidence interval (95% CI) = 1.91-4.84) and DR5 serological group ( $p = 0.0006$ , OR = 2.39, 95% CI = 1.49-3.83) and a protective association of DRB1\*09:01 ( $p = 0.0004$ ,  $P_c = 0.0110$ , OR = 0.34, 95% CI = 0.18-0.66) with AOSD, and amino acid residues 86 and 98 of the DR $\beta$  chain were protectively associated with AOSD. MEFV variants were identified in 49 patients with AOSD (56.3%). The predisposing effect of DR5 was confirmed only in patients with AOSD who had MEFV variants and not in those without MEFV variants. Additionally, DR5 in patients with AOSD are associated with macrophage activation syndrome (MAS) and steroid pulse therapy.

**CONCLUSION:** The DRB1\*15:01 and DR5 are both associated with AOSD susceptibility in Japanese subjects. A protective association between the DRB1\*09:01 allele and AOSD was also observed in these patients. Our data also highlight the effects of DRB1 alleles in susceptibility to AOSD.

DOI: 10.1186/s13075-017-1406-x

PMCID: PMC5596459

PMID: 28899403 [Indexed for MEDLINE]

623. Clin Exp Immunol. 2018 Jan;191(1):11-18. doi: 10.1111/cei.13049. Epub 2017 Oct 6.

Is Behçet's disease a 'class 1-opathy'? The role of HLA-B\*51 in the pathogenesis of Behçet's disease.

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Erratum in

Clin Exp Immunol. 2018 Mar;191(3):373.

The association between carriage of the human leucocyte antigen (HLA)-B\*51 allele and development of Behçet's disease (BD) has been known since the early 1970s, but the exact mechanisms responsible for its role in pathogenesis remain



much-debated. In an effort to explain the disease process, it has been suggested that BD constitutes one of a newly termed group of diseases, the 'MHC-I-opathies'. Other MHC-I-opathies include ankylosing spondylitis and HLA-B\*27-associated spondyloarthropathies and HLA-C\*0602-associated skin psoriasis. Recent work analysing the peptidome of HLA-B\*51 suggests that altered peptide presentation by HLA-B\*51 is vital to the disease process. In this review, we argue that immune receptor interactions with HLA-B\*51 or the HLA-B\*51-peptide complex could lead to development of inflammation in BD. The evidence for CD8+ T cell involvement is weak, and based on emerging studies it seems more likely that natural killer (NK) or other cell interactions, perhaps mediated by leucocyte immunoglobulin-like receptor (LILR) or killer immunoglobulin-like receptor (KIR) receptors, are culpable in pathogenesis. HLA misfolding leading directly to inflammation is another hypothesis for BD pathogenesis that deserves greater investigation. Ultimately, greater understanding of HLA-B\*51's unique role in BD will probably lead to improved development of therapeutic strategies.

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DOI: 10.1111/cei.13049

PMCID: PMC5721257

PMID: 28898393 [Indexed for MEDLINE]

624. Scand J Rheumatol. 2018 May;47(3):251-254. doi: 10.1080/03009742.2017.1342273. Epub 2017 Sep 12.

A homozygous mutation in the PSMB8 gene in a case with proteasome-associated autoinflammatory syndrome.

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DOI: 10.1080/03009742.2017.1342273

PMID: 28895430 [Indexed for MEDLINE]

625. Intern Med J. 2017 Sep;47(9):1086-1088. doi: 10.1111/imj.13538.

Long-term efficacy and safety of the interleukin-1 inhibitors anakinra and canakinumab in refractory Behçet disease uveitis and concomitant bladder papillary carcinoma.

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DOI: 10.1111/imj.13538

PMID: 28891187 [Indexed for MEDLINE]

626. J Allergy Clin Immunol Pract. 2017 Nov - Dec;5(6):1551-1555.e1. doi: 10.1016/j.jaip.2017.06.033. Epub 2017 Sep 6.

Evidence Refuting the Existence of Autoimmune/Autoinflammatory Syndrome Induced by Adjuvants (ASIA).

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Autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA) was described in 2011. Over time the condition and its triggers have broadened to include several autoimmune disorders, the macrophagic myofasciitis syndrome, the Gulf war syndrome, the sick building syndrome, siliconosis, and the chronic fatigue syndrome. The aluminum-containing adjuvants in the hepatitis B vaccine and the human papillomavirus vaccine in particular have been stated to be the major causes of the disorder. Here, we review the specificity of the diagnostic criteria for ASIA. We also examine relevant human data, pertaining to causation, particularly from patients undergoing allergen-specific immunotherapy (IT). Patients undergoing allergen-specific IT receive 100 to 500 times more injected aluminum over 3 to 5 years, compared with hepatitis B and human papillomavirus vaccine recipients. In a large pharmacoepidemiological study, in contrast to case series of ASIA, patients receiving aluminum-containing allergen IT preparations were shown to have a lower incidence of autoimmune disease. In another clinical trial, there were no increases in exacerbations in a cohort of patients with systemic lupus erythematosus immunized with the hepatitis B vaccine. Current data do not support the causation of ASIA by vaccine adjuvants containing aluminum, which should be of reassurance to patients undergoing routine immunizations as well as to those undergoing allergen-specific IT.

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DOI: 10.1016/j.jaip.2017.06.033

PMID: 28888842 [Indexed for MEDLINE]

627. Vaccine. 2017 Oct 9;35(42):5522-5526. doi: 10.1016/j.vaccine.2017.08.018. Epub 2017 Sep 4.

Debate on vaccines and autoimmunity: Do not attack the author, yet discuss it methodologically.

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Since Jenner, vaccines and vaccinations have stirred a hot, highly polarized debate, leading to contrasting positions and feelings, ranging from acritical enthusiasm to blind denial. On the one hand, we find anti-vaccination movements which divulge and disseminate misleading information, myths, prejudices, and even frauds, with the main aim of denying that vaccination practices represent a major public health measure, being effective in controlling infectious diseases and safeguarding the wellbeing of entire communities. Recently, the authors of many vaccine safety investigations are being personally criticized rather than the actual science being methodologically assessed and critiqued. Unfortunately, this could result in making vaccine safety science a "hazardous occupation". Critiques should focus on the science and not on the authors and on the scientists that publish reasonably high-quality science suggesting a problem with a given vaccine. These scientists require adequate professional protection so there are not disincentives to publish and to carry out researches in the field. The issues for vaccine safety are not dissimilar to other areas such as medical errors and drug safety.

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DOI: 10.1016/j.vaccine.2017.08.018

PMID: 28882443 [Indexed for MEDLINE]

628. Diabetes. 2017 Dec;66(12):3061-3071. doi: 10.2337/db17-0106. Epub 2017 Sep 6.

Type 1 Interferons Potentiate Human CD8+ T-Cell Cytotoxicity Through a STAT4- and Granzyme B-Dependent Pathway.

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Events defining the progression to human type 1 diabetes (T1D) have remained elusive owing to the complex interaction between genetics, the immune system, and the environment. Type 1 interferons (T1-IFN) are known to be a constituent of the autoinflammatory milieu within the pancreas of patients with T1D. However, the capacity of IFN $\alpha/\beta$  to modulate human activated autoreactive CD8+ T-cell (cytotoxic T lymphocyte) responses within the islets of patients with T1D has not been investigated. Here, we engineer human  $\beta$ -cell-specific cytotoxic T lymphocytes and demonstrate that T1-IFN augments cytotoxicity by inducing rapid phosphorylation of STAT4, resulting in direct binding at the granzyme B promoter within 2 h of exposure. The current findings provide novel insights concerning the regulation of effector function by T1-IFN in human antigen-experienced CD8+ T cells and provide a mechanism by which the presence of T1-IFN potentiates diabetogenicity within the autoimmune islet.

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DOI: 10.2337/db17-0106

PMCID: PMC5697952

PMID: 28877912 [Indexed for MEDLINE]

## Can the Thiol/Disulfide Imbalance Be a Predictor of Colchicine Resistance in Familial Mediterranean Fever?

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Familial Mediterranean fever (FMF) is a chronic autoinflammatory condition characterized by fever attacks and recurrent polyserositis. Subclinical inflammation that persists during attack-free periods can result in oxidative stress (OS) damage. Thiol groups bind to reactive oxygen radicals and protect cells and tissues from OS damage. The aim of this study was to investigate the relationship between thiol-disulfide balance and colchicine resistance in FMF patients during an attack or attack-free period. A newly developed spectrophotometric method was used to measure native thiol (NT) and disulfide (DS) levels in FMF patients and an age-sex matched group of healthy controls. NT and DS levels were compared in FMF patients 1) with vs. without colchicine resistance; and 2) during an attack (FMF-AP) vs. attack-free period (FMF-AFP). A total of 118 FMF patients and 60 healthy controls were studied. NT ( $P < 0.001$ ) and total thiol (TT) ( $P < 0.001$ ) levels in FMF patients were significantly lower compared to healthy controls. NT ( $P = 0.030$ ) and TT ( $P = 0.010$ ) levels of FMF-AP patients were significantly lower than that of FMF-AFP patients. FMF-AP patients had significantly higher DS levels than FMF-AFP patients ( $P = 0.039$ ). Compared to FMF patients without colchicine resistance, elevated levels of DS ( $P = 0.019$ ) but not NT ( $P = 0.620$ ) and TT ( $P = 0.718$ ) were found in those with colchicine resistance. Thiol-disulfide homeostasis is altered in FMF patients during an attack period and this imbalance may be associated with colchicine resistance.

DOI: 10.3346/jkms.2017.32.10.1588

PMCID: PMC5592171

PMID: 28875601 [Indexed for MEDLINE]

Conflict of interest statement: The authors have no potential conflicts of interest to disclose.

630. Scand J Rheumatol. 2018 Jul;47(4):331-333. doi: 10.1080/03009742.2017.1363281. Epub 2017 Sep 2.

Comparison of serum inflammatory cytokine concentrations in familial Mediterranean fever and rheumatoid arthritis patients.

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DOI: 10.1080/03009742.2017.1363281

PMID: 28868950 [Indexed for MEDLINE]

631. Case Rep Nephrol Dial. 2017 Jul 11;7(2):102-107. doi: 10.1159/000478006. eCollection 2017 May-Aug.

AA Amyloidosis and Atypical Familial Mediterranean Fever with Exon 2 and 3 Mutations.

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A 54-year-old Japanese man presented with recurrent abdominal pain, fever lasting >5 days, and renal failure. AA amyloidosis was proven by renal and gastric biopsy. Symptoms subsided with the administration of colchicine, but a subsequent recurrence of symptoms did not respond to colchicine. Mediterranean fever gene (MEFV) analysis showed that he was heterozygous for mutations in exon 2 (E148Q/R202Q) and exon 3 (P369S/R408Q), although he had none of the exon 10



mutations known to be closely related to AA amyloidosis. He did not respond to infliximab, but tocilizumab therapy was successful. The present case is a rare report of AA amyloidosis associated with familial Mediterranean fever in Japan.

DOI: 10.1159/000478006

PMCID: PMC5567010

PMID: 28868300

632. Curr Opin Immunol. 2017 Dec;49:20-26. doi: 10.1016/j.coi.2017.08.004. Epub 2017 Sep 1.

Hemophagocytic syndrome: primary forms and predisposing conditions.

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Hemophagocytic lymphohistiocytosis (HLH, also referred to as hemophagocytic syndrome) is a life-threatening condition in which uncontrolled activation of lymphocytes and macrophages, and thus the secretion of large amounts of inflammatory cytokines, leads to a severe hyperinflammatory state. Over the last few decades, researchers have characterized primary forms of HLH caused by genetic defects that impair lymphocytes' cytotoxic machinery. Other genetic causes of HLH not related to impaired cytotoxicity have also recently been identified. Furthermore, the so-called 'acquired' forms of HLH are encountered in the context of severe infections, autoimmune and autoinflammatory diseases, malignancy, and metabolic disorders, and may also be associated with primary immunodeficiencies. This implies that a variety of disease mechanisms can lead to HLH. Today's research seeks to gain a better understanding of the various pathogenetic and environmental factors that converge to induce HLH.

633. Genet Mol Biol. 2017 Jul-Sep;40(3):688-697. doi: 10.1590/1678-4685-GMB-2016-0234. Epub 2017 Aug 31.

Alternatively spliced MEFV transcript lacking exon 2 and its protein isoform pyrin-2d implies an epigenetic regulation of the gene in inflammatory cell culture models.

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The function of gene body DNA methylation in alternative splicing, and its relation to disease pathogenesis is not fully elucidated. The gene for familial Mediterranean fever (MEFV) encodes the pyrin protein and contains a 998 bp CpG island, covering the second exon, which is differentially methylated in FMF patients compared to healthy controls. Our further observation of increased exon 2-spliced MEFV transcript in leukocytes of FMF patients provoked us to test the role of exon methylation in alternative splicing using inflammatory cell culture models. First, in vitro exon methylation triggered an increased level of exon 2 exclusion using a splicing cassette in a promyelocytic leukemia cell line (HL-60). HL-60 cells subjected to methylating and demethylating agents, as well as cells differentiated to neutrophil-like cells, exhibited different levels of spliced/unspliced transcripts. We observed increased levels of spliced transcripts in neutrophil-like ( $p = 0.0005$ ), activated ( $p = 0.0034$ ) and methylated cells ( $p < 0.0001$ ), whereas decreased levels in demethylated cells ( $p$

= 0.0126) compared to control untreated HL-60 cells. We also showed that the protein isoform of pyrin lacking the exon 2 has an adverse subcellular localization in neutrophil-like cells. Therefore, it remains in the cytoplasm rather than the nucleus. This may point to an epigenetic involvement in an important inflammatory gene.

DOI: 10.1590/1678-4685-GMB-2016-0234

PMCID: PMC5596369

PMID: 28863210

634. Pharmacol Res. 2017 Nov;125(Pt B):188-200. doi: 10.1016/j.phrs.2017.08.012. Epub 2017 Aug 30.

A signalome screening approach in the autoinflammatory disease TNF receptor associated periodic syndrome (TRAPS) highlights the anti-inflammatory properties of drugs for repurposing.

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TNF receptor associated periodic syndrome (TRAPS) is an autoinflammatory disease caused by mutations in TNF Receptor 1 (TNFR1). Current therapies for TRAPS are limited and do not target the pro-inflammatory signalling pathways that are central to the disease mechanism. Our aim was to identify drugs for repurposing as anti-inflammatories based on their ability to down-regulate molecules associated with inflammatory signalling pathways that are activated in TRAPS. This was achieved using rigorously optimized, high through-put cell culture and reverse phase protein microarray systems to screen compounds for their effects on the TRAPS-associated inflammatory signalome. 1360 approved, publically available, pharmacologically active substances were investigated for their effects on 40 signalling molecules associated with pro-inflammatory signalling pathways that are constitutively upregulated in TRAPS. The drugs were screened at four 10-fold concentrations on cell lines expressing both wild-type (WT) TNFR1 and TRAPS-associated C33Y mutant TNFR1, or WT TNFR1 alone; signalling molecule levels were then determined in cell lysates by the reverse-phase protein microarray. A novel mathematical methodology was developed to rank the compounds for their ability to reduce the expression of signalling molecules in the C33Y-TNFR1 transfectants towards the level seen in the WT-TNFR1 transfectants. Seven high-ranking drugs were selected and tested by RPPA for effects on the same 40 signalling molecules in lysates of peripheral blood mononuclear cells (PBMCs) from C33Y-TRAPS patients compared to PBMCs from normal controls. The fluoroquinolone antibiotic lomefloxacin, as well as others from this class of compounds, showed the most significant effects on multiple pro-inflammatory signalling pathways that are constitutively activated in TRAPS; lomefloxacin dose-dependently significantly reduced expression of 7/40 signalling molecules across the Jak/Stat, MAPK, NF- $\kappa$ B and PI3K/AKT pathways. This study demonstrates the power of signalome screening for identifying candidates for drug repurposing.

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DOI: 10.1016/j.phrs.2017.08.012

PMID: 28860008 [Indexed for MEDLINE]

635. BMC Med Genet. 2017 Aug 31;18(1):97. doi: 10.1186/s12881-017-0457-9.

Living kidney transplantation between brothers with unrecognized renal amyloidosis as the first manifestation of familial Mediterranean fever: a case

report.

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**BACKGROUND:** Familial Mediterranean fever is an autosomal recessive disease characterized by recurrent episodes of fever and polyserositis and by the onset of reactive amyloid-associated amyloidosis. Amyloidosis due to familial Mediterranean fever can lead to end-stage renal disease, culminating in kidney transplantation for some patients. In this study, we report the clinical outcome of two brothers with familial Mediterranean fever who were the inadvertent donor and recipient, respectively, of a kidney. Subsequently, they were diagnosed with renal amyloidosis secondary to familial Mediterranean fever and were successfully treated with anakinra and colchicine.

**CASE PRESENTATION:** Two brothers with familial Mediterranean fever and renal amyloidosis were the inadvertent donor and recipient, respectively, of a kidney. The recipient had presented recurrent acute febrile episodes of familial Mediterranean fever, developed nephrotic syndrome secondary to amyloidosis and needed bilateral nephrectomy and chronic dialysis. His elder brother, in apparent good health, donated his left kidney to his brother. Immediately after the kidney transplantation, both the donor and recipient presented massive proteinuria, impaired renal function and elevated serum amyloid A levels. Biopsies of the brothers' kidneys showed amyloidosis. Genetic studies thereafter revealed a homozygous variant for the MEFV gene (NM\_000243.2.c.2082G > A; p.M694I) in both brothers. At this point, both the donor and recipient were treated with colchicine and anakinra, resulting in improved renal function, decreased proteinuria, undetectable serum amyloid A levels and stable renal function at 62 months of follow-up and no major adverse effects.

CONCLUSIONS: In familial Mediterranean fever, analyses of the MEFV gene should be performed in potential live kidney donors from a direct family member (either between siblings or between parents and children). In addition, genetic studies are required when consanguinity is suspected between members involved in the living transplant. Finally, anakinra could be a safe adjuvant therapy combined with colchicine for patients with familial Mediterranean fever and amyloidosis, including those with successful kidney transplantation.

DOI: 10.1186/s12881-017-0457-9

PMCID: PMC5579934

PMID: 28859624 [Indexed for MEDLINE]

636. Rheumatology (Oxford). 2017 Sep 1;56(9):1597-1606. doi: 10.1093/rheumatology/kex222.

Familial Mediterranean fever in children and adolescents: factors for colchicine dosage and predicting parameters for dose increase.

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**Objectives:** The aim was to analyse factors influencing the individual colchicine dose in children with FMF, to evaluate the impact of dose adjustment on the clinical course and inflammation and to identify clinical parameters and biomarkers that predict dose increase in the near future.

**Methods:** Data from 409 paediatric FMF patients (4566 visits) derived from the national auto-inflammatory diseases registry were analysed. Serum concentrations of S100 molecules were determined by ELISA.

**Results:** The age-dependent colchicine dose is influenced by the present genotype. The body surface area is the anthropometric parameter that correlates best with the applied dosages. Colchicine introduction and dose increase lead to significant reduction of clinical symptoms and inflammation. During established colchicine therapy, an increase of one single biomarker increases the likelihood of a dose increment in the next 12 months with a factor of 1.62-1.94. A combination of biomarkers including S100 molecules increases this odds ratio up to 4.66 when analysing all patients and up to 7.27 when analysing patients with a high risk of severe disease.

**Conclusion:** Colchicine therapy is currently guided mainly by the occurrence of clinical symptoms and serological inflammation. Other factors, such as the genotype, the body surface area and biomarkers, will help to manage colchicine therapy in a more individualized fashion. The additional analysis of S100 molecules as sensitive biomarkers will help to identify patients at risk for dose increases in the near future.

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DOI: 10.1093/rheumatology/kex222

PMID: 28859329 [Indexed for MEDLINE]

## CANDLE Syndrome As a Paradigm of Proteasome-Related Autoinflammation.

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CANDLE syndrome (Chronic Atypical Neutrophilic Dermatositis with Lipodystrophy and Elevated temperature) is a rare, genetic autoinflammatory disease due to abnormal functioning of the multicatalytic system proteasome-immunoproteasome. Several recessive mutations in different protein subunits of this system, located in one single subunit (monogenic, homozygous, or compound heterozygous) or in two different ones (digenic and compound heterozygous), cause variable defects in catalytic activity of the proteasome-immunoproteasome. The final result is a sustained production of type 1 interferons (IFNs) that can be very much increased by banal triggers such as cold, stress, or viral infections. Patients start very early in infancy with recurrent or even daily fevers, characteristic skin lesions, wasting, and a typical fat loss, all conferring the patients a unique and unmistakable phenotype. So far, no treatment has been effective for the treatment of CANDLE syndrome; the JAK inhibitor baricitinib seems to be partially helpful. In this article, a review in depth all the pathophysiological, clinical, and laboratory features of CANDLE syndrome is provided.

DOI: 10.3389/fimmu.2017.00927

PMCID: PMC5552674

PMID: 28848544

638. Proc Natl Acad Sci U S A. 2017 Sep 12;114(37):E7766-E7775. doi: 10.1073/pnas.1702946114. Epub 2017 Aug 28.

NLRP3 mutation and cochlear autoinflammation cause syndromic and nonsyndromic hearing loss DFNA34 responsive to anakinra therapy.

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The NLRP3 inflammasome is an intracellular innate immune sensor that is expressed in immune cells, including monocytes and macrophages. Activation of the NLRP3 inflammasome leads to IL-1 $\beta$  secretion. Gain-of-function mutations of NLRP3 result in abnormal activation of the NLRP3 inflammasome, and cause the autosomal dominant systemic autoinflammatory disease spectrum, termed cryopyrin-associated periodic syndromes (CAPS). Here, we show that a missense mutation, p.Arg918Gln (c.2753G > A), of NLRP3 causes autosomal-dominant sensorineural hearing loss in two unrelated families. In family LMG446, hearing loss is accompanied by autoinflammatory signs and symptoms without serologic evidence of inflammation as part of an atypical CAPS phenotype and was reversed or improved by IL-1 $\beta$  blockade therapy. In family LMG113, hearing loss segregates without any other target-organ manifestations of CAPS. This observation led us to explore the possibility that resident macrophage/monocyte-like cells in the cochlea can mediate local autoinflammation via activation of the NLRP3 inflammasome. The NLRP3 inflammasome

can indeed be activated in resident macrophage/monocyte-like cells in the mouse cochlea, resulting in secretion of IL-1 $\beta$ . This pathway could underlie treatable sensorineural hearing loss in DFNA34, CAPS, and possibly in a wide variety of hearing-loss disorders, such as sudden sensorineural hearing loss and Meniere's disease that are elicited by pathogens and processes that stimulate innate immune responses within the cochlea.

DOI: 10.1073/pnas.1702946114

PMCID: PMC5604003

PMID: 28847925 [Indexed for MEDLINE]

Conflict of interest statement: Conflict of interest statement: L.B. serves on the advisory boards for Sobi and Novartis. H.M.H. serves as a consultant for Sobi, a speaker and consultant for Novartis, and receives research support from Bristol-Myers Squibb. R.G.-M. receives research support from Sobi, Novartis, Regeneron, and Eli Lilly.

639. Rheumatol Clin. 2017 Aug 21. pii: S1699-258X(17)30185-7. doi: 10.1016/j.reuma.2017.07.009. [Epub ahead of print]

Coexistence of Sarcoidosis and Gouty Arthritis.

[Article in English, Spanish]

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Sarcoidosis is an inflammatory disease with unknown cause characterized by non-caseating granuloma formations. It may present with bilateral hilar lymphadenopathy, skin lesions, the involvement of eye and symptoms on the locomotor system. Gouty arthritis is an autoinflammatory disease characterized by hyperuricemia, recurrent arthritis attacks and the deposition of monosodium urate crystals in the joints and the surrounding tissues. We reported the coexistence of sarcoidosis and gouty arthritis in this paper.

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DOI: 10.1016/j.reuma.2017.07.009

PMID: 28838825

640. Neuropediatrics. 2017 Oct;48(5):402. doi: 10.1055/s-0037-1599783. Epub 2017 Aug 24.

Erratum: Neurological Manifestations in Familial Mediterranean Fever: Results of 22 Children from a Reference Center in Kayseri, an Urban Area in Central Anatolia, Turkey.

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Erratum for

Neuropediatrics. 2017 Apr;48(2):79-85.

DOI: 10.1055/s-0037-1599783

PMID: 28837982

Conflict of interest statement: Disclosure The authors report no conflicts of interest in this work.

641. Innate Immun. 2017 Oct;23(7):578-583. doi: 10.1177/1753425917727063. Epub 2017 Aug 24.

A novel nucleotide oligomerisation domain 2 mutation in a family with Blau syndrome: Phenotype and function.

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Mutations in the nucleotide binding domain of the PRR, NOD2, are associated with the autoinflammatory diseases Blau syndrome and early-onset sarcoidosis. Current theories suggest that constitutive activation of the NOD2 pathway may be responsible for pathogenesis of these diseases. Here, we report the phenotype of a kindred with Blau syndrome caused by a novel NOD2 mutation (p.E383D). Signaling protein and cytokine expression were examined, and the results of these experiments challenge current theories of constitutive NOD2 activation in the pathophysiology of Blau syndrome.

DOI: 10.1177/1753425917727063

PMID: 28836875 [Indexed for MEDLINE]

642. Ann Rheum Dis. 2017 Dec;76(12):2085-2094. doi: 10.1136/annrheumdis-2017-211473. Epub 2017 Aug 23.

A novel Pyrin-Associated Autoinflammation with Neutrophilic Dermatositis mutation further defines 14-3-3 binding of pyrin and distinction to Familial Mediterranean Fever.

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**OBJECTIVE:** Pyrin-Associated Autoinflammation with Neutrophilic Dermatositis (PAAND) is a recently described monogenic autoinflammatory disease. The causal p.S242R MEFV mutation disrupts a binding motif of the regulatory 14-3-3 proteins within pyrin. Here, we investigate a family with clinical features consistent with PAAND in whom the novel p.E244K MEFV mutation, located in the +2 site of the 14-3-3 binding motif in pyrin, has been found.

**METHODS:** Multiplex cytokine analyses were performed on p.E244K patient and

control serum. Peripheral blood mononuclear cells were stimulated ex vivo with lipopolysaccharide (LPS). In vitro, inflammasome complex formation was evaluated by flow cytometry of Apoptosis-associated Speck-like protein containing a Caspase recruitment domain (ASC) specks. Interleukin-1 $\beta$  (IL-1 $\beta$ ) and IL-18 production was quantified by ELISA. The ability of the p.E244K pyrin mutation to interact with 14-3-3 was assessed by immunoprecipitation.

RESULTS: PAAND p.E244K patient serum displayed a different cytokine profile compared with patients with Familial Mediterranean Fever (FMF). In overexpression models, p.E244K pyrin was associated with decreased 14-3-3 binding and increased ASC speck formation. THP-1 monocytes expressing PAAND pyrin mutations demonstrated spontaneous caspase-1-dependent IL-1 $\beta$  and IL-18 secretion, as well as cell death, which were significantly greater than those of wild-type and the FMF-associated mutation p.M694V.

CONCLUSION: In PAAND, disruption of the +2 position of a 14-3-3 binding motif in pyrin results in its constitutive activation, with spontaneous production of IL-1 $\beta$  and IL-18, associated with inflammatory cell death. The altered serum cytokine profile may explain the different clinical features exhibited by PAAND patients compared with those with FMF.

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DOI: 10.1136/annrheumdis-2017-211473

PMCID: PMC5687562

PMID: 28835462 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: None declared.

643. Immunology. 2018 Jan;153(1):105-117. doi: 10.1111/imm.12815. Epub 2017 Oct 19.

Transcriptional repressor Blimp1 regulates follicular regulatory T-cell homeostasis and function.

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The B-lymphocyte-induced maturation protein 1 (Blimp1) regulates T-cell homeostasis and function. Loss of Blimp1 could double the proportion of follicular regulatory T (Tfr) cells. However, the effects that Blimp1 may have on the function of Tfr cells remain unknown. Here we document the function for Blimp1 in Tfr cells in vitro and in vivo. Data presented in this study demonstrate that Tfr cells indirectly inhibit the activation and differentiation of B cells by negatively regulating follicular helper T cells, so lowering the secretion of antibody. Lack of Blimp1 makes the immune suppression function of Tfr cells impaired in vitro. In the in vivo study, adoptive transfer of Tfr cells could reduce immune responses in germinal centres and relieve the muscle weakness symptoms of mice with experimental autoimmune myasthenia gravis. Blimp1 deficiency resulted in reduced suppressive ability of Tfr cells. This study identifies that Tfr cells are potent suppressors of immunity and are controlled by Blimp1.

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DOI: 10.1111/imm.12815

PMCID: PMC5721240

PMID: 28833081 [Indexed for MEDLINE]

644. Br J Dermatol. 2018 Feb;178(2):350-356. doi: 10.1111/bjd.15896. Epub 2018 Jan 3.

Colchicine: an ancient drug with novel applications.

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Colchicine is a treatment for gout that has been used for more than a millennium. It is the treatment of choice for familial Mediterranean fever and its associated complication, amyloidosis. The 2009 U.S. Food and Drug Administration approval of colchicine as a new drug had research consequences. Recent investigations with large cohorts of patients with gout who have been taking colchicine for years have demonstrated novel applications within oncology, immunology, cardiology and dermatology. Some emerging dermatological uses include the treatment of epidermolysis bullosa acquisita, leucocytoclastic vasculitis, aphthous stomatitis and others. In this work we relate the history and the new horizon of this ancient medicine.

© 2017 British Association of Dermatologists.

DOI: 10.1111/bjd.15896

PMCID: PMC5812812 [Available on 2019-02-01]

PMID: 28832953

645. *Pediatr Rheumatol Online J.* 2017 Aug 22;15(1):67. doi: 10.1186/s12969-017-0193-x.

Autoimmune phenotype with type I interferon signature in two brothers with ADA2 deficiency carrying a novel CECR1 mutation.

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**BACKGROUND:** Loss-of-function CECR1 mutations cause polyarteritis nodosa (PAN) with childhood onset, an autoinflammatory disorder without significant signs of autoimmunity. Herein we describe the unusual presentation of an autoimmune phenotype with constitutive type I interferon activation in siblings with adenosine deaminase 2 (ADA2) deficiency.

**CASE PRESENTATION:** We describe two siblings with early-onset recurrent strokes, arthritis, oral ulcers, discoid rash, peripheral vascular occlusive disease and high antinuclear antibody titers. Assessment of interferon signatures in blood revealed constitutive type I interferon activation. Aicardi-Goutières syndrome (AGS) was suspected, but no mutation in the known AGS genes were detected. Whole exome sequencing identified compound heterozygosity for a known and a novel mutation in the CECR1 gene. Functional consequences of the mutations were demonstrated by marked reduction in ADA2 catalytic activity.

**CONCLUSIONS:** Our findings demonstrate that ADA2 deficiency can cause an unusual autoimmune phenotype extending the phenotypic spectrum of PAN. Constitutive interferon I activation in patient blood suggests a possible role of type I interferon in disease pathogenesis which may have therapeutic implications.

DOI: 10.1186/s12969-017-0193-x

PMCID: PMC5568374

PMID: 28830446 [Indexed for MEDLINE]

646. Rheumatol Int. 2018 Jan;38(1):67-74. doi: 10.1007/s00296-017-3796-0. Epub 2017 Aug 21.

Familial Mediterranean fever in childhood: a single-center experience.

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The aim of this study is to present demographic and clinical features, MEFV mutation variations, and treatment response of a large number of pediatric familial Mediterranean fever (FMF) patients from a single tertiary centre. Moreover, we aimed to investigate the current outcome of FMF, namely frequency of amyloidosis in children with FMF. We evaluated 708 FMF patients who were followed up in our clinic and who were under colchicine treatment for at least 6 months. The data were recorded from patient records and also verified by negotiations with patients and parents. The male/female proportion of the cohort was 1.05/1 (n = 362/346). Abdominal pain (89.5%, n = 634) was the most common manifestation of FMF episodes, followed by fever (88.8%, n = 629) and arthritis (40.7%, n = 288). However, arthritis in 23 (8%) of the 288 cases was not self-limited; and they subsequently diagnosed with juvenile idiopathic arthritis in addition to FMF. Homozygote or heterozygote M694V mutation was more frequent in patients with arthritis (63.2%) and chronic arthritis (69.6%) than the whole cohort (53.8%). Erythrocyte sedimentation rate and CRP level were in high levels even during attack-free period in 13.9% (n = 97/697) and 11% (n = 78/670) of the patients, respectively. Proteinuria was found in ten patients (1.4%). Amyloidosis was confirmed by renal biopsy in only two of these cases who were homozygous for M694V and compound heterozygous for M694V/M680I. 47 (6.6%) subjects were considered as colchicine resistant. Homozygote M694V mutation was the most frequent mutation in those resistant cases (63.8%, n = 30), followed by compound heterozygote mutation of M694V/M680I (6.3%, n = 3). Homozygous M694V mutation are still the most frequent mutation and associated with the most severe clinical

picture and the worst outcome in Turkish children. M694V genotype seems to be more frequently associated with arthritis as well as with chronic arthritis than other genotypes. Recurrence of FMF episodes as well as amyloidosis could only be managed via strict compliance to colchicine treatment. Frequency of amyloidosis significantly decreased compared to the previous studies. A favorable outcome could be obtained with the anti IL-1 in colchicine-resistant FMF patients.

DOI: 10.1007/s00296-017-3796-0

PMID: 28828621 [Indexed for MEDLINE]

647. Sci Rep. 2017 Aug 16;7(1):8453. doi: 10.1038/s41598-017-09164-7.

Mutational profile of rare variants in inflammasome-related genes in Behçet disease: A Next Generation Sequencing approach.

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Behçet's disease (BD) is an immune-mediated systemic disorder with a well-established association with HLA class I and other genes. BD has clinical overlap with many autoinflammatory diseases (AIDs). The aim of this study was to investigate the role of rare variants in seven genes involved in AIDs: CECR1, MEFV, MVK, NLRP3, NOD2, PSTPIP1 and TNFRSF1A using a next generation sequencing (NGS) approach in 355 BD patients. To check global association of each gene, 4 tests: SKAT, CollapseBt, C( $\alpha$ ) and weighted KBAC were used. Databases: 1000 Genomes Project Phase 3, Infevers, HGMD and ClinVar and algorithms: PolyPhen2 and SIFT were consulted to collect information of the 62 variants found. All the genes resulted associated using SKAT but only 3 (MVK, NOD2 and PSTPIP1) with C( $\alpha$ ) and weighted KBAC. When all the genes are considered, 40 variants were associated to AIDs in clinical databases and 25 were predicted as pathogenic at least by one of the algorithms. Including only MVK, NOD2 and PSTPIP1, the associated to AIDs variants found in BD were 20 and the predicted as pathogenic, 12. The maxima contribution corresponds to NOD2. This study supports influence of rare variants

in genes involved in AIDs in the pathogenesis of BD.

DOI: 10.1038/s41598-017-09164-7

PMCID: PMC5559572

PMID: 28814775

648. JCI Insight. 2017 Aug 17;2(16). pii: 94838. doi: 10.1172/jci.insight.94838. [Epub ahead of print]

Rilonacept maintains long-term inflammatory remission in patients with deficiency of the IL-1 receptor antagonist.

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**BACKGROUND:** Deficiency of IL-1 receptor antagonist (DIRA) is a rare autoinflammatory disease that presents with life-threatening systemic inflammation, aseptic multifocal osteomyelitis, and pustulosis responsive to IL-1-blocking treatment. This study was performed (a) to investigate rilonacept, a long-acting IL-1 inhibitor, in maintaining anakinra-induced inflammatory remission in DIRA patients, (b) to determine doses needed to maintain remission, and (c) to evaluate the safety and pharmacokinetics of rilonacept in young children (<12 years).

**METHODS:** Six mutation-positive DIRA patients (children, ages 3-6 years), treated with daily anakinra, were enrolled into an open-label pilot study of subcutaneous

rilonacept for 24 months. Clinical symptoms and inflammatory blood parameters were measured at all visits. A loading dose (4.4 mg/kg) was administered, followed by once weekly injections (2.2 mg/kg) for 12 months. Dose escalation (4.4 mg/kg) was allowed if inflammatory remission was not maintained. Subjects in remission at 12 months continued rilonacept for an additional 12 months.

**RESULTS:** Five of six patients required dose escalation for findings of micropustules. Following dose escalation, all patients were in remission on weekly rilonacept administration, with stable laboratory parameters for the entire study period of 24 months. All children are growing at normal rates and have normal heights and weights. Quality of life improved while on rilonacept. No serious adverse events were reported.

**CONCLUSION:** Rilonacept was found to maintain inflammatory remission in DIRA patients. The once weekly injection was well tolerated and correlated with increased quality of life, most likely related to the lack of daily injections.

**TRIAL REGISTRATION:** ClinicalTrials.gov NCT01801449.

**FUNDING:** NIH, NIAMS, and NIAID.

DOI: 10.1172/jci.insight.94838

PMCID: PMC5621891

PMID: 28814674

649. Methods Mol Biol. 2017;1656:143-152. doi: 10.1007/978-1-4939-7237-1\_8.

Purification of Cyclic GMP-AMP from Viruses and Measurement of Its Activity in Cell Culture.

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Erratum in

Sensing of cytoplasmic DNA by cGAS is essential for the initiation of immune responses against several viruses. cGAS also plays important roles in some autoinflammatory and autoimmune diseases and may be involved in immune responses targeting cancer cells. Once activated, cGAS catalyzes the formation of the di-nucleotide 2'-3'-cyclic GMP-AMP (cGAMP), which propagates a signaling cascade leading to the production of type I interferons (IFNs). Interestingly, cGAMP is incorporated into enveloped viruses and is transferred to newly infected cells by virions. In this article, we describe a method to purify cGAMP from viral particles and a bioassay to measure its activity. This assay takes advantage of a reporter cell line that expresses the genes encoding green fluorescent protein (GFP) and firefly luciferase under the control of the IFN $\beta$  promoter, allowing the testing of several samples in a single experiment taking not more than 3 days.

DOI: 10.1007/978-1-4939-7237-1\_8

PMCID: PMC6126575

PMID: 28808967 [Indexed for MEDLINE]

650. Cardiovasc J Afr. 2017 May/Jun;28(3):154-158. doi: 10.5830/CVJA-2016-074.

Assessment of myocardial repolarisation parameters in patients with familial Mediterranean fever.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is a chronic, recurrent auto-inflammatory disease characterised by self-terminating attacks of fever and sterile polyserositis. The main cause of death in auto-inflammatory diseases is cardiovascular events. Additionally, auto-inflammatory diseases have potential effects on the myocardial repolarisation parameters, including the T-wave

peak-to-end (Tp-Te) interval, cTp-Te interval (corrected Tp-Te) and the cTp-Te/QT ratio. The aim of this study was to analyse the efficacy of myocardial repolarisation alterations in anticipation of cardiovascular risks in patients with FMF.

**METHODS:** This study included 66 patients with FMF and 58 healthy control subjects. Tp-Te and cTp-Te intervals and the cTp-Te/QT ratio were measured from the 12-lead electrocardiogram.

**RESULTS:** In electrocardiographic parameters, analysis of QT, QT dispersion, corrected QT (QTc) and QTc dispersion were similar between the groups. The Tp-Te and cTp-Te intervals and Tp-Te/QT and cTp-Te/QT ratios were significantly prolonged in FMF patients. Multivariate linear regression analyses indicated that erythrocyte sedimentation rate was an independent predictor of a prolonged cTp-Te interval.

**CONCLUSIONS:** Our study revealed that when compared with control subjects, Tp-Te and cTp-Te intervals and cTp-Te/QT ratio were increased in FMF patients.

DOI: 10.5830/CVJA-2016-074

PMCID: PMC5558142

PMID: 28759086

651. *Pediatr Ann.* 2017 Aug 1;46(8):e309-e313. doi: 10.3928/19382359-20170717-01.

An Overview of Hemophagocytic Lymphohistiocytosis.

Esteban YM, de Jong JLO, Teshler MS.

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening syndrome characterized by a dysregulated hyperinflammatory response associated with aberrant activation of lymphocytes and macrophages that results in hypercytokinemia. It is classically divided into two types: (1) primary or familial HLH and (2) secondary HLH. Familial HLH is generally an autosomal recessive condition, whereas secondary HLH is usually associated with infectious diseases, autoinflammatory and autoimmune diseases (where it is more commonly known as macrophage activation syndrome), malignancy, immunosuppression, hematopoietic stem cell transplantation, organ transplantation, HIV infection, and metabolic diseases. Although its clinical presentation is often similar to bacterial sepsis or systemic inflammatory response syndrome, HLH can be life-threatening. As such, it is imperative to recognize and diagnose HLH in a



timely manner to optimize care. [Pediatr Ann. 2017;46(8):e309-e313.].

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DOI: 10.3928/19382359-20170717-01

PMID: 28806468 [Indexed for MEDLINE]

652. PLoS One. 2017 Aug 11;12(8):e0182967. doi: 10.1371/journal.pone.0182967. eCollection 2017.

MEFV M694V mutation has a role in susceptibility to ankylosing spondylitis: A meta-analysis.

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**OBJECTIVE:** The aim of the current study was to determine the contributions of several common mutations in the Mediterranean fever (MEFV) gene, namely, E148Q, M680I, M694V and V726A, to ankylosing spondylitis (AS) susceptibility.

**METHODS:** Two investigators independently searched the literature regarding the association of MEFV with AS in the PubMed, EMBASE, Web of Science, and Scopus databases. They independently selected eligible articles and then extracted data from the included studies. The associations between MEFV mutations and AS risk were assessed with odds ratios (ORs) and 95% confidence intervals (95% CI). Further analyses were conducted with STATA 12.0 software (Stata Corp.; College Station, Texas, USA).

**RESULTS:** Four mutations (E148Q, M680I, M694V and V726A) were genotyped in 869 AS cases and 879 controls from the 8 eligible studies. Of the four mutations, M694V (pooled OR: 3.330, 95% CI: 2.129-5.208) was found to be associated with AS through overall analysis. However, the other mutations demonstrated no relation with AS (pooled ORs: 1.295, 1.258, 1.778; 95% CI: 0.886-1.891, 0.688-2.298 and 0.938-3.371). No significant publication bias was discovered in the meta-analysis.

**CONCLUSIONS:** The present study indicates that the MEFV M694V mutation may contribute to the pathogenesis of AS. The associations between the other

mutations and AS need to be validated with more relevant and well-designed studies.

DOI: 10.1371/journal.pone.0182967

PMCID: PMC5553723

PMID: 28800602 [Indexed for MEDLINE]

653. Clin Sci (Lond). 2017 Aug 10;131(17):2241-2256. doi: 10.1042/CS20170098. Print 2017 Sep 1.

Cytokines of the IL-1 family: recognized targets in chronic inflammation underrated in organ transplantations.

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Interleukin 1 (IL-1) family is a group of cytokines with multiple local and systemic effects, which regulates both innate and adaptive immune responses. Generally, most IL-1 family cytokines express prevailing pro-inflammatory activities (IL-1 $\alpha$ , IL-1 $\beta$ , IL-18, IL-33, IL-36  $\alpha$ ,  $\beta$ ,  $\gamma$ ), whereas others are anti-inflammatory (IL-1Ra (IL-1 receptor antagonist), IL-36Ra, IL-38, IL-37). In addition to their immunomodulatory roles, some of them are also involved in the physiological modulation of homeostatic processes and directly affect mRNA transcription. IL-1 family cytokines bind to specific receptors composed of a ligand-binding chain and an accessory chain. The pro-inflammatory effects of IL-1 family cytokines are regulated on the level of transcription, enzymatic processing of precursors, release of soluble antagonists, and expression of decoy receptors. Members of the IL-1 family regulate the recruitment and activation of effector cells involved in innate and adaptive immunity, but they are also involved in the pathogenesis of chronic disorders, including inflammatory bowel disease, rheumatoid arthritis, and various autoimmune and autoinflammatory diseases. There are only limited data regarding the role of IL-1 cytokines in transplantation. In recent years, targeted therapeutics affecting IL-1 have been used in multiple clinical studies. In addition to the recombinant IL-1Ra,

anakinra (highly effective in autoinflammatory diseases and tested for other chronic diseases), the monoclonal antibodies canakinumab, gevokizumab, and rilonacept (a long-acting IL-1 receptor fusion protein) provide further options to block IL-1 activity. Furthermore, new inhibitors of IL-18 (GSK 1070806, ABT-325, rIL-18BP (IL-18 binding protein)) and IL-33 (CNTO-7160) are presently under clinical studies and other molecules are being developed to target IL-1 family cytokines.

© 2017 The Author(s). Published by Portland Press Limited on behalf of the Biochemical Society.

DOI: 10.1042/CS20170098

PMID: 28798075 [Indexed for MEDLINE]

654. Intern Med. 2017 Sep 1;56(17):2353-2360. doi: 10.2169/internalmedicine.8473-16. Epub 2017 Aug 10.

Adult-onset Chronic Recurrent Multifocal Osteomyelitis with High Intensity of Muscles Detected by Magnetic Resonance Imaging, Successfully Controlled with Tocilizumab.

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Chronic recurrent multifocal osteomyelitis (CRMO) is an autoinflammatory bone disorder that generally occurs in children and predominantly affects the long bones with marginal sclerosis. We herein report two cases of adult-onset CRMO involving the tibial diaphysis bilaterally, accompanied by polyarthritis.

Magnetic resonance imaging (MRI) showed both tibial osteomyelitis and high intensity of the extensive lower leg muscles. Anti-interleukin-6 therapy with tocilizumab (TCZ) effectively controlled symptoms and inflammatory markers in both patients. High intensity of the lower leg muscles detected by MRI also improved. These cases demonstrate that CRMO should be included in the differential diagnosis of adult patients with bone pain, inflammation, and high intensity of the muscles detected by MRI. TCZ may therefore be an effective therapy for muscle inflammation of CRMO.

DOI: 10.2169/internalmedicine.8473-16

PMCID: PMC5635314

PMID: 28794369 [Indexed for MEDLINE]

655. Australas J Dermatol. 2018 May;59(2):138-140. doi: 10.1111/ajd.12697. Epub 2017 Aug 9.

Hidradenitis suppurativa: A neglected disease in Indigenous Australians.

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We report the first case series of hidradenitis suppurativa in patients of Indigenous Australian heritage. The incidence and ethnicity of populations affected by this condition are not known. The high comorbid disease burden and socioeconomic disadvantage that is well recognised in the Indigenous Australian population poses significant challenges to therapeutic outcomes.

© 2017 The Australasian College of Dermatologists.

DOI: 10.1111/ajd.12697

PMID: 28791681 [Indexed for MEDLINE]

656. Sci Rep. 2017 Aug 8;7(1):7553. doi: 10.1038/s41598-017-07975-2.

Signs of innate immune activation and premature immunosenescence in psoriasis patients.

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Psoriasis is a chronic inflammatory disease that affects skin and is associated with systemic inflammation and many serious comorbidities ranging from metabolic syndrome to cancer. Important discoveries about psoriasis pathogenesis have enabled the development of effective biological treatments blocking the T helper 17 pathway. However, it has not been settled whether psoriasis is a T cell-mediated autoimmune disease or an autoinflammatory disorder that is driven by exaggerated innate immune signalling. Our comparative gene expression and hierarchical cluster analysis reveal important gene circuits involving innate receptors. Innate immune activation is indicated by increased absent in melanoma 2 (AIM2) inflammasome gene expression and active caspase 1 staining in psoriatic lesional skin. Increased eomesodermin (EOMES) expression in lesional and non-lesional skin is suggestive of innate-like virtual memory CD8<sup>+</sup> T cell infiltration. We found that signs of systemic inflammation were present in most of the patients, correlated with the severity of the disease, and pointed to IL-6 involvement in the pathogenesis of psoriatic arthritis. Among the circulating T cell subpopulations, we identified a higher proportion of terminally differentiated or senescent CD8<sup>+</sup> T cells, especially in patients with long disease duration, suggesting premature immunosenescence and its possible

implications for psoriasis co-morbidities.

DOI: 10.1038/s41598-017-07975-2

PMCID: PMC5548718

PMID: 28790368

657. Isr Med Assoc J. 2017 Jul;19(7):461-462.

Pseudoseptic Arthritis with Low Synovial Fluid Glucose in Familial Mediterranean Fever.

Awisat A(1), Slobodin G(1)(2), Jiries N(1), Rozenbaum M(1), Rimar D(1)(2), Boulman N(1), Kaly L(1), Zilber K(1), Ginsberg S(1), Rosner I(1)(2).

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PMID: 28786265 [Indexed for MEDLINE]

658. Isr Med Assoc J. 2017 Jul;19(7):444-447.

Evolving Frontiers in the Treatment of Periodic Fever, Aphthous Stomatitis, Pharyngitis, Cervical Adenitis (PFAPA) Syndrome.

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BACKGROUND: Fevers recurring at a nearly predictable rate every 3-8 weeks are the

signature symptom of periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome, an acquired autoinflammatory disorder which recurs in association with at least one sign among aphthous stomatitis, pharyngitis, and/or cervical lymph node enlargement without clinical signs related to upper respiratory airways or other localized infections. The disease usually has a rather benign course, although it might relapse during adulthood after a spontaneous or treatment-induced resolution in childhood. The number of treatment choices currently available for PFAPA syndrome has grown in recent years, but data from clinical trials dedicated to this disorder are limited to small cohorts of patients or single case reports. The response of PFAPA patients to a single dose of corticosteroids is usually striking, while little data exist for treatment with cimetidine and colchicine. Preliminary interesting results have been published with regard to vitamin D supplementation in PFAPA syndrome, while inhibition of interleukin-1 might represent an intriguing treatment for PFAPA patients who have not responded to standard therapies. Tonsillectomy has been proven curative in many studies related to PFAPA syndrome, although the evidence of its efficacy is not widely shared by different specialists, including pediatricians, rheumatologists and otorhinolaryngologists.

PMID: 28786261 [Indexed for MEDLINE]

659. Isr Med Assoc J. 2017 Jul;19(7):415-419.

Intravitreal Dexamethasone Implant as an Adjunct Weapon for Severe and Refractory Uveitis in Behçet's Disease.

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**BACKGROUND:** The evidence on the use of dexamethasone implants in the treatment of Behçet's disease (BD)-related uveitis is limited to a few cases.

**OBJECTIVES:** To evaluate the efficacy of dexamethasone implants on ocular functional, morphological, and clinical parameters in BD patients with severe refractory uveitis.

**METHODS:** Five eyes from five BD patients were enrolled. A single intravitreal dexamethasone injection was applied to each eye. Best corrected visual acuity (BCVA), central macular thickness (CMT) assessed with optical coherence tomography, retinal vasculitis assessed by fluorescein angiography, vitreous haze score (Nussenblatt scale), intraocular pressure (IOP), and lens status (LOCS III, Lens Opacities Classification System III) were recorded at baseline and at 1, 3, and 6 month follow-up visits.

**RESULTS:** At baseline, all eyes showed marked macular edema and 4/5 had concomitant active retinal vasculitis. Mean BCVA was increased from baseline at each control visit with a mean improvement of  $0.26 \pm 0.18$  lines at 6 months follow-up. Mean CMT decreased from baseline at each control visit with a mean improvement at 6 months follow-up of  $198.80 \pm 80.08$   $\mu\text{m}$ . At the end of the study, none of the eyes showed macular edema and the mean CMT was  $276.80 \pm 24.94$   $\mu\text{m}$ . Retinal vasculitis resolved in all eyes. One eye experienced an IOP spike during treatment that resolved spontaneously, and one eye developed a clinically significant lens opacity at 6 months follow-up.

**CONCLUSIONS:** Treatment with a dexamethasone implant in BD-uveitis and inflammatory macular edema was safe and effective as an additional treatment combined with systemic immunomodulatory drugs.



660. Intern Med. 2017 Aug 15;56(16):2233-2236. doi: 10.2169/internalmedicine.8274-16. Epub 2017 Aug 1.

Cold Exposure Related Fever with an Mediterranean Fever (MEFV) Gene Mutation.

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Familial Mediterranean fever (FMF) is a genetic autoinflammatory disease characterized by recurrent fever with serosal inflammation. We experienced a 53-year-old male who had been suffering from periodic attacks with slight fever and myalgia which were mainly triggered by cold exposure in winter. Although his clinical course did not satisfy the criteria for familial Mediterranean fever, heterozygous E148Q/M694I mutation in the Mediterranean fever (MEFV) gene was detected. Further attacks were prevented by treatment with colchicine. Attention should therefore be paid to the possibility of atypical FMF symptoms, which should be accurately diagnosed by genetic analyses to prevent the development of amyloidosis.

DOI: 10.2169/internalmedicine.8274-16

PMCID: PMC5596290

PMID: 28781304 [Indexed for MEDLINE]

661. Semin Arthritis Rheum. 2018 Feb;47(4):575-577. doi: 10.1016/j.semarthrit.2017.07.003. Epub 2017 Jul 10.

Adult onset Still's disease occurring during pregnancy: Case-report and literature review.

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**INTRODUCTION:** Adult onset Still's disease is a rare affection classified among non-hereditary autoinflammatory diseases. We here report a case of AOSD revealed during pregnancy with a life-threatening presentation along with a review of 19 cases from literature.

**CASE:** A 38-years old woman was treated in our department for diffuse systemic sclerosis and associated Sjögren syndrome. She was pregnant and presented with acute fever and arthralgias. Laboratory data revealed mild liver cytolysis but a large screening for infectious and auto-immune diseases was negative and hepato-biliar imaging was normal. Ferritin levels were at 41 000 ng/mL with glycosylated ferritin less than 5%. The diagnosis of AOSD was stated and because of persistent fever and polyarthralgias, after exclusion of active infection, steroids were started (prednisone 1 mg/kg) associated with colchicine, which allowed clinical remission and C-reactive protein significant decrease.

**CONCLUSION:** Pregnancy-revealed AOSD appears to be a specific subset of the disease with a systemic course, flares on first and second trimester, obstetrical complications such as prematurity and IUGR sometimes leading to life-threatening situations requiring parenteral corticotherapy and intravenous immunoglobulins.

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DOI: 10.1016/j.semarthrit.2017.07.003

PMID: 28781105 [Indexed for MEDLINE]

662. *Australas J Dermatol.* 2018 Feb;59(1):e70-e73. doi: 10.1111/ajd.12669. Epub 2017 Aug 3.

Acute generalized exanthematous pustulosis and polyarthrititis associated with a novel CARD14 mutation.

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Acute generalised exanthematous pustulosis (AGEP) is a rare toxicoderma characterised by an acute onset rash, with many sterile pustules on the surface, high fever and increased acute phase reactants. We report the case of a patient who presented to the dermatology department with an AGEP and polyarthrititis, in which a novel CARD14 mutation was identified. The pathophysiological mechanism of AGEP remains unclear, although mutations in the IL36RN gene have been identified in a small subset of AGEP patients. Similarly, mutations in the CARD14 gene have been linked to pustular types of psoriasis and familial cases of pityriasis rubra pilaris; however, there are no reports associating mutations in the CARD14 gene with AGEP.

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DOI: 10.1111/ajd.12669

PMID: 28776328 [Indexed for MEDLINE]

663. *FEBS Lett.* 2017 Oct;591(19):3022-3041. doi: 10.1002/1873-3468.12771. Epub 2017 Aug 11.

Cellular metabolism of tumor-associated macrophages - functional impact and consequences.

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Macrophages are innate immune cells that play a role not only in host defense against infections, but also in the pathophysiology of autoimmune and autoinflammatory disorders, as well as cancer. An important feature of macrophages is their high plasticity, with high ability to adapt to environmental changes by adjusting their cellular metabolism and immunological phenotype. Macrophages are one of the most abundant innate immune cells within the tumor microenvironment that have been associated with tumor growth, metastasis, angiogenesis and poor prognosis. In the context of cancer, however, so far little is known about metabolic changes in macrophages, which have been shown to determine functional fate of the cells in other diseases. Here, we review the current knowledge regarding the cellular metabolism of tumor-associated macrophages (TAMs) and discuss its implications for cell function. Understanding the regulation of the cellular metabolism of TAMs may reveal novel therapeutic targets for treatment of malignancies.

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DOI: 10.1002/1873-3468.12771

PMID: 28771701 [Indexed for MEDLINE]

664. Korean Circ J. 2017 Jul;47(4):483-489. doi: 10.4070/kcj.2016.0400. Epub 2017 Jul 21.

# Aortic Flow Propagation Velocity in Patients with Familial Mediterranean Fever: an Observational Study.

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**BACKGROUND AND OBJECTIVES:** Systemic inflammation has an important role in the initiation of atherosclerosis, which is associated with arterial stiffness (AS).

Aortic flow propagation velocity (APV) is a new echocardiographic parameter of aortic stiffness. The relationship between systemic inflammation and AS has not yet been described in patients with familial Mediterranean fever (FMF). We aimed to investigate the early markers of AS in patients with FMF by measuring APV and carotid intima-media thickness (CIMT).

**SUBJECTS AND METHODS:** Sixty-one FMF patients (43 women; mean age  $27.3 \pm 6.7$  years) in an attack-free period and 57 healthy individuals (36 women; mean age  $28.8 \pm 7.1$  years) were included in this study. The individuals with atherosclerotic risk factors were excluded from the study. The flow propagation velocity of the descending aorta and CIMT were measured to assess AS.

**RESULTS:** APV was significantly lower ( $60.2 \pm 16.5$  vs.  $89.5 \pm 11.6$  cm/sec,  $p < 0.001$ ) and CIMT was significantly higher ( $0.49 \pm 0.09$  vs.  $0.40 \pm 0.10$  mm,  $p < 0.001$ ) in the FMF group compared to the control group. There were significant correlations between APV and mean CIMT ( $r = -0.424$ ,  $p < 0.001$ ), erythrocyte sedimentation rate (ESR) ( $r = -0.198$ ,  $p = 0.032$ ), and left ventricle ejection fraction ( $r = 0.201$ ,  $p = 0.029$ ). APV and the ESR were independent predictors of FMF in logistic regression analysis (OR = -0.900, 95% CI = 0.865-0.936,  $p < 0.001$  and OR = -1.078, 95% CI = 1.024-1.135,  $p = 0.004$ , respectively). Mean CIMT and LVEF were independent factors associated with APV in linear regression analysis ( $\beta = -0.423$ ,  $p < 0.001$  and  $\beta = 0.199$ ,  $p = 0.017$ , respectively).

**CONCLUSION:** We demonstrated that APV was lower in FMF patients and is related to

CIMT. According to our results, APV may be an independent predictor of FMF.

DOI: 10.4070/kcj.2016.0400

PMCID: PMC5537150

PMID: 28765740

Conflict of interest statement: The authors have no financial conflicts of interest.

665. Pediatr Emerg Care. 2017 Sep;33(9):e48-e51. doi: 10.1097/PEC.0000000000001251.

Massive Pericardial Effusion and Tamponade Can Be a First Sign of Familial Mediterranean Fever.

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Cardiac involvement is a rare initial presentation of familial Mediterranean fever (FMF). We described 2 children with massive pericardial effusion and cardiac tamponade, who were later diagnosed as having FMF based on clinical and laboratory findings. Therefore, in children presenting with massive pericardial effusion, FMF should be considered as one of the differential diagnoses. In addition, massive pericardial effusion is a serious clinical condition that requires emergency therapeutic approach including pericardiocentesis. For medical treatment, colchicine is the first line therapy, but in resistant cases, other anti-inflammatory drugs can be used for extra anti-inflammatory effect.

DOI: 10.1097/PEC.0000000000001251

PMID: 28763406 [Indexed for MEDLINE]

666. Expert Opin Investig Drugs. 2017 Sep;26(9):1049-1061. doi: 10.1080/13543784.2017.1361928. Epub 2017 Aug 4.

Investigational drugs in systemic vasculitis.

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**INTRODUCTION:** Treatment of systemic vasculitis is based on glucocorticoids (GC) in association with immunosuppressive therapy. There are still unmet needs, including earlier onset of response, more targeted therapies, reduction of relapse-risk and decrease of long-term GC and classic immunosuppressants toxicities. Areas covered: In this review, we discuss investigational drugs in early phase clinical trials for induction of remission in vasculitis. We focus on ANCA-associated vasculitis, Behçet's disease, giant cell arteritis, Takayasu arteritis, and cryoglobulinemic vasculitis. We performed a comprehensive review of articles published on pubmed and a review of clinical trials registered online ( <https://clinicaltrials.gov> ) for each vasculitis. Expert opinion: Recent progress in the pathogenesis identifies new therapeutic targets. Some of these therapies are promising in GC sparing effects, in reducing relapse rate, and for their safety profile. These results need to be confirmed in large-scale phase III studies.

DOI: 10.1080/13543784.2017.1361928

PMID: 28758504 [Indexed for MEDLINE]

667. Med Clin (Barc). 2017 Dec 7;149(11):510-511. doi: 10.1016/j.medcli.2017.06.045. Epub 2017 Jul 27.

Effectiveness of Infliximab in colchicine resistant familial Mediterranean fever.

[Article in English, Spanish]

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DOI: 10.1016/j.medcli.2017.06.045

PMID: 28756998

668. Z Rheumatol. 2018 Mar;77(2):127-134. doi: 10.1007/s00393-017-0354-9.

[IL-1-blockade with Anakinra during pregnancy : Retrospective analysis of efficacy and safety in female patients with familial Mediterranean fever].

[Article in German]

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OBJECTIVE: To retrospectively assess and analyze the clinical efficacy and safety of off-label interleukin-1 (IL-1) blockade with anakinra during pregnancy of patients with familial Mediterranean fever (FMF).

METHODS: Retrospective analysis of clinical and laboratory parameters making use of an electronic database system. Detailed descriptions of the genotype and phenotype of FMF are given and the course of the pregnancy and fetal development are reported.



**RESULTS:** The data of three patients and a total of four pregnancies under treatment with anakinra were analyzed. All patients were of Mediterranean origin, fulfilled the Tel Hashomer criteria for diagnosis of FMF and had a confirmed mutation in the MEFV gene. In all patients, treatment with anakinra was initiated due to an insufficient treatment response to colchicine. Anakinra led to a rapid response in all patients. In three pregnancies anakinra treatment was continued during the whole pregnancy, while in one pregnancy anakinra was started in the second trimester because of uncontrolled FMF activity. Fetal development was normal in all pregnancies. In two patients the fetuses were carried to term, while in one patient a primary cesarean section was carried out in week 33 because of an increased risk for complications. All children showed an unremarkable early childhood development without any signs of an existing disease.

**CONCLUSION:** The data of our retrospective analysis suggest that IL-1-blockade by anakinra is an effective and safe treatment in pregnant women suffering from FMF, which can reliably prevent disease flares. In the four pregnancies presented the use of anakinra did not result in impaired fetal and (early) childhood development.

DOI: 10.1007/s00393-017-0354-9

PMID: 28752409

669. Rheumatol Int. 2018 Jan;38(1):25-35. doi: 10.1007/s00296-017-3775-5. Epub 2017 Jul 27.

Biological therapies for the treatment of Behçet's disease-related uveitis beyond TNF-alpha blockade: a narrative review.

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Intraocular inflammation is one of the more relevant complications of Behçet's disease (BD), which tends to respond poorly to different medications. The ocular histopathologic changes are basically identical to those occurring in other organs and consist in a necrotizing leukocytoclastic obliterative vasculitis, which is probably immune complex-mediated and affects both arteries and veins of all sizes. There are growing evidences showing the potential role of biologic agents other than anti-tumor necrosis factor (TNF)- $\alpha$  agents in the management of ocular-BD, which have been collected in this review, including interleukin-1 and interleukin-6 blockade, secukinumab, ustekinumab, daclizumab, rituximab, and alemtuzumab. Further large studies are needed to fully elucidate and establish the clinical efficacy of these different tools in the refractory ocular manifestations of BD.

DOI: 10.1007/s00296-017-3775-5  
PMID: 28752230 [Indexed for MEDLINE]

670. Pediatr Rheumatol Online J. 2017 Jul 27;15(1):57. doi: 10.1186/s12969-017-0188-7.

Co-existence of Blau syndrome and NAID? Diagnostic challenges associated with presence of multiple pathogenic variants in NOD2 gene: a case report.

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**BACKGROUND:** Pediatric autoinflammatory diseases are rare and still poorly understood conditions resulting from defective genetic control of innate immune system, inter alia from anomalies of NOD2 gene. The product of this gene is Nod2 protein, taking part in maintenance of immune homeostasis. Clinical form of resultant autoinflammatory condition depends on NOD2 genotype; usually patients with NOD2 defects present with Blau syndrome, NOD2-associated autoinflammatory disease (NAID) or Crohn's disease.

**CASE PRESENTATION:** We present the case of a 7-year-old girl with co-existing symptoms of two rare diseases, Blau syndrome and NAID. Overlapping manifestations of two syndromes raised a significant diagnostic challenge, until next-generation molecular test (NGS) identified presence of three pathogenic variants of NOD2 gene: P268S, IVS8+158, 1007 fs, and established the ultimate diagnosis.

**CONCLUSION:** Presence of multiple genetical abnormalities resulted in an ambiguous clinical presentation with overlapping symptoms of Blau syndrome and NAID. Final diagnosis of autoinflammatory disease opened new therapeutic possibilities, including the use of biological treatments.

DOI: 10.1186/s12969-017-0188-7

PMCID: PMC5531019

PMID: 28750667 [Indexed for MEDLINE]

671. PLoS One. 2017 Jul 27;12(7):e0181874. doi: 10.1371/journal.pone.0181874. eCollection 2017.

Clinical impact of a targeted next-generation sequencing gene panel for autoinflammation and vasculitis.

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**BACKGROUND:** Monogenic autoinflammatory diseases (AID) are a rapidly expanding group of genetically diverse but phenotypically overlapping systemic inflammatory disorders associated with dysregulated innate immunity. They cause significant morbidity, mortality and economic burden. Here, we aimed to develop and evaluate the clinical impact of a NGS targeted gene panel, the "Vasculitis and Inflammation Panel" (VIP) for AID and vasculitis.

**METHODS:** The Agilent SureDesign tool was used to design 2 versions of VIP; VIP1 targeting 113 genes, and a later version, VIP2, targeting 166 genes. Captured and indexed libraries (QXT Target Enrichment System) prepared for 72 patients were sequenced as a multiplex of 16 samples on an Illumina MiSeq sequencer in 150bp paired-end mode. The cohort comprised 22 positive control DNA samples from patients with previously validated mutations in a variety of the genes; and 50 prospective samples from patients with suspected AID in whom previous Sanger based genetic screening had been non-diagnostic.

**RESULTS:** VIP was sensitive and specific at detecting all the different types of known mutations in 22 positive controls, including gene deletion, small INDELS, and somatic mosaicism with allele fraction as low as 3%. Six/50 patients (12%) with unclassified AID had at least one class 5 (clearly pathogenic) variant; and 11/50 (22%) had at least one likely pathogenic variant (class 4). Overall, testing with VIP resulted in a firm or strongly suspected molecular diagnosis in 16/50 patients (32%).

**CONCLUSIONS:** The high diagnostic yield and accuracy of this comprehensive targeted gene panel validate the use of broad NGS-based testing for patients with suspected AID.

DOI: 10.1371/journal.pone.0181874  
PMCID: PMC5531484  
PMID: 28750028 [Indexed for MEDLINE]

672. Clin Rheumatol. 2018 May;37(5):1309-1317. doi: 10.1007/s10067-017-3773-8. Epub 2017 Jul 26.

Unique histologic features of tonsils from patients with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome.

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The objective of this study is to compare the histology and immune cell composition of tonsils from patients with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome to those from patients with obstructive sleep apnea (OSA). Patients with PFAPA and age-matched controls with OSA who had undergone tonsillectomy at Vanderbilt Children's Hospital were recruited. After informed consent, archival paraffin-embedded, formalin-fixed tonsil tissues were obtained. Sizes of major histologic regions were measured. Cores of germinal centers, crypts, and squamous epithelium were assembled on a tissue microarray for immunohistochemical staining and digital image analysis. Features of tonsils from PFAPA and OSA patients were compared with Wilcoxon signed-rank test. Samples from 16 cases with PFAPA and 16 controls with OSA were evaluated. Tonsils from PFAPA cases had significantly smaller germinal centers (0.18 vs. 0.47 mm<sup>2</sup>,  $p = 0.001$ ) and wider squamous epithelia (176 vs. 138  $\mu\text{m}$ ,  $p = 0.008$ ) than those of OSA patients. The percentages of B and T lymphocytes and

myeloid cells were comparable in germinal centers, crypts, and squamous epithelia from PFAPA and OSA patients. Longer time from the last febrile episode in PFAPA cases was associated with larger germinal center area (Spearman's  $\rho = 0.61$ ,  $p = 0.02$ ). We found differences in the sizes of germinal centers and squamous epithelia in tonsils of patients with PFAPA and OSA, but the cellular compositions within these areas were comparable. Our results suggest that tonsils from patients with PFAPA change histologically over time with enlarging germinal centers following a febrile episode. Additional studies are needed to understand the pathogenesis of PFAPA.

DOI: 10.1007/s10067-017-3773-8

PMID: 28748511 [Indexed for MEDLINE]

673. Nihon Rinsho Meneki Gakkai Kaishi. 2017;40(3):169-173. doi: 10.2177/jsci.40.169.

Autoinflammatory diseases in dermatology: DITRA and CAMPS.

[Article in Japanese]

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Deficiency of interleukin thirty-six receptor antagonist (DITRA) and CARD14 mediated psoriasis (CAMPS) are autoinflammatory diseases in dermatology. The causative genes of DITRA and CAMPS have been identified recently. In this paper, IL36RN and CARD14, the causative gene for DITRA and CAMPS, respectively were explained. In addition, clinical features and therapies for generalized pustular psoriasis not associated with psoriasis vulgaris (GPP without PsV), and pityriasis rubra pilaris type V (PRP type V) were described. GPP without PsV and PRP type V are representative diseases of DITRA and CAMPS, respectively.

DOI: 10.2177/jsci.40.169

PMID: 28747603 [Indexed for MEDLINE]

674. Ter Arkh. 2017;89(6):4-20. doi: 10.17116/terarkh20178964-20.

[Autoinflammatory diseases and kidney involvement].

[Article in Russian; Abstract available in Russian from the publisher]

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Autoinflammatory disease (AID) is a new concept formulated from the results of studying the pathogenesis of familial periodic fevers, a heterogeneous group of genetically determined diseases characterized by causelessly recurrent exacerbations of the inflammatory process due to genetically determined disorders of innate immunity and accompanied by uncontrolled hypersecretion of interleukin-1 (IL-1). These mechanisms were a basic model for understanding a wide range of rheumatologic and other inflammatory diseases of the internal organs. The late diagnosis of AIDs and their ineffective treatment increase the risk for the development and progression of secondary AA amyloidosis. Elaboration of both clinical and effective laboratory criteria for diagnosing autoinflammation is of great importance for determining the tactics of anti-inflammatory therapy and prevention of complications.

Publisher: Аутовоспалительные заболевания (ABЗ) - новое понятие, сформулированное по результатам изучения патогенеза семейных периодических лихорадок - гетерогенной группы генетически детерминированных заболеваний, характеризующихся беспричинно повторяющимися обострениями воспалительного процесса вследствие генетически детерминированных нарушений врожденного иммунитета и сопровождающихся бесконтрольной гиперсекрецией интерлейкина-1 (IL-1). Эти механизмы оказались базовой моделью для понимания широкого круга ревматологических и других воспалительных заболеваний внутренних органов. Поздняя диагностика ABЗ и их неэффективное лечение увеличивают риск развития и прогрессирования вторичного AA-амилоидоза. Для определения тактики противовоспалительной терапии, предотвращения осложнений большое значение имеет разработка как клинических, так

и эффективных лабораторных критериев диагностики аутовоспаления.

DOI: 10.17116/terarkh20178964-20

PMID: 28745684 [Indexed for MEDLINE]

675. Open Access Rheumatol. 2017 Jul 11;9:123-129. doi: 10.2147/OARRR.S114447. eCollection 2017.

Muckle-Wells syndrome: clinical perspectives.

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Muckle-Wells syndrome (MWS) is a rare autoinflammatory disorder. It is due to NLRP3 gene mutations, responsible for excessive caspase-1 activation and interleukin 1 $\beta$  processing. MWS is the intermediate phenotype of severity of cryopyrin-associated periodic syndrome. Urticarial rash, conjunctivitis, recurrent fever, arthralgia, and fatigue are the main clinical manifestations of MWS. Yet, sensorineural hearing loss and renal amyloidosis can occur after long term evolution. Patients' quality of life has been drastically improved with the advent of IL-1 inhibitors. This review reports recent findings in MWS, particularly genotype/phenotype correlation, and discusses the clinical perspectives of this disease in a time of efficient treatment.

DOI: 10.2147/OARRR.S114447

PMCID: PMC5513904

PMID: 28744167

Conflict of interest statement: Disclosure TA Tran has received consulting fees from Novartis, Sobi, and Abbvie. His institution has received research fees from Novartis. The author reports no other conflicts of interest in this work.

676. Neth J Med. 2017 Jul;75(6):247-249.

Pitfall of modern genetics: recurrent erysipelas masquerading as autoinflammatory



disease.

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A patient presented with recurrent episodes of fever and skin rash for eight years. DNA analysis of the NLRP3 gene revealed a mutation associated with autoinflammatory disease. After an initial positive response to the biological anakinra, the patient deteriorated. Reassessment revealed recurrent erysipelas. In conclusion, sometimes erysipelas-like skin rash is real erysipelas, and DNA results are not always the final answer.

PMID: 28741584 [Indexed for MEDLINE]

677. Mol Genet Metab. 2017 Nov;122(3):134-139. doi: 10.1016/j.ymgme.2017.07.006. Epub 2017 Jul 20.

Neonatal detection of Aicardi Goutières Syndrome by increased C26:0 lysophosphatidylcholine and interferon signature on newborn screening blood spots.

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**BACKGROUND:** Aicardi Goutières Syndrome (AGS) is a heritable interferonopathy associated with systemic autoinflammation causing interferon (IFN) elevation, central nervous system calcifications, leukodystrophy and severe neurologic sequelae. An infant with TREX1 mutations was recently found to have abnormal C26:0 lysophosphatidylcholine (C26:0 Lyso-PC) in a newborn screening platform for X-linked adrenoleukodystrophy, prompting analysis of this analyte in retrospectively collected samples from individuals affected by AGS.

**METHODS:** In this study, we explored C26:0 Lyso-PC levels and IFN signatures in newborn blood spots and post-natal blood samples in 19 children with a molecular and clinical diagnosis of AGS and in the blood spots of 22 healthy newborns. We used Nanostring nCounter™ for IFN-induced gene analysis and a high-performance liquid chromatography with tandem mass spectrometry (HPLC MS/MS) newborn screening platform for C26:0 Lyso-PC analysis.

**RESULTS:** Newborn screening cards from patients across six AGS associated genes were collected, with a median disease presentation of 2months. Thirteen out of 19 (68%) children with AGS had elevations of first tier C26:0 Lyso-PC ( $>0.4\mu\text{M}$ ), that would have resulted in a second screen being performed in a two tier screening system for X-linked adrenoleukodystrophy (X-ALD). The median (95%CI) of first tier C26:0 Lyso-PC values in AGS individuals ( $0.43\mu\text{M}$  [ $0.37\text{--}0.48$ ]) was higher than that seen in controls ( $0.21\mu\text{M}$  [ $0.21\text{--}0.21$ ]), but lower than X-ALD individuals ( $0.72\mu\text{M}$  [ $0.59\text{--}0.84$ ])( $p<0.001$ ). Fourteen of 19 children had elevated expression of IFN signaling on blood cards relative to controls (Sensitivity 73.7%, 95%CI 51-88%, Specificity 95%, 95% CI 78-99%) including an individual with delayed disease presentation (36months of age). All five AGS patients with negative IFN signature at birth had RNASEH2B mutations. Consistency of agreement between IFN

signature in neonatal and post-natal samples was high (0.85).

**CONCLUSION:** This suggests that inflammatory markers in AGS can be identified in the newborn period, before symptom onset. Additionally, since C26:0 Lyso-PC screening is currently used in X-ALD newborn screening panels, clinicians should be alert to the fact that AGS infants may present as false positives during X-ALD screening.

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DOI: 10.1016/j.ymgme.2017.07.006

PMCID: PMC5722655

PMID: 28739201 [Indexed for MEDLINE]

678. Nature. 2017 Aug 24;548(7668):461-465. doi: 10.1038/nature23449. Epub 2017 Jul 24.

cGAS surveillance of micronuclei links genome instability to innate immunity.

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DNA is strictly compartmentalized within the nucleus to prevent autoimmunity; despite this, cyclic GMP-AMP synthase (cGAS), a cytosolic sensor of double-stranded DNA, is activated in autoinflammatory disorders and by DNA damage. Precisely how cellular DNA gains access to the cytoplasm remains to be determined. Here, we report that cGAS localizes to micronuclei arising from genome instability in a mouse model of monogenic autoinflammation, after exogenous DNA damage and spontaneously in human cancer cells. Such micronuclei occur after mis-segregation of DNA during cell division and consist of chromatin surrounded by its own nuclear membrane. Breakdown of the micronuclear envelope, a

process associated with chromothripsis, leads to rapid accumulation of cGAS, providing a mechanism by which self-DNA becomes exposed to the cytosol. cGAS is activated by chromatin, and consistent with a mitotic origin, micronuclei formation and the proinflammatory response following DNA damage are cell-cycle dependent. By combining live-cell laser microdissection with single cell transcriptomics, we establish that interferon-stimulated gene expression is induced in micronucleated cells. We therefore conclude that micronuclei represent an important source of immunostimulatory DNA. As micronuclei formed from lagging chromosomes also activate this pathway, recognition of micronuclei by cGAS may act as a cell-intrinsic immune surveillance mechanism that detects a range of neoplasia-inducing processes.

DOI: 10.1038/nature23449

PMCID: PMC5870830

PMID: 28738408 [Indexed for MEDLINE]

679. Curr Opin Immunol. 2017 Dec;49:1-8. doi: 10.1016/j.coi.2017.07.007. Epub 2017 Jul 22.

Psoriasis: a mixed autoimmune and autoinflammatory disease.

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In recent years marked progress has been made in our understanding of the critical biologic and immunologic pathways involved in psoriasis. Genetic studies have demonstrated that susceptibility to psoriasis involves components of both

the adaptive and innate immune system and not surprisingly activation of both of these arms of the immune system is found in psoriatic skin. While adaptive immune responses predominate in chronic plaque psoriasis, innate and autoinflammatory responses dominate in pustular forms of psoriasis, with other clinical subtypes extending on a spectrum between plaque and pustular psoriasis. This makes psoriasis a unique disease where both autoimmune and autoinflammatory responses co-exist, with the balance between the two being critical in shaping its clinical presentation.

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DOI: 10.1016/j.coi.2017.07.007

PMCID: PMC5705427

PMID: 28738209 [Indexed for MEDLINE]

680. J Mol Biol. 2018 Jan 19;430(2):142-152. doi: 10.1016/j.jmb.2017.07.012. Epub 2017 Jul 19.

Mechanisms of NLRP1-Mediated Autoinflammatory Disease in Humans and Mice.

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NLRP1 was the first NOD-like receptor described to form an inflammasome, recruiting ASC to activate caspase-1, which processes interleukin-1 $\beta$  and interleukin-18 to their active form. A wealth of new genetic information has now redefined our understanding of this innate immune sensor. Specifically, rare loss-of-function variants in the N-terminal pyrin domain indicate that this part

of NLRP1 is autoinhibitory and normally acts to prevent a familial autoinflammatory skin disease associated with cancer. In the absence of a ligand to trigger human NLRP1, these mutations have now confirmed the requirement of NLRP1 autolytic cleavage within the FIIND domain, which had previously been implicated in NLRP1 activation. Autolytic cleavage generates a C-terminal fragment of NLRP1 containing the CARD domain which then forms an ASC-dependent inflammasome. The CARD domain as an inflammasome linker is consistent with the observation that under some conditions, particularly for mouse NLRP1, caspase-1 can be engaged directly, and although it is no longer processed, it is still capable of producing mature IL-1 $\beta$ . Additional rare variants in a linker region between the LRR and FIIND domains of NLRP1 also cause autoinflammatory disease in both humans and mice. This new genetic information is likely to provide for more mechanistic insight in the years to come, contributing to our understanding of how NLRP1 functions as an innate immune sensor of infection and predisposes to autoimmune or autoinflammatory diseases.

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DOI: 10.1016/j.jmb.2017.07.012

PMID: 28733143

681. Immunopharmacol Immunotoxicol. 2017 Oct;39(5):253-258. doi: 10.1080/08923973.2017.1350704. Epub 2017 Jul 20.

STING signalling: an emerging common pathway in autoimmunity and cancer.

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The equipoise between the disease states of cancer and autoinflammation has perhaps been underappreciated in clinical practice and biomedical research. However, since the discover of STING (stimulator of interferon genes) as an integral regulator of innate immunity, a wealth of information has implicated this signaling pathway in both of these diseases. Under cellular homeostasis, STING serves to detect - and promote immune defense against - DNA viruses and intracellular bacteria, as described in its initial discovery. The role of STING

has since been expanded to include tumor surveillance and immune responses to cancer; indeed, defective STING responses are associated with certain cancers. Conversely, constitutive activation of this pathway can result in autoinflammatory disease, whereby STING is over-stimulated by self-DNA. This review explores the current state of STING research, concluding that further elucidation of the details of the STING pathway may offer novel therapeutics for these diseases, which are of considerable clinical gravity.

DOI: 10.1080/08923973.2017.1350704

PMID: 28724326 [Indexed for MEDLINE]

682. Cell Rep. 2017 Jul 18;20(3):668-682. doi: 10.1016/j.celrep.2017.06.073.

XIAP Loss Triggers RIPK3- and Caspase-8-Driven IL-1 $\beta$  Activation and Cell Death as a Consequence of TLR-MyD88-Induced cIAP1-TRAF2 Degradation.

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X-linked Inhibitor of Apoptosis (XIAP) deficiency predisposes people to pathogen-associated hyperinflammation. Upon XIAP loss, Toll-like receptor (TLR) ligation triggers RIPK3-caspase-8-mediated IL-1 $\beta$  activation and death in myeloid cells. How XIAP suppresses these events remains unclear. Here, we show that TLR-MyD88 causes the proteasomal degradation of the related IAP, cIAP1, and its adaptor, TRAF2, by inducing TNF and TNF Receptor 2 (TNFR2) signaling. Genetically, we define that myeloid-specific cIAP1 loss promotes TLR-induced RIPK3-caspase-8 and IL-1 $\beta$  activity in the absence of XIAP. Importantly, deletion of TNFR2 in XIAP-deficient cells limited TLR-MyD88-induced cIAP1-TRAF2 degradation, cell death, and IL-1 $\beta$  activation. In contrast to TLR-MyD88, TLR-TRIF-induced interferon (IFN) $\beta$  inhibited cIAP1 loss and consequent cell death. These data reveal how, upon XIAP deficiency, a TLR-TNF-TNFR2 axis drives cIAP1-TRAF2 degradation to allow TLR or TNFR1 activation of RIPK3-caspase-8 and IL-1 $\beta$ . This mechanism may explain why XIAP-deficient patients can exhibit symptoms reminiscent of patients with activating inflammasome mutations.

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DOI: 10.1016/j.celrep.2017.06.073

PMID: 28723569 [Indexed for MEDLINE]

683. Immunity. 2017 Jul 18;47(1):183-198.e6. doi: 10.1016/j.immuni.2017.06.017.

Induced-Pluripotent-Stem-Cell-Derived Primitive Macrophages Provide a Platform for Modeling Tissue-Resident Macrophage Differentiation and Function.

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Comment in

Immunity. 2017 Jul 18;47(1):10-12.

Tissue macrophages arise during embryogenesis from yolk-sac (YS) progenitors that give rise to primitive YS macrophages. Until recently, it has been impossible to isolate or derive sufficient numbers of YS-derived macrophages for further study, but data now suggest that induced pluripotent stem cells (iPSCs) can be driven to

undergo a process reminiscent of YS-hematopoiesis in vitro. We asked whether iPSC-derived primitive macrophages (iMacs) can terminally differentiate into specialized macrophages with the help of growth factors and organ-specific cues. Co-culturing human or murine iMacs with iPSC-derived neurons promoted differentiation into microglia-like cells in vitro. Furthermore, murine iMacs differentiated in vivo into microglia after injection into the brain and into functional alveolar macrophages after engraftment in the lung. Finally, iPSCs from a patient with familial Mediterranean fever differentiated into iMacs with pro-inflammatory characteristics, mimicking the disease phenotype. Altogether, iMacs constitute a source of tissue-resident macrophage precursors that can be used for biological, pathophysiological, and therapeutic studies.

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DOI: 10.1016/j.immuni.2017.06.017

PMID: 28723550 [Indexed for MEDLINE]

684. Nat Immunol. 2017 Jul 19;18(8):832-842. doi: 10.1038/ni.3777.

The monogenic autoinflammatory diseases define new pathways in human innate immunity and inflammation.

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Erratum in

Nat Immunol. 2017 Oct 18;18(11):1271.

Autoinflammatory diseases were first recognized nearly 20 years ago as distinct clinical and immunological entities caused by dysregulation in the innate immune system. Since then, advances in genomic techniques have led to the identification of new monogenic disorders and their corresponding signaling pathways. Here we review these monogenic autoinflammatory diseases, ranging from periodic fever syndromes caused by dysregulated inflammasome-mediated production of the cytokine

IL-1 $\beta$  to disorders arising from perturbations in signaling by the transcription factor NF- $\kappa$ B, ubiquitination, cytokine signaling, protein folding, type I interferon production and complement activation, and we further examine their molecular mechanisms. We also explore the overlap among autoinflammation, autoimmunity and immunodeficiency, and pose a series of unanswered questions that are expected to be central in autoinflammatory disease research in the coming decade.

DOI: 10.1038/ni.3777

PMID: 28722725 [Indexed for MEDLINE]

685. Clin Rheumatol. 2018 Jan;37(1):265-270. doi: 10.1007/s10067-017-3758-7. Epub 2017 Jul 18.

Two Chinese pedigrees of Blau syndrome with thirteen affected members.

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Blau syndrome (BS) is a rare autosomal dominant autoinflammatory disease characterized by the clinical triad of dermatitis, arthritis, and uveitis. It is caused by mutations in nucleotide-binding oligomerization domain-containing protein-2 (NOD2) gene. BS has been widely reported in Caucasians but cases documented in China are scarce. We reported two Chinese families with BS, which were by far the two largest pedigrees in the Chinese population. We identified two unrelated families with BS. The phenotypes and genotypes of these patients were reviewed and compared with previous cohorts. The proband of the first family was a 32-year-old Chinese Han woman, who had dermatitis, polyarthritis, and intermittent fever since the age of 6, bilateral panuveitis since 12. During her

disease course, she lost her vision and developed hand flexion contractures. The proband of the second family was a 36-year-old Chinese Han woman, who had dermatitis and bilateral panuveitis since the age of 7, persistent polyarthritis since 13. Additional 7 and 4 family members were affected in the first and second families, respectively, and pedigree analysis suggested autosomal dominant inheritance. Genetic testing in both families identified the heterozygous c.1000 C > T, R334W mutation in NOD2 gene. Only one patient had recurrent fever as an expanded manifestation beyond the classical triad. BS can occur in multiple ethnic groups including the Chinese Han population. Our 11 adult patients constituted the largest adult cohort of BS ever reported in China. Lack of recognition of BS led to a significant delay in diagnosis. A considerable percentage of patients did not demonstrate the full spectrum of the classical triad, further complicating the diagnosis.

DOI: 10.1007/s10067-017-3758-7

PMID: 28721627 [Indexed for MEDLINE]

686. Arthritis Rheumatol. 2017 Nov;69(11):2241-2246. doi: 10.1002/art.40217. Epub 2017 Oct 12.

De Novo Human Herpesvirus 8 Tumors Induced by Rituximab in Autoimmune or Inflammatory Systemic Diseases.

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**OBJECTIVE:** Human herpesvirus 8 (HHV-8), also known as Kaposi's sarcoma (KS)-associated herpesvirus, is involved in KS and other tumors, including multicentric Castleman's disease and primary effusion lymphoma. Rituximab (RTX) is currently used for the treatment of several autoimmune or inflammatory diseases and humoral organ transplant rejection. De novo HHV-8 tumors induced by RTX used for these indications have not been reported previously. This study was undertaken to evaluate de novo HHV-8 tumors induced by RTX.

**METHODS:** In this retrospective study, we investigated the clinical, virologic, and pathologic features of 5 HIV-negative male patients with HHV-8 tumors induced by RTX therapy.

**RESULTS:** Patients were all immunocompromised by previous treatments, which consisted of steroids and/or immunosuppressive agents, and received RTX for insufficient response, disease progression, or transplant rejection. They developed HHV-8 tumors a median of 4 months after beginning treatment with RTX (range 3-13 months). Four patients had at least 1 risk factor for HHV-8, including a high Fitzpatrick skin phototype (of >3) (n = 3) and homosexuality (n = 1). Four patients developed KS (all 4 had skin lesions and 2 had visceral involvement), and 1 patient developed a solid primary effusion lymphoma. RTX was discontinued in all patients, and immunosuppressants were reduced when feasible. After a median follow-up of 20 months, 2 patients died. Remission of KS was complete in 1 patient and partial in 1 patient, and 1 patient had progression.

**CONCLUSION:** Our findings indicate that patients who have a high skin phototype and are at risk of HHV-8 should be carefully screened for HHV-8 before RTX therapy. The safety of RTX, especially in nonlymphomatous disorders, should be carefully evaluated in patients at risk of HHV-8 tumors.

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DOI: 10.1002/art.40217

PMID: 28719723 [Indexed for MEDLINE]

## Schnitzler Syndrome: a Review.

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**PURPOSE OF REVIEW:** We focus on recent advances in diagnosis and therapeutic strategies, as well as on pathogenesis of Schnitzler syndrome.

**RECENT FINDINGS:** New diagnostic criteria were established, and their external validity was assessed in a retrospective cohort study. The cytokine interleukin-1 (IL-1) plays a crucial role in the pathogenesis of the Schnitzler syndrome, and this explains the spectacular efficiency of IL-1 blocking therapies. The Schnitzler syndrome is now considered as a late-onset acquired autoinflammatory syndrome in which the cytokine IL-1 plays a crucial role. IL-1 blocking therapies are efficient on the inflammation-linked symptoms but not on the monoclonal component. Therefore, they probably don't reduce the risk of the development of lymphoproliferative disorders that remains the main prognostic issue. The link between autoinflammation and the monoclonal component needs to be further elucidated.

DOI: 10.1007/s11926-017-0673-5

PMID: 28718061 [Indexed for MEDLINE]

688. Expert Rev Clin Pharmacol. 2017 Oct;10(10):1119-1128. doi: 10.1080/17512433.2017.1356719. Epub 2017 Jul 27.

Drug management of neutrophilic dermatoses.

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**INTRODUCTION:** Neutrophilic dermatoses are a heterogeneous group of chronic, cutaneous inflammatory conditions characterized by the accumulation of neutrophils in the skin and by systemic inflammation. Neutrophilic dermatoses can be idiopathic or associated with other inflammatory or systemic diseases, including the group of the hereditary, autoinflammatory syndromes. Clinical management is challenging, due to limited clinical evidence and lack of clinical practice guidelines. Areas covered: This review provides an overview of current therapeutic management of the three prototypical neutrophilic dermatoses, aseptic pustulosis of the folds, Sweet syndrome and pyoderma gangrenosum. In addition, we describe innovative, pathogenesis-oriented treatment approaches, which are based on recent advances in the pathophysiology of neutrophilic dermatoses and autoinflammatory syndromes. The increasing role of the IL-1 cytokine family in initiating neutrophilic inflammation in both idiopathic and syndromic disease opened the way for the use of targeted biological treatment. Another promising treatment strategy is aimed at blocking downstream effector cytokines, such as IL12/23 and IL-17, involved in the autoinflammatory immune cascade. Expert commentary: In chronic-recurrent and syndromic cases of neutrophilic dermatoses, there is an unmet clinical need for long-term, continuous disease control. Future controlled clinical studies will optimize the use of targeted-biological agents in sequential or combination treatment strategies.

DOI: 10.1080/17512433.2017.1356719

PMID: 28715916 [Indexed for MEDLINE]

689. Mod Rheumatol. 2017 Nov;27(6):1031-1035. doi: 10.1080/14397595.2017.1285857. Epub 2017 Feb 21.

Certolizumab Pegol treatment in Behcet's disease with different organ involvement: A multicenter retrospective observational study.

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**OBJECTIVES:** The purpose of the present study was to describe our experience with the recombinant Fab' antibody fragment against TNF- $\alpha$  Certolizumab Pegol (CZP) in patients with Behçet's disease (BD) refractory to standardized therapies and previous biologic agents.

**METHODS:** Retrieved data including demographic characteristics, clinical manifestations, and previous treatments were collected in three different specialized Rheumatologic Units in Italy. In order to evaluate disease activity, the BD current activity form (BDCAF) has been used before starting CZP therapy and at each visit during treatment.

**RESULTS:** Thirteen BD patients (mean age  $42.6 \pm 8.8$  years) with a disease duration of  $8.80 \pm 6.9$  years, underwent CZP treatment for  $6.92 \pm 3.52$  months. Six patients (46.15%) experienced a worsening of symptoms after  $4.16 \pm 1.21$  months, whereas a satisfactory response was achieved in seven patients (53.84%) who were still on CZP therapy at the last follow-up visit (after  $9.28 \pm 3.03$  months of treatment). The mean decrease of BDCAF between the first and last visit was  $0.308 \pm 1.84$  without reaching significant difference (mean  $8.3 \pm 1.3$  and  $8 \pm 2.08$ , respectively;  $p = .51$ ). During the whole study period, CZP was well tolerated in all patients except one who developed a generalized cutaneous reaction after the third administration.

**CONCLUSIONS:** These results suggest that despite an improvement of clinical manifestations has been observed in more than half of the patients, it is not possible to draw firm conclusions about the effectiveness of CZP in BD and further studies with larger cohorts of patients are warranted. Whether the

increase of CZP dosage may ensure a better clinical response remains an unsolved issue that needs to be considered.

DOI: 10.1080/14397595.2017.1285857

PMID: 28712320 [Indexed for MEDLINE]

690. Rheum Dis Clin North Am. 2017 Aug;43(3):327-345. doi: 10.1016/j.rdc.2017.04.011.

Genomics, Biology, and Human Illness: Advances in the Monogenic Autoinflammatory Diseases.

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The monogenic autoinflammatory diseases are a group of illnesses with prominent rheumatic manifestations that are characterized by genetically determined recurrent sterile inflammation and are thus inborn errors of innate immunity. Molecular targeted therapies against inflammatory cytokines, such as interleukin 1 and tumor necrosis factor, and intracellular cytokine signaling pathways have proved effective in many cases. Emerging next-generation sequencing technologies have accelerated the identification of previously unreported genes causing autoinflammatory diseases. This review covers several of the prominent recent advances in the field of autoinflammatory diseases, including gene discoveries, the elucidation of new pathogenic mechanisms, and the development of effective targeted therapies.

Published by Elsevier Inc.

DOI: 10.1016/j.rdc.2017.04.011

PMCID: PMC5564228

PMID: 28711137 [Indexed for MEDLINE]

691. Arthritis Rheumatol. 2017 Nov;69(11):2203-2208. doi: 10.1002/art.40215. Epub 2017 Oct 12.

Defective Early B Cell Tolerance Checkpoints in Sjögren's Syndrome Patients.

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**OBJECTIVE:** Central and peripheral B cell tolerance checkpoints are defective in many patients with autoimmune diseases, but the functionality of each discrete checkpoint has not been assessed in patients with Sjögren's syndrome (SS). We undertook this study to assess this functionality in SS patients.

**METHODS:** Using a polymerase chain reaction-based approach that allows us to clone and express, in vitro, recombinant antibodies produced by single B cells, we tested the reactivity of recombinant antibodies cloned from single CD19<sup>+</sup>CD21<sup>low</sup>

CD10+IgM<sup>high</sup> CD27<sup>-</sup> newly emigrant/transitional B cells and  
CD19+CD21+CD10-IgM+CD27<sup>-</sup> mature naive B cells from 5 SS patients.

RESULTS: We found that the frequencies of newly emigrant/transitional B cells expressing polyreactive antibodies were significantly increased in SS patients compared to those in healthy donors, revealing defective central B cell tolerance in SS patients. Frequencies of mature naive B cells expressing autoreactive antibodies were also significantly increased in SS patients, thereby illustrating an impaired peripheral B cell tolerance checkpoint in these patients.

CONCLUSION: Defective counterselection of developing autoreactive B cells observed in SS patients is a feature common to many other autoimmune diseases and may favor the development of autoimmunity by allowing autoreactive B cells to present self antigens to T cells.

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DOI: 10.1002/art.40215

PMCID: PMC6062007

PMID: 28704602 [Indexed for MEDLINE]

692. Rev Med Suisse. 2017 Jan 11;13(544-545):20-22.

[Hope for chronic inflammatory diseases : the anti-IL-6 receptor monoclonal antibody tocilizumab].

[Article in French; Abstract available in French from the publisher]

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Vasculitis like Horton's disease, some autoinflammatory syndromes (Behcet's, Still's diseases) often require long term treatment with steroids, and therefore are associated with non acceptable adverse events, especially when resistant to treatment. Recently, a number of controlled prospective clinical trials are supporting the interest of the anti-IL-6 receptor monoclonal antibody tocilizumab in these chronic inflammatory conditions et may soon be recognized as second intention therapeutic approach.

Publisher: Certaines vasculites comme la maladie de Horton en particulier, certaines pathologies auto-inflammatoires (maladies de Behcet, de Still) imposent aux patients des traitements de longue durée par les stéroïdes et donc les exposent à des effets secondaires à long terme souvent inacceptables dans les formes résistantes. Depuis peu, quelques études contrôlées, prospectives sont venues soutenir l'intérêt de l'antirécepteur de l'IL-6 monoclonal dans ces pathologies, et laissent penser qu'il puisse prochainement devenir un traitement de seconde intention dans le Horton notamment.

PMID: 28703529 [Indexed for MEDLINE]

Conflict of interest statement: L'auteur n'a déclaré aucun conflit d'intérêts en relation avec cet article.

693. J Eur Acad Dermatol Venereol. 2017 Nov;31(11):1809-1816. doi: 10.1111/jdv.14464. Epub 2017 Sep 7.

Recognizing syndromic hidradenitis suppurativa: a review of the literature.

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Hidradenitis suppurativa (HS) is an inflammatory skin disease causing painful inflammation and suppuration. It may occur in rare syndromes: follicular occlusion, Bazex-Dupré-Christol, Down's, KID, PAPASH, PASS, PASH, and SAPHO syndromes, as well as Dowling-Degos disease. An overview of syndromic HS may inform the search for aetiological factors in HS. PubMed, Ovid and Web of Science were systematically searched using '(hidradenitis OR acne invers\*) AND (syndrome OR KID OR PASS OR PAPA OR PASH OR SAPHO OR bazex-dupre OR 'dowling degos' OR triad OR tetrad)' and Cochrane Library using 'hidradenitis OR acne invers\*'. A total of 82 articles were included in the final review. We summarize 134 cases collected from the 82 included articles. The syndromes are discussed, focusing on etiopathogenesis, clinical presentation and treatment. This study is based on case reports; therefore, conclusions may be subject to the selection bias. These

syndromes are rare; however, it is important to recognize them, as treating them may require a different approach. Three subtypes of syndromic hidradenitis are suggested: syndromes with known genetic abnormalities, syndromes characterized by follicular plugging or structural defects, and syndromes with possible autoinflammatory pathogenesis. There was no universally effective treatment for syndromic HS, and treatment was individualized.

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DOI: 10.1111/jdv.14464

PMID: 28696038 [Indexed for MEDLINE]

694. Autoimmun Rev. 2017 Sep;16(9):897-902. doi: 10.1016/j.autrev.2017.07.001. Epub 2017 Jul 8.

Does type-I interferon drive systemic autoimmunity?

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Type-I interferon (IFN)-mediated immune response involves both innate and adaptive immune system and has a pivotal role in antiviral defence. A complex interplay of intracellular signaling pathways and tight regulatory systems drive the IFN activation. The observation of an aberrant stimulation of this system as a common molecular basis in peculiar inherited autoimmune and autoinflammatory disorders led to the concept of "type I interferonopathies". But the precise genetic dissection of this growing spectrum of diseases adds more and more complexity to the comprehension of this concept and a lot of unsolved questions remain such as how type I IFN can drive systemic inflammation in these clinically and genetically heterogeneous diseases.

695. *Pediatr Rheumatol Online J*. 2017 Jul 11;15(1):56. doi: 10.1186/s12969-017-0183-z.

Bone metabolism and inflammatory characteristics in 14 cases of chronic nonbacterial osteomyelitis.

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**BACKGROUND:** Chronic nonbacterial osteomyelitis (CNO) is a multifocal autoinflammatory disease that often impairs daily life in children. This study aimed to investigate the bone metabolic and inflammatory characteristics of patients with CNO, and to assess the differences between responders and nonresponders to conservative treatment.

**METHODS:** We investigated the clinical symptoms; laboratory data including inflammatory and bone metabolic biomarkers; and imaging findings from plain radiography, magnetic resonance imaging (MRI), fluorodeoxyglucose-positron emission tomography (FDG-PET), and dual-energy x-ray absorption (DEXA) in 14 patients with CNO. All patients underwent first-line treatment comprising systemic nonsteroidal anti-inflammatory drugs with or without bisphosphonate. According to the response to the first-line treatment, the patients were divided into the clinical remission/partial response group and the no response group. The differences in bone metabolic and inflammatory characteristics between the two groups were assessed.

**RESULTS:** All patients had low bone mineral density assessed with DEXA. The bone metabolic biomarkers (bone-specific alkaline phosphatase and tartrate-resistant

acid phosphatase 5b) were increased in boys of all ages and in young girls. Multiple inflammatory regions were detected in all patients by using FDG-PET including asymptomatic regions. The no response group had higher immunoglobulin G (IgG) and a greater number of bone inflammatory lesions detected on MRI than the clinical remission/partial response group.

CONCLUSION: Our data indicate the involvement of abnormal bone turnover, necessity of whole-body scanning, and association of higher serum IgG levels and greater numbers of inflammatory lesions with prolonged disease activity in patients with CNO.

DOI: 10.1186/s12969-017-0183-z

PMCID: PMC5504748

PMID: 28693592 [Indexed for MEDLINE]

696. Cureus. 2017 Jun 7;9(6):e1321. doi: 10.7759/cureus.1321.

Delay in the Diagnosis of Adult-Onset Still's Disease.

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Adult-onset Still's disease (AOSD) is a systemic autoinflammatory disease characterized by symptoms including spiking fever, arthralgia, myalgia, maculopapular rash, and pharyngitis. The lack of diagnostic biomarker, non-specific clinical presentation, and the rarity of AOSD often result in a significant delay in diagnosis and treatment. While the average time of initial presentation to diagnosis is four months, we present a case of AOSD diagnosis three years after initial onset of classical symptoms. By reporting the case of delayed diagnosis for AOSD, we hope to raise awareness in our medical community about the diagnostic difficulty in AOSD. The present case describes an otherwise healthy male who presented with typical symptoms of AOSD, but the diagnosis of AOSD was missed during his first presentation. In the second flaring episode, the diagnosis of AOSD was established. He had an excellent therapeutic response to anakinra and prednisone during the acute flaring episode. He is currently in complete remission on methotrexate as maintenance therapy.



DOI: 10.7759/cureus.1321

PMCID: PMC5501706

PMID: 28690954

Conflict of interest statement: The authors have declared that no competing interests exist.

697. Hum Genome Var. 2017 Jun 15;4:17023. doi: 10.1038/hgv.2017.23. eCollection 2017.

The detection of a novel insertion mutation in exon 2 of the MEFV gene associated with familial mediterranean fever in a moroccan family.

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Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease that is inherited in an autosomal recessive manner and is caused by mutations in the MEFV gene. As the name indicates, FMF occurs within families and is more common in individuals of Mediterranean descent than in persons of any other ethnicity. To date, 314 mutations have been reported. We studied a Moroccan family with a total of five members, including a mother who was presenting with symptoms of FMF, while her four children remained asymptomatic. The five patients were screened by DNA sequencing of exon 2 and exon 10 of the MEFV gene. Then, complete exome sequencing analysis of the MEFV gene was done for the patients in whom a novel mutation was detected. This analysis identified a novel single base Cytosine (C) insertion mutation in the coding region of the MEFV gene, named c.441dupC (p. Glu148Argfs\*5 or E148RfsX5), which resulted in a mutated Pyrin/Marenostrin protein. This is the first report of a new mutation in exon 2 of the MEFV gene in a Moroccan family. This novel insertion mutation may provide important information for further studies of FMF pathogenesis.

DOI: 10.1038/hgv.2017.23

PMCID: PMC5494187

PMID: 28690860

Conflict of interest statement: The authors declare no conflict of interest.

698. Front Immunol. 2017 Jun 23;8:720. doi: 10.3389/fimmu.2017.00720. eCollection 2017.

Insight into the Endocrine System and the Immune System: A Review of the Inflammatory Role of Prolactin in Rheumatoid Arthritis and Psoriatic Arthritis.

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Rheumatoid arthritis (RA) is a chronic autoimmune disease that affects females three times more frequently than males. A potential role for hormones, such as prolactin (PRL), may in part explain this phenomenon. The risk of developing RA is increased in women who are lactating after the first pregnancy, which might be related to breastfeeding and the release of PRL. Other studies found a protective effect of PRL on RA development. Some studies have reported that hyperprolactinemia is more common in RA and serum PRL levels are correlated with several disease parameters, although others could not confirm these findings. Overall the plasma PRL levels are on average not elevated in RA. Previously, a small number of open-label clinical trials using bromocriptine, which indirectly decreases PRL levels, were performed in RA patients and showed clinical benefit,

although others found the opposite effect. Locally produced PRL at the site of inflammation may have a crucial role in RA as well, as it has been shown that PRL can be produced by synovial macrophages. Locally produced PRL has both pro-inflammatory and anti-inflammatory effects in arthritis. Psoriatic arthritis (PsA) is also an autoinflammatory disease, in which the prolactin receptor is also expressed in macrophages. The aim of this review is to provide an overview of the potential role of PRL signaling in inflammatory joint diseases (RA and PsA) and its potential as a therapeutic target.

DOI: 10.3389/fimmu.2017.00720

PMCID: PMC5481306

PMID: 28690611

699. Clin Rev Allergy Immunol. 2018 Feb;54(1):114-130. doi: 10.1007/s12016-017-8621-8.

A Comprehensive Review of Neutrophilic Diseases.

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Comment in

Z Rheumatol. 2018 Jun;77(5):350-352.

Neutrophilic dermatoses are a group of conditions characterized by the accumulation of neutrophils in the skin and clinically presenting with polymorphic cutaneous lesions, including pustules, bullae, abscesses, papules, nodules, plaques and ulcers. In these disorders, the possible involvement of almost any organ system has led to coin the term 'neutrophilic diseases'. Neutrophilic diseases have close clinicopathological similarities with the autoinflammatory diseases, which present with recurrent episodes of inflammation in the affected organs in the absence of infection, allergy and frank autoimmunity. Neutrophilic diseases may be subdivided into three main groups: (1) deep or hypodermal forms whose paradigm is pyoderma gangrenosum, (2) plaque-type or dermal forms whose prototype is Sweet's syndrome and (3) superficial or epidermal forms among which amicrobial pustulosis of the folds may be considered the model. A fourth subset of epidermal/dermal/hypodermal forms has been recently added to the classification of neutrophilic diseases due to the emerging role of the syndromic pyoderma gangrenosum variants, whose pathogenesis has shown a relevant autoinflammatory component. An increasing body of evidence supports the role of pro-inflammatory cytokines like interleukin (IL)-1-beta, IL-17 and tumour necrosis factor (TNF)-alpha in the pathophysiology of neutrophilic diseases similarly to classic monogenic autoinflammatory diseases, suggesting common physiopathological mechanisms. Moreover, mutations of several genes involved in autoinflammatory diseases are likely to play a role in the pathogenesis of neutrophilic diseases, giving rise to regarding them as a spectrum of polygenic autoinflammatory conditions. In this review, we focus on clinical aspects, histopathological features and pathophysiological mechanisms of the paradigmatic forms of neutrophilic diseases, including pyoderma gangrenosum, Sweet's syndrome, amicrobial pustulosis of the folds and the main syndromic presentations of pyoderma gangrenosum. A simple approach for diagnosis and management of these disorders has also been provided.

DOI: 10.1007/s12016-017-8621-8

PMID: 28688013 [Indexed for MEDLINE]

700. J Drugs Dermatol. 2017 Jun 1;16(6):625-627.

Schnitzler Syndrome With Delirium and Vertigo: The Utility of Neurologic Manifestations in Diagnosis.

Tolkachjov SN, Wetter DA.

Schnitzler syndrome (SS) is an autoinflammatory dermatosis that often goes undiagnosed for 5-6 years. Patients typically carry a diagnosis of urticaria; however, their cutaneous symptoms fail to respond to typical urticaria therapies and lack symptoms such as pruritus. Additionally, patients with SS may see multiple providers for nonspecific complaints of fever, lymphadenopathy, arthralgias, and bone pain. A correct diagnosis is paramount, as close to 20% of patients may develop a lymphoproliferative disorder and appropriate treatment may ameliorate all symptoms.<sup>1</sup> We report 2 cases of SS misdiagnosed as urticaria for years in order to illuminate diagnostic pearls, histopathological findings, and treatment modalities. Additionally, we highlight the importance of neurologic disturbances in this rare but important differential diagnosis of urticaria.

J Drugs Dermatol. 2017;16(6):625-627.

PMID: 28686783 [Indexed for MEDLINE]

701. Autoimmunity. 2017 Nov;50(7):422-427. doi: 10.1080/08916934.2017.1344976. Epub 2017 Jul 7.

Management of hydrocephalus associated with autoimmune diseases: a series of 19 cases.

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**OBJECTIVES:** To analyze the diagnosis and treatment of hydrocephalus associated with autoimmune diseases and to explore the possible mechanism of hydrocephalus in these patients.

**METHODS:** A retrospective case series study was conducted at Peking Union Medical College Hospital, Beijing, China. Files were retrieved from the hospital archives by screening records from Jan 1990 to Jan 2016. Medical records were screened for data regarding (1) the number of patients diagnosed with hydrocephalus associated with autoimmune diseases, (2) the clinical manifestation of hydrocephalus associated with autoimmune disease, and (3) the outcomes of these patients treated with medication or ventriculoperitoneal shunt (VPS).

**RESULTS:** A total of 19 of 19,643 hospitalized autoimmune diseases patients were found to have hydrocephalus. Seven of the 19 patients had systemic lupus erythematosus (SLE), 3 patients had Sjögren's syndrome, 2 patients had rheumatoid arthritis (RA), 1 patient had connective tissue disease, 1 patient had juvenile idiopathic arthritis (JIA), 1 patient had Guillain-Barre syndrome (GBS), 1 patient had systemic sclerosis, 1 patient had Crohn's disease, 1 patient had relapsing polychondritis (RPC), and 1 patient had autoinflammatory disease (AID). Of the 19 patients, 13 received medication treatment, and the most commonly used drugs were corticosteroids and mannitol. A total of 6 patients received both medication therapy and VPS treatment with a programmable valve. After average follow-up lengths of 11 months for patients who received VPS and 8.2 for patients who received medical treatment, the clinical symptoms of patients treated by VPS or medication were improved (83% (5/6) vs. 15.4% (2/13), respectively), patients were in stable condition (17% (1/6) vs. 30.8% (4/13), respectively), and mortality decreased (0% vs. 53.8% (7/13), respectively).

**CONCLUSIONS:** VPS along with corticosteroids and immunosuppressants represents an effective treatment approach for patients who suffer from hydrocephalus associated with autoimmune diseases.

DOI: 10.1080/08916934.2017.1344976

PMID: 28686532 [Indexed for MEDLINE]

702. Mol Cell Pediatr. 2017 Dec;4(1):7. doi: 10.1186/s40348-017-0073-y. Epub 2017 Jul 6.

The molecular pathophysiology of chronic non-bacterial osteomyelitis (CNO)-a systematic review.

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Chronic non-bacterial osteomyelitis (CNO) belongs to the growing spectrum of autoinflammatory diseases and primarily affects the skeletal system. Peak onset ranges between 7 and 12 years of age. The clinical spectrum of CNO covers sometimes asymptomatic inflammation of single bones at the one end and chronically active or recurrent multifocal osteitis at the other. Despite the intense scientific efforts, the exact molecular mechanisms of CNO remain unknown. Recent data suggest CNO as a genetically complex disorder with dysregulated TLR4/MAPK/inflammasome signaling cascades resulting in an imbalance between pro- and anti-inflammatory cytokine expression, leading to osteoclast activation and osteolytic lesions. In this manuscript, the current understanding of molecular patho-mechanisms in CNO will be discussed.

DOI: 10.1186/s40348-017-0073-y

PMCID: PMC5500598

PMID: 28685269

703. Isr Med Assoc J. 2016 Sep;18(9):571.

Autoimmune/inflammatory syndrome leading to macrophage activation syndrome: An example of autoinflammatory spectrum disorder?

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PMID: 28681590 [Indexed for MEDLINE]

704. Noro Psikiyatr Ars. 2017 Jun;54(2):105-107. doi: 10.5152/npa.2016.12396. Epub 2016 Dec 8.

Changes in Cerebral Blood Flow in Patients with Familial Mediterranean Fever.

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**INTRODUCTION:** It is known that there is a relationship between systemic inflammation and atherosclerosis. Atherosclerosis is one of the best-known causes of cerebrovascular diseases. The aim of this study was to assess cerebral blood flow velocity using transcranial Doppler (TCD) ultrasonography in patients with familial Mediterranean fever (FMF).

**METHODS:** A total of 30 patients aged from 20 to 50 years with FMF were enrolled in the FMF group consecutively. The control group (non-FMF group) consisted of 30 age- and sex-matched randomly selected patients without FMF who had other diagnoses such as fibromyalgia and did not have risk factors for atherosclerosis. Bilateral peak-systolic, end-diastolic, and mean blood flow velocities in the middle cerebral artery (MCA), values of Gosling's pulsatility index, and values of Pourcelot's resistance index were recorded using TCD ultrasonography by a neurosonologist blinded to the FMF and control groups.

**RESULTS:** There were 30 participants in the FMF group in remission (male/female:



4/26, mean age: 34.7±5.9 years) and 30 participants in the control group (male/female: 4/26, mean age: 32.3±4.7 years). C-reactive protein levels and bilateral blood flow velocities in the MCA were significantly higher in the FMF group than in the control group.

**CONCLUSIONS:** This study suggests that persistent clinical and subclinical inflammation in patients with FMF causes an increase in cerebral blood flow velocities. Our findings provide an insight into this association between FMF and cerebrovascular diseases.

DOI: 10.5152/npa.2016.12396

PMCID: PMC5491658

PMID: 28680306

**Conflict of interest statement:** Conflict of Interest: No conflict of interest was declared by the authors.

705. Eur J Clin Invest. 2017 Sep;47(9):622-629. doi: 10.1111/eci.12783. Epub 2017 Aug 2.

A novel cluster of patients with Familial Mediterranean Fever (FMF) in southern Italy.

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**BACKGROUND:** Familial Mediterranean Fever (FMF) is an autosomal recessive autoinflammatory disorder characterised by recurrent attacks of fever and serositis (peritonitis, pleuritic or synovitis) affecting mainly populations of Mediterranean origin.

**AIM:** To describe a relatively new cluster of FMF subjects from Apulia and Basilicata regions (southern Italy).

**PATIENTS AND METHODS:** Subjects were screened for FMF using the Tel-Hashomer

criteria and genetic analysis. Demographic data were taken from patients' files and direct interviews. Patients were investigated about attack duration, intensity and site, body temperature, skin manifestations and overall quality of life before and after treatment with colchicine. Inflammatory parameters were also measured between these periods.

RESULTS: Forty-nine subjects had FMF (M : F = 26 : 23, age 38 years  $\pm$  2 SE) and followed-up up to 8 years. The age at disease onset was 22.1 years  $\pm$  1.2SE and the diagnostic delay was 15.5 years  $\pm$  1.9SE. The majority of patients (82%) suffered from abdominal pain, and 35% had undergone prior abdominal surgery or laparotomy. Severity score (ISSF) was mild in 43% of patients and intermediate in 57% of patients. Serum amyloid A (SAA) was increased in 20% of patients ( $16.9 \pm 3.7$ , normal range  $< 6.4$  mg/dL). In over 95% of patients, inflammation markers, duration and intensity of febrile painful attacks, quality of life and ISSF score improved dramatically following colchicine treatment.

CONCLUSION: The Apulia region represents a new endemic area for FMF. Clinical presentation of FMF can be misleading and requires a complete and early workup to recognise the disease and avoid unjustified surgery. Colchicine remains the gold standard therapy to prevent FMF attacks and fatal long-term complications.

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DOI: 10.1111/eci.12783

PMID: 28678379 [Indexed for MEDLINE]

706. Dtsch Med Wochenschr. 2017 Jul;142(13):969-978. doi: 10.1055/s-0043-103468. Epub 2017 Jul 3.

[Autoinflammatory Diseases as a Differential Diagnosis of Fever of Unknown Origin].

[Article in German]

Kümmerle-Deschner JB.

Fever is the most leading symptom of autoinflammatory diseases (AID). Therefore, AID have to be considered in differential diagnosis concerning fever of unknown origin. Unspecific Inflammatory manifestations may lead to misinterpretations that possibly cause irreversible organ damage. Effective treatment options are

available and imply profound diagnostics.

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DOI: 10.1055/s-0043-103468

PMID: 28672419 [Indexed for MEDLINE]

Conflict of interest statement: Interessenkonflikt: Jasmin Kümmerle-Deschner führte klinische Studien mit Novartis durch und erhielt Vortragshonorare von Novartis und SOBI.

707. J Allergy Clin Immunol. 2017 Dec;140(6):1545-1547. doi: 10.1016/j.jaci.2017.05.019. Epub 2017 Jun 28.

Autoinflammatory keratinization diseases.

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DOI: 10.1016/j.jaci.2017.05.019

PMID: 28668225

708. J Med Case Rep. 2017 Jul 2;11(1):178. doi: 10.1186/s13256-017-1317-0.

Serum cytokine profile in pediatric Sweet's syndrome: a case report.

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**BACKGROUND:** Sweet's syndrome is characterized by fever, leukocytosis, and tender erythematous papules or nodules. It is a rare condition, particularly in the pediatric population, and has recently been proposed to be an autoinflammatory disease that occurs due to innate immune system dysfunction, involving several cytokines, which causes abnormally increased inflammation. To the best of our knowledge, no report has documented the cytokine profile in a pediatric patient with Sweet's syndrome.

**CASE PRESENTATION:** A previously healthy 34-month-old Japanese girl was hospitalized because of remittent fever and pain in her right lower extremity with erythematous nodules. A skin biopsy of the eruption revealed dermal perivascular neutrophilic infiltration with no evidence of vasculitis, which led to the diagnosis of Sweet's syndrome. She was prescribed with orally administered prednisolone and a prompt response was observed; then, the prednisolone dose was tapered. During treatment she developed upper and lower urinary tract infections, after which her cutaneous symptoms failed to improve despite increasing the prednisolone dosage. To avoid long-term use of systemic corticosteroids, orally administered potassium iodide was initiated, but it was unsuccessful. However, orally administered colchicine along with prednisolone effectively ameliorated her symptoms, and prednisolone dosage was reduced again. We analyzed the circulating levels of interleukin-1 $\beta$ , interleukin-6, interleukin-18, neopterin, and soluble tumor necrosis factor receptors I and II, in order to clarify the pathogenesis of Sweet's syndrome. Of these cytokines, only interleukin-6 levels were elevated prior to orally administered prednisolone therapy. Following therapy, the elevated interleukin-6 levels gradually diminished to almost normal levels; interleukin-1 $\beta$  and interleukin-18 stayed within normal ranges throughout the treatment. Neopterin became marginally elevated after the start of treatment. Both soluble tumor necrosis factor receptor I and soluble tumor necrosis factor receptor II levels increased shortly after the onset of urinary tract infections.

**CONCLUSIONS:** This is the first case report of pediatric Sweet's syndrome in which serum cytokine levels were investigated. Future studies should gather more

evidence to elucidate the pathophysiology of Sweet's syndrome.

DOI: 10.1186/s13256-017-1317-0

PMCID: PMC5494139

PMID: 28668093 [Indexed for MEDLINE]

709. Front Med (Lausanne). 2017 Jun 12;4:78. doi: 10.3389/fmed.2017.00078. eCollection 2017.

## The Therapeutic Role of Interleukin-1 Inhibition in Idiopathic Recurrent Pericarditis: Current Evidence and Future Challenges.

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Recurrent pericarditis is a common complication of acute pericarditis (15-30%) for which, in most cases, no underlying etiology is found [idiopathic recurrent pericarditis (IRP)]. IRP is currently viewed as an autoinflammatory disease with characteristic recurrent episodes of sterile inflammation. According to the most recent Guidelines, the initial treatment regimen consists of a combination of aspirin or non-steroidal anti-inflammatory drugs with colchicine followed by the addition of corticosteroids in resistant or intolerant cases. Despite this treatment approach, a number of patients either do not respond or cannot tolerate the above therapies. For this refractory group, small case series and a recent randomized controlled trial have shown that interleukin-1 inhibition with anakinra is a rapidly acting, highly efficient, steroid-sparing, and safe therapeutic intervention. In this perspective, we discuss the available clinical evidence and our own clinical experience as well as the future prospects of this novel therapeutic approach for patients with IRP.

DOI: 10.3389/fmed.2017.00078

PMCID: PMC5466978

710. Front Pharmacol. 2017 Jun 13;8:369. doi: 10.3389/fphar.2017.00369. eCollection 2017.

Response to Interleukin-1 Inhibitors in 140 Italian Patients with Adult-Onset Still's Disease: A Multicentre Retrospective Observational Study.

Colafrancesco S(1), Priori R(1), Valesini G(1), Argolini L(2), Baldissera E(3), Bartoloni E(4), Cammelli D(5)(6), Canestrari G(7), Cantarini L(8), Cavallaro E(9), Cavalli G(3)(10), Cerrito L(11), Cipriani P(12), Dagna L(3)(10), Marchi G(9), Vita S(9), Emmi G(5), Ferraccioli G(7), Frassi M(13), Galeazzi M(8), Gerli R(4), Giacomelli R(12), Gremese E(7), Iannone F(14), Lapadula G(14), Lopalco G(14), Manna R(11), Mathieu A(15), Montecucco C(16), Mosca M(17), Piazza I(18), Piga M(15), Pontikaki I(2), Romano M(2), Rossi S(16), Rossini M(18), Ruscitti P(12), Silvestri E(5), Stagnaro C(17), Talarico R(17), Tincani A(13), Viapiana O(18), Vitiello G(6), Fabris F(19), Bindoli S(19), Punzi L(19), Galozzi P(19), Sfriso P(19).

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Background: Interleukin (IL)-1 plays a crucial role in the pathogenesis of Adult onset Still's disease (AOSD). Objectives: To evaluate the efficacy and safety of anakinra (ANA) and canakinumab (CAN) in a large group of AOSD patients. Methods: Data on clinical, serological features, and concomitant treatments were retrospectively collected at baseline and after 3, 6, and 12 months from AOSD patients (Yamaguchi criteria) referred by 18 Italian centers. Pouchot's score was used to evaluate disease severity. Results: One hundred forty patients were treated with ANA; 4 were subsequently switched to CAN after ANA failure. The systemic pattern of AOSD was identified in 104 (74.2%) of the ANA-treated and in 3 (75%) of the CAN-treated groups; the chronic-articular type of AOSD was identified in 48 (25.8%) of the ANA-treated and in 1 (25%) of the CAN-treated groups. Methotrexate (MTX) was the most frequent disease modifying anti-rheumatic drug (DMARD) used before beginning ANA or CAN [91/140 (75.8%), 2/4 (50%), respectively]. As a second-line biologic DMARD therapy in 29/140 (20.7%) of the patients, ANA was found effective in improving all clinical and serological manifestations ( $p < 0.0001$ ), and Pouchot's score was found to be significantly reduced at all time points ( $p < 0.0001$ ). No differences in treatment response were identified in the ANA-group when the patients were stratified according to age, sex, disease pattern or mono/combination therapy profile. ANA primary and secondary inefficacy at the 12-month time point was 15/140 (10.7%) and 11/140

(7.8%), respectively. Adverse events (AEs) [mainly represented by in situ (28/47, 59.5%) or diffuse (12/47, 25.5%) skin reactions and infections (7/47, 14.8%)] were the main causes for discontinuation. Pouchot's score and clinical and serological features were significantly ameliorated at all time points ( $p < 0.0001$ ) in the CAN-group, and no AEs were registered during CAN therapy. Treatment was suspended for loss of efficacy only in one case (1/4, 25%). Conclusion: This is the largest retrospective observational study evaluating the efficacy and safety of IL-1 inhibitors in AOSD patients. A good response was noted at 3 months after therapy onset in both the ANA- and CAN-groups. Skin reaction may nevertheless represent a non-negligible AE during ANA treatment.

DOI: 10.3389/fphar.2017.00369

PMCID: PMC5469286

PMID: 28659802

711. Cells. 2017 Jun 28;6(3). pii: E16. doi: 10.3390/cells6030016.

Assessing Autophagy in Mouse Models and Patients with Systemic Autoimmune Diseases.

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Autophagy is a tightly regulated mechanism that allows cells to renew themselves through the lysosomal degradation of proteins, which are misfolded or produced in excess, and of damaged organelles. In the context of immunity, recent research has specially attempted to clarify its roles in infection, inflammation and autoimmunity. Autophagy has emerged as a spotlight in several molecular pathways and trafficking events that participate to innate and adaptive immunity.

Deregulation of autophagy has been associated to several autoimmune diseases, in particular to systemic lupus erythematosus. Nowadays, however, experimental data on the implication of autophagy in animal models of autoimmunity or patients remain limited. In our investigations, we use Murphy Roths Large (MRL)/lymphoproliferation (lpr) lupus-prone mice as a mouse model for lupus and secondary Sjögren's syndrome, and, herein, we describe methods applied routinely to analyze different autophagic pathways in different lymphoid organs and tissues (spleen, lymph nodes, salivary glands). We also depict some techniques used to analyze autophagy in lupus patient's blood samples. These methods can be adapted to the analysis of autophagy in other mouse models of autoinflammatory diseases. The understanding of autophagy implication in autoimmune diseases could prove to be very useful for developing novel immunomodulatory strategies. Our attention should be focused on the fact that autophagy processes are interconnected and that distinct pathways can be independently hyper-activated or downregulated in distinct organs and tissues of the same individual.

DOI: 10.3390/cells6030016

PMCID: PMC5617962

PMID: 28657591

Conflict of interest statement: M.W. was supported in part by an ImmuPharma France doctoral fellowship; N.S. is a salaried employee of ImmuPharma France; and S.M. is consultant of ImmuPharma. The remaining authors declare no conflicting financial interests.

712. J Eur Acad Dermatol Venereol. 2018 Jan;32(1):e16-e17. doi: 10.1111/jdv.14432. Epub 2017 Jul 28.

A familial mediterranean fever flare induced by a drug reaction with eosinophilia

and systemic symptoms.

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DOI: 10.1111/jdv.14432

PMID: 28653374

713. Microbiome. 2017 Jun 23;5(1):63. doi: 10.1186/s40168-017-0278-2.

Aberrant intestinal microbiota due to IL-1 receptor antagonist deficiency promotes IL-17- and TLR4-dependent arthritis.

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**BACKGROUND:** Perturbation of commensal intestinal microbiota has been associated with several autoimmune diseases. Mice deficient in interleukin-1 receptor antagonist (Il1rn  $-/-$  mice) spontaneously develop autoimmune arthritis and are susceptible to other autoimmune diseases such as psoriasis, diabetes, and encephalomyelitis; however, the mechanisms of increased susceptibility to these autoimmune phenotypes are poorly understood. We investigated the role of interleukin-1 receptor antagonist (IL-1Ra) in regulation of commensal intestinal microbiota, and assessed the involvement of microbiota subsets and innate and adaptive mucosal immune responses that underlie the development of spontaneous arthritis in Il1rn  $-/-$  mice.

**RESULTS:** Using high-throughput 16S rRNA gene sequencing, we show that IL-1Ra critically maintains the diversity and regulates the composition of intestinal microbiota in mice. IL-1Ra deficiency reduced the intestinal microbial diversity and richness, and caused specific taxonomic alterations characterized by overrepresented *Helicobacter* and underrepresented *Ruminococcus* and *Prevotella*. Notably, the aberrant intestinal microbiota in Il1rn  $-/-$  mice specifically potentiated IL-17 production by intestinal lamina propria (LP) lymphocytes and skewed the LP T cell balance in favor of T helper 17 (Th17) cells, an effect transferable to WT mice by fecal microbiota. Importantly, LP Th17 cell expansion and the development of spontaneous autoimmune arthritis in Il1rn  $-/-$  mice were attenuated under germ-free condition. Selective antibiotic treatment revealed that tobramycin-induced alterations of commensal intestinal microbiota, i.e., reduced *Helicobacter*, *Flexispira*, *Clostridium*, and *Dehalobacterium*, suppressed arthritis in Il1rn  $-/-$  mice. The arthritis phenotype in Il1rn  $-/-$  mice was previously shown to depend on Toll-like receptor 4 (TLR4). Using the ablation of both IL-1Ra and TLR4, we here show that the aberrations in the Il1rn  $-/-$  microbiota are partly TLR4-dependent. We further identify a role for TLR4 activation in the intestinal lamina propria production of IL-17 and cytokines involved in Th17 differentiation preceding the onset of arthritis.

**CONCLUSIONS:** These findings identify a critical role for IL1Ra in maintaining the

natural diversity and composition of intestinal microbiota, and suggest a role for TLR4 in mucosal Th17 cell induction associated with the development of autoimmune disease in mice.

DOI: 10.1186/s40168-017-0278-2

PMCID: PMC5481968

PMID: 28645307 [Indexed for MEDLINE]

714. Front Pediatr. 2017 Jun 7;5:128. doi: 10.3389/fped.2017.00128. eCollection 2017.

Effects of Anakinra on Health-Related Quality of Life in a Patient with 1129G>A/928G>A Mutations in MVK Gene and Heterozygosity for the Mutation 2107C>A in CIAS1 Gene.

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Mevalonate kinase deficiency impairs several aspects of the patient's quality of life, thus early diagnosis and treatment are required to improve health-related quality of life (HRQOL). A 15-year-old patient with double heterozygosity for the mutations 1129G>A and 928G>A in MVK gene, heterozygosity for the mutation 2107C>A in CIAS1 gene and hyper-IgD syndrome phenotype, has been treated with anakinra with a reduction of 50% in the number of fever episodes per month, a reduction of 33% in the days of fever for each attack and normal blood tests in the intercritical phase. The RAND 36-Item Health Survey has been used for the assessment of HRQOL before and after the treatment with anakinra. The patient's quality of life showed an overall improvement of 27%; results showed a better improvement in role limitations due to physical health (50%).

DOI: 10.3389/fped.2017.00128

PMCID: PMC5461265

PMID: 28638818

715. Genomics Inform. 2017 Jun;15(2):65-68. doi: 10.5808/GI.2017.15.2.65. Epub 2017 Jun 15.

A Variant in RUNX3 Is Associated with the Risk of Ankylosing Spondylitis in Koreans.

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Ankylosing spondylitis (AS) is a chronic autoinflammatory disease that affects the spine and sacroiliac joints. Regarding its etiology, although HLA-B27 is known to be the strongest genetic factor of AS, much evidence suggests the potential contribution of non-MHC genes to the susceptibility to AS. Most of these non-MHC genes have been discovered in non-Asian populations; however, just some of them have been validated in Koreans. In this study, we aimed to identify additional AS-associated single-nucleotide polymorphism (SNP) candidates by replicating the candidate SNPs in Korean AS patients and healthy controls. For this, we selected three SNPs (rs11249215 in RUNX3, rs6556416 in IL12B, and rs8070463 in TBKBP1), which were previously reported as risk factors of AS but have not been studied in Koreans, and performed genotyping assays using a total of 1138 Korean samples (572 AS patients and 566 healthy controls). Of the three SNP candidates, one SNP in RUNX3 (rs11249215) was significantly associated with the risk of AS (odds ratio, 1.31; 95% confidence interval, 1.02 to 1.68,  $p = 0.03$ ). These results will be helpful in elucidating the pathogenesis of AS and may be useful for developing AS risk prediction models in Koreans.

DOI: 10.5808/GI.2017.15.2.65

PMCID: PMC5478709

PMID: 28638311

716. Curr Rheumatol Rep. 2017 Jul;19(7):41. doi: 10.1007/s11926-017-0670-8.

Autoinflammatory Diseases with Periodic Fevers.

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**PURPOSE OF REVIEW:** One purpose of this review was to raise awareness for the new autoinflammatory syndromes. These diseases are increasingly recognized and are in the differential diagnosis of many disease states. We also aimed to review the latest recommendations for the diagnosis, management, and treatment of these patients.

**RECENT FINDINGS:** Familial Mediterranean fever (FMF), cryopyrin-associated periodic syndrome (CAPS), tumor necrosis factor receptor-associated periodic fever syndrome (TRAPS), and hyperimmunoglobulinemia D and periodic fever syndrome/mevalonate kinase deficiency (HIDS/MVKD) are the more common autoinflammatory diseases that are characterized by periodic fevers and attacks of inflammation. Recently much collaborative work has been done to understand the characteristics of these patients and to develop recommendations to guide the physicians in the care of these patients. These recent recommendations will be summarized for all four diseases. FMF is the most common periodic fever disease. We need to further understand the pathogenesis and the role of single mutations in the disease. Recently, the management and treatment of the disease have been nicely reviewed. CAPS is another interesting disease associated with severe complications. Anti-interleukin-1 (anti-IL-1) treatment provides cure for these patients. TRAPS is characterized by the longest delay in diagnosis; thus, both pediatricians and internists should be aware of the characteristic features and the follow-up of these patients. HIDS/MVKD is another autoinflammatory diseases characterized with fever attacks. The spectrum of disease manifestation is rather large in this disease, and we need further research on biomarkers for the optimal

management of these patients.

DOI: 10.1007/s11926-017-0670-8

PMID: 28631068 [Indexed for MEDLINE]

717. J Orthop Case Rep. 2017 Jan-Feb;7(1):75-78. doi: 10.13107/jocr.2250-0685.69.

Chronic Recurrent Multifocal Osteomyelitis: A Case Report with Atypical Presentation.

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**INTRODUCTION:** Chronic recurrent multifocal osteomyelitis (CRMO) is a rare autoinflammatory condition. The clinical picture consists of sterile osteomyelitis, typically with multiple-site lesions in the metaphysis of long bones and not uncommonly, symmetrical bone involvement. It is a poorly understood entity, whose prognosis, etiology and ideal treatment are still controversial.

The authors report a case of unifocal presentation with an atypical location.

**CASE REPORT:** A previously healthy 12-year-old Caucasian girl came to our institution due to progressive pain on her left thigh for the previous 3 months. The initial X-ray showed a permeative, diaphyseal lesion of her left femur, with marked periosteal reaction. The differential initially included Ewing's sarcoma, osteosarcoma, subacute osteomyelitis, and Langerhans cell histiocytosis. Needle and open biopsies demonstrated the presence of chronic inflammatory infiltrate, with fibrosis, but no signs of neoplastic disease. Serologic and microbiological studies failed to demonstrate an infectious etiology. The patient was treated with nonsteroid anti-inflammatories, corticosteroids, and bisphosphonates for 6 months. Although no antibiotics were employed, the patient showed clinical and radiological improvement, at 18-month follow-up.

**CONCLUSIONS:** CRMO is a rare condition, and the absence of specific features constitutes a diagnostic challenge. A high level of suspicion is paramount to avoid unnecessary biopsies and repeated antibiotic regimens. Unifocal presentation of this disease, atypical locations, and absence of recurrence have all been previously reported, with the evidence pointing to a shared etiological

process with no distinction being made between these variants. For this reason, the authors believe that the term "nonbacterial osteomyelitis" might be a more all-embracing designation.

DOI: 10.13107/jocr.2250-0685.69

PMCID: PMC5458704

PMID: 28630846

Conflict of interest statement: Conflict of Interest: Nil

718. Clin Exp Rheumatol. 2017 Nov-Dec;35 Suppl 108(6):113-115. Epub 2017 Jun 19.

Haematological involvement associated with a mild autoinflammatory phenotype, in two patients carrying the E250K mutation of PSTPIP1.

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**OBJECTIVES:** Hyperzincaemia/hypercalprotectinemia (Hz/Hc) syndrome is a recently described condition caused by a specific de novo mutation (E250K) affecting PSTPIP1 gene. It has a phenotype distinct from classical pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome that includes severe systemic and cutaneous inflammation, hepatosplenomegaly, arthritis without sequelae, pancytopenia and failure to thrive.

**METHODS:** We describe an 8-year-old boy who presented recurrent right knee swelling mimicking septic arthritis and persistent bone marrow involvement, without cutaneous involvement.

**RESULTS:** Molecular analysis of the PSTPIP1 gene revealed the presence of a



heterozygous E250K mutation. No growth failure was detected nor in the patient neither in his mother, carrying the same variant. Blood zinc and calprotectin MRP8/14 concentrations of the patient were found to be markedly increased. Therapy with anakinra was started with rapid disappearance of clinical symptoms and normalization of CRP levels in 24 hours, but persistence of bone marrow involvement.

**CONCLUSIONS:** The patient described has a milder phenotype, with no skin features, minor episodes of arthritis with no sequelae and normal growth. Compared to the patients with de novo mutations described in the literature, familial cases seem to have a milder phenotype. Our case further confirms the lack of efficacy of anakinra on bone marrow involvement.

PMID: 28628471 [Indexed for MEDLINE]

719. Clin Rheumatol. 2017 Aug;36(8):1707-1713. doi: 10.1007/s10067-017-3715-5. Epub 2017 Jun 18.

Familial Mediterranean fever, review of the literature.

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Familial Mediterranean fever (FMF) is the most common monogenic periodic fever syndrome and characterized by recurrent episodes of fever, serositis, arthritis, dermal manifestations, and long-term renal complications. The MEFV gene was described in 1997 as the gene responsible for FMF and is inherited in autosomal recessive manner. It encodes mutated protein pyrin, an important player in the innate immune system and the component of inflammasome which leads to exaggerated inflammatory response through uncontrolled production of interleukin-1. The recent progress in molecular genetics and understanding of pathogenesis showed a more complicated picture of FMF inheritance, penetrance, and pathogenesis. The pathogenesis is not completely understood although the gene responsible for FMF has been identified. Whether the pyrin mutation effect in FMF is due to a loss of function or a gain of function is still controversial. The diagnosis is mainly

clinical and the genetic testing is indicated to support it. Colchicine remains the mainstay of treatment of FMF since 1972. It decreases the attacks, improves quality of life, and prevents amyloidosis. The recent advances in genetic testing and molecular studies has led to the development of new therapies of interleukin-1 inhibitors; anakinra, canakinumab, and rilonacept.

DOI: 10.1007/s10067-017-3715-5

PMID: 28624931 [Indexed for MEDLINE]

720. Intern Emerg Med. 2017 Oct;12(7):947-955. doi: 10.1007/s11739-017-1691-z. Epub 2017 Jun 15.

Quality of life impairment in Behçet's disease and relationship with disease activity: a prospective study.

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Our aim was to prospectively investigate the impact of Behçet's disease (BD), disease activity, and clinical and demographic characteristics on different aspects of quality of life (QoL) measured by the short-form (SF)-36 QoL scale. We administered the SF-36 to 37 consecutive BD patients in different moments of disease activity, and to 23 healthy controls (HC). The eight subcategories of the SF-36 underwent statistical analysis for identifying differences and correlations. Compared to HC, BD patients showed significantly lower mean scores in all SF-36 QoL subscales except mental health and role-emotional. Females showed a poorer QoL compared to males. Disease activity evaluated by the BD

Current Activity Form inversely correlated with physical functioning ( $\rho = -0.68$ ,  $p < 0.0001$ ), bodily pain ( $\rho = -0.68$ ,  $p < 0.0001$ ), role-physical ( $\rho = -0.64$ ,  $p < 0.0001$ ), vitality ( $\rho = -0.64$ ,  $p < 0.0001$ ), general health ( $\rho = -0.64$ ,  $p < 0.0001$ ), social functioning ( $\rho = -0.50$ ,  $p = 0.0002$ ), mental health ( $\rho = -0.48$ ,  $p = 0.0004$ ), and role-emotional ( $\rho = -0.40$ ,  $p = 0.003$ ). Mucosal, central nervous system (CNS), musculoskeletal and ocular manifestations were the main factors that negatively affected QoL in BD. For ocular disease, physical functioning was significantly impaired in patients with panuveitis compared to other ocular manifestations ( $p = 0.0002$ ). Best-corrected visual acuity was inversely correlated with social functioning ( $\rho = -0.53$ ,  $p < 0.0001$ ), role-physical ( $\rho = -0.48$ ,  $p < 0.0001$ ), bodily pain ( $\rho = -0.46$ ,  $p = 0.02$ ), and mental health ( $\rho = -0.43$ ,  $p < 0.0001$ ). Patients with BD have a poorer QoL compared to HC, particularly for women, while the decline of QoL is closely related to the overall disease activity of BD. Single organ involvements may affect independently specific SF-36 subscales, especially mucosal, CNS, musculoskeletal, and ocular manifestations.

DOI: 10.1007/s11739-017-1691-z

PMID: 28620840 [Indexed for MEDLINE]

721. *Physiol Rev.* 2017 Jul 1;97(3):1165-1209. doi: 10.1152/physrev.00026.2016.

Posttranslational Modification as a Critical Determinant of Cytoplasmic Innate Immune Recognition.

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Cell surface innate immune receptors can directly detect a variety of extracellular pathogens to which cytoplasmic innate immune sensors are rarely

exposed. Instead, within the cytoplasm, the environment is rife with cellular machinery and signaling pathways that are indirectly perturbed by pathogenic microbes to activate intracellular sensors, such as pyrin, NLRP1, NLRP3, or NLRC4. Therefore, subtle changes in key intracellular processes such as phosphorylation, ubiquitination, and other pathways leading to posttranslational protein modification are key determinants of innate immune recognition in the cytoplasm. This concept is critical to establish the "guard hypothesis" whereby otherwise homeostatic pathways that keep innate immune sensors at bay are released in response to alterations in their posttranslational modification status. Originally identified in plants, evidence that a similar guardlike mechanism exists in humans has recently been identified, whereby a mutation that prevents phosphorylation of the innate immune sensor pyrin triggers a dominantly inherited autoinflammatory disease. It is also noteworthy that even when a cytoplasmic innate immune sensor has a direct ligand, such as bacterial peptidoglycan (NOD1 or NOD2), RNA (RIG-I or MDA5), or DNA (cGAS or IFI16), it can still be influenced by posttranslational modification to dramatically alter its response. Therefore, due to their existence in the cytoplasmic milieu, posttranslational modification is a key determinant of intracellular innate immune receptor functionality.

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DOI: 10.1152/physrev.00026.2016

PMID: 28615462 [Indexed for MEDLINE]

722. Colchicine.

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In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2018-.  
2018 Oct 27.

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Colchicine is approved for gout prophylaxis and treatment of acute gouty flares.  
It is also approved for treatment of familial Mediterranean fever.[1][2]

PMID: 28613754

723. Rev Assoc Med Bras (1992). 2017 Apr;63(4):303-306. doi: 10.1590/1806-9282.63.04.303.

Chronic recurrent multifocal osteomyelitis exhibiting predominance of periosteal reaction.

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Chronic recurrent multifocal osteomyelitis is an idiopathic nonpyogenic autoinflammatory bone disorder involving multiple sites, with clinical progression persisting for more than 6 months and which may have episodes of remission and exacerbation in the long term. It represents up to 2-5% of the cases of osteomyelitis, with an approximate incidence of up to 4/1,000,000 individuals, and average age of disease onset estimated between 8-11 years, predominantly in females. The legs are the most affected, with a predilection for metaphyseal regions along the growth plate. We describe the case of a female patient, aged 2 years and 5 months, with involvement of the left ulna, right jaw and left tibia, showing a predominance of periosteal reaction as main finding.

DOI: 10.1590/1806-9282.63.04.303

PMID: 28614530 [Indexed for MEDLINE]

724. Case Rep Pathol. 2017;2017:9752908. doi: 10.1155/2017/9752908. Epub 2017 May 18.

Benign Multicystic Peritoneal Mesothelioma: A Rare Condition in an Uncommon Gender.

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Benign Multicystic Peritoneal Mesothelioma (BMPM) is a rare condition that arises from the abdominal peritoneum. Fewer than 200 cases have been reported worldwide. BMPM usually affects premenopausal women and is extremely rare in men. Many factors are suspected to contribute to its development, such as previous surgery, endometriosis, and familial Mediterranean fever. The main management is surgical resection; however, it is estimated that the recurrence rate is up to 50%. Malignant transformation is rare. We report a case series of three male patients who were diagnosed with BMPM and were treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC).

DOI: 10.1155/2017/9752908

PMCID: PMC5451755

PMID: 28607791

725. Curr Pharm Des. 2017;23(32):4893-4905. doi: 10.2174/1381612823666170613080919.

Targeting the Tumor Microenvironment by Intervention in Interleukin-1 Biology.

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The importance of anti-tumor immunity in the outcome of cancer is now unequivocally established and recent achievements in the field have stimulated the development of new immunotherapeutical approaches. In invasive tumors, widespread inflammation promotes invasiveness and concomitantly also inhibits anti-tumor immune responses. We suggest that efficient tumor treatment should target both

the malignant cells and the tumor microenvironment. Interleukin-1 (IL-1) is a pro-inflammatory as well as an immunostimulatory cytokine that is abundant in the tumor microenvironment. Manipulation of IL-1 can thus serve as an immunotherapeutical approach to reduce inflammation/immunosuppression and thus enhance anti-tumor immunity. The two major IL-1 agonistic molecules are IL-1 $\alpha$  and IL-1 $\beta$ , which bind to the same IL-1 signaling receptor and induce the same array of biological activities. The IL-1 receptor antagonist (IL-Ra) is a physiological inhibitor of IL-1 that binds to its receptor without transmission of activation signals and thus serves as a decoy target. We have demonstrated that IL-1 $\alpha$  and IL-1 $\beta$  are different in terms of the producing cells and their compartmentalization and the amount. IL-1 $\alpha$  is mainly expressed intracellularly, in the cytosol, in the nucleus or exposed on the cell membrane, however, it is rarely secreted. IL-1 $\beta$  is active only as a secreted molecule that is mainly produced by activated myeloid cells. We have shown different functions of IL-1 $\alpha$  and IL-1 $\beta$  in the malignant process. Thus, in its membrane-associated form, IL-1 $\alpha$  is mainly immunostimulatory, while IL-1 $\beta$  that is secreted into the tumor microenvironment is mainly pro-inflammatory and promotes tumorigenesis, tumor invasiveness and immunosuppression. These distinct functions of the IL-1 agonistic molecules are mainly manifested in early stages of tumor development and the patterns of their expression dictate the direction of the malignant process. Here, we suggest that IL-1 modulation can serve as an effective mean to tilt the balance between inflammation and immunity in tumor sites, towards the latter. Different agents that neutralize IL-1, mainly the IL-Ra and specific antibodies, exist. They are safe and FDA-approved. The IL-1Ra has been widely and successfully used in patients with Rheumatoid arthritis, autoinflammatory diseases and various other diseases that have an inflammatory component. Here, we provide the rationale and experimental evidence for the use of anti-IL-1 agents in cancer patients, following first line therapy to debulk the major tumor's mass. The considerations and constraints of using anti-IL-1 treatments in cancer are also discussed. We hope that this review will stimulate studies that will fasten the application of IL-1 neutralization at the bedside of cancer patients.

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DOI: 10.2174/1381612823666170613080919

PMID: 28606052

## Severity and frequency of restless legs syndrome in patients with familial Mediterranean fever.

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**OBJECTIVE:** Restless legs syndrome (RLS) is a common sensory motor disorder. RLS is an urge to move the extremities that may be accompanied by dysesthesias, and significantly affects quality of life of affected patients. The frequency of RLS is higher in different systemic inflammatory diseases. Familial Mediterranean fever (FMF) is an inherited inflammatory disease characterized by attacks of polyserositis, arthritis, and fever. The prevalence of RLS in patients with FMF is unknown. This study aimed to evaluate the prevalence rate of RLS in a sample of patients with FMF and compare this prevalence with that of a matched normal population.

**METHOD:** A total of 60 patients with FMF and 60 healthy controls were studied. All participants underwent a neurological examination. Diagnostic criteria as proposed by the International Restless Legs Syndrome Study Group (IRLSSG) were used to define RLS. The IRLSSG rating scale for the severity of RLS was applied to determine the severity of symptoms.

**RESULTS:** The prevalence of RLS was not significantly different between patients and controls. Although the mean International Restless Legs Syndrome Rating Scale (IRLSRS) scores tended to be higher in patients compared with controls, this difference was not significant. When each item of the severity scale was compared between the two groups, significantly higher scores were found in some items of the IRLSRS in patients with FMF compared with controls.

**CONCLUSION:** According to this result, RLS symptoms in patients with FMF were more frequent and lasted longer than those in controls.



PMID: 28606022 [Indexed for MEDLINE]

727. Curr Opin Rheumatol. 2017 Sep;29(5):506-515. doi: 10.1097/BOR.0000000000000422.

No shortcuts: new findings reinforce why nuance is the rule in genetic autoinflammatory syndromes.

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**PURPOSE OF REVIEW:** Practitioners dazed by the evolving concept of autoinflammation are in good company. Despite the clinical challenges autoinflammatory patients present, their study has been fundamental to our understanding of basic human inflammation. This review will focus on the ways in which recent discoveries in genetically mediated autoinflammation broaden and refine the concept.

**RECENT FINDINGS:** Major developments in pyrin inflammasome biology, defective ubiquitination, and the hyperferritinemic syndromes will be highlighted.

**SUMMARY:** We offer a brief discussion of discordance, convergence, genotype, and phenotype in autoinflammation. Additionally, we introduce the concepts of mutation dose effect and hybrid nomenclature. Overall, we hope to provide an update on developments in the field of autoinflammation, some conceptual tools to help navigate the rising tide of discovery, and some encouragement that keeping up with developments in autoinflammation is both exciting and necessary.

DOI: 10.1097/BOR.0000000000000422

PMID: 28604422 [Indexed for MEDLINE]

728. Clin Exp Rheumatol. 2017 Nov-Dec;35 Suppl 108(6):108-112. Epub 2017 Jun 9.

The liver in familial Mediterranean fever: is it involved?

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**OBJECTIVES:** Familial Mediterranean fever (FMF) is characterised by recurrent attacks of fever and serositis. It may affect the peritoneum, pleura, synovia and the skin. Usually the liver is intact in FMF. Recently, this concept was challenged by some groups which claimed that hepatitis is a feature of FMF and that non-alcoholic liver disease (NAFLD) and cryptogenic cirrhosis are more common among FMF patients. Scope of this paper is to critically review the relevant literature and to answer the question whether or not the liver is involved in FMF.

**METHODS:** We used Medline, Embase, Scopus and Web of Science database for searching articles dealing with FMF and the liver since 1960. We also reviewed some manuscripts which were not identified by the above searching engines.

**RESULTS:** Some cases reported that hepatitis is a feature of FMF based upon transaminase elevations without liver biopsy. Due to this questionable diagnosis and the paucity of similar reports, it seems that hepatitis is not a feature of FMF. Cryptogenic cirrhosis is considered as the end stage of NAFLD. Since NAFLD is prevalent in 25% of the general population it is more plausible to relate the occurrence of cryptogenic cirrhosis in FMF patients to NAFLD rather than to FMF. M694V mutation carriage was relatively more frequent among FMF patients with cryptogenic cirrhosis or "hepatitis".

**CONCLUSIONS:** The literature review indicates that FMF and liver disease are not generally associated. However, carriage of M694V mutations may play a role in the pathogenesis of liver disease.

PMID: 28598780 [Indexed for MEDLINE]

729. Clin Exp Rheumatol. 2017 Jul-Aug;35(4):623-629. Epub 2017 Jun 6.

What could we learn from the sub-analysis of a single nation cohort in a worldwide study? Lessons from the results observed in the Italian cohort of the GO-MORE trial.

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**OBJECTIVES:** GO-MORE Trial investigated the use of Golimumab (GLM) in 3280 rheumatoid arthritis (RA) patients worldwide. At present, the burden of arthritis is greater in poorer countries than in developed countries due to socioeconomic disparities, thus suggesting the usefulness of subgroup investigations. We aimed to evaluate GLM as add-on therapy for RA patients in the Italian cohort of GO-MORE trial and compared the clinical characteristics between Italian patients and the enrolled patients worldwide.

**METHODS:** Ninety-eight Italian patients with active RA, fulfilling the 1987 ACR criteria were enrolled. Statistical analyses were performed to assess: i. the differences in baseline characteristics; ii. the efficacy after 6 months; between Italian and Rest of the World GO-MORE populations.

**RESULTS:** Compared to the worldwide population, Italian patients showed a lower value of disease activity and a significantly short disease duration. Unlike the worldwide patients, the large majority of Italian patients received biologic therapy after the failure of the first synthetic DMARD and were not treated by high methotrexate dosage. After 6 months of GLM treatment, no differences were observed in the therapeutic response. Italian patients reported a positive autoinjection experience mirroring the worldwide results.

**CONCLUSIONS:** The analysis of the Italian GO-MORE subset confirms that differences among patients may be shown, depending on different approaches in different health systems. GLM in the Italian patients showed a favourable benefit/risk profile and the positive autoinjection experience may help with patient's

compliance and survival of the treatment.

PMID: 28598774 [Indexed for MEDLINE]

730. Clin Exp Rheumatol. 2017 May-Jun;35 Suppl 104(2):7. Epub 2017 May 29.

Are children with familial Mediterranean fever really vitamin D deficient?

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Comment on

Pediatr Rheumatol Online J. 2016 Apr 27;14 (1):28.

PMID: 28598319 [Indexed for MEDLINE]

731. Clin Genet. 2018 Jan;93(1):92-102. doi: 10.1111/cge.13070. Epub 2017 Sep 26.

Genetic epidemiology of familial Mediterranean fever through integrative analysis of whole genome and exome sequences from Middle East and North Africa.

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Familial Mediterranean fever (FMF), an autosomal recessive and rare autoinflammatory disease is caused by genetic mutations in the MEFV gene and is highly prevalent in the Mediterranean basin. Although the carrier frequency of specific disease variants in the MEFV gene has been reported from isolated studies, a comprehensive view of variants in the Mediterranean region has not been possible due to paucity of data. The recent availability of whole-genome and whole-exome datasets prompted us to study the genetic epidemiology of MEFV variants in the region. We assembled data from 5 datasets encompassing whole-genome and whole-exome datasets for 2115 individuals from multiple subpopulations in the region and also created a compendium for MEFV genetic variants, which were further systematically annotated as per the American College of Medical Genetics and Genomics (ACMG) guidelines. Our analysis points to significant differences in allele frequencies in the subpopulations, and the carrier frequency for MEFV genetic variants in the population to be about 8%. The MEFV gene appears to be under natural selection from our analysis. To the best of our knowledge, this is the most comprehensive study and analysis of population epidemiology of MEFV gene variants in the Middle East and North African populations.

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DOI: 10.1111/cge.13070

PMID: 28597968 [Indexed for MEDLINE]

732. Sci Rep. 2017 Jun 7;7(1):3018. doi: 10.1038/s41598-017-03251-5.

Enhancement of Th1/Th17 inflammation by TRIM21 in Behçet's disease.

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The etiology of Behçet's disease (BD), a chronic, multisystemic autoinflammatory and autoimmune disease, remains unknown; however, researchers have postulated that infectious agents, such as herpes simplex virus, are significant triggering factors of BD. Tripartite motif-containing (TRIM) proteins exhibit antiviral properties, mediating antiviral defense mechanisms. The purpose of this study was to investigate TRIM21 protein expression in the monocytes of BD patients and to identify the role of TRIM21 in immune dysregulation in BD. In this study, the expression of TRIM21 and related molecules, including interferon regulatory factor 8 (IRF8), was analyzed in monocytes from BD patients. Functional analyses using small interfering RNA and co-culture with responder T cells were performed to examine the pathological role of TRIM21 in BD. Peripheral blood monocytes from BD patients showed increased TRIM21 expression and decreased IRF8 expression compared with that in monocytes from healthy controls. TRIM21 was found to decrease IRF8 expression. BD monocytes facilitated Th1 and Th17 differentiation of co-cultured T cells, and knock-down of TRIM21 expression by small interfering RNA inhibited this differentiation. In conclusion, TRIM21 played a pivotal role in regulating the secretion of proinflammatory cytokines in monocytes of BD patients.

DOI: 10.1038/s41598-017-03251-5

PMCID: PMC5462739

PMID: 28592884

733. J Periodontal Res. 2017 Dec;52(6):994-1003. doi: 10.1111/jre.12467. Epub 2017 Jun 7.

R202Q/M694V as novel MEFV gene mutations in chronic periodontitis and familial Mediterranean fever.

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**BACKGROUND AND OBJECTIVE:** Familial Mediterranean fever (FMF) and chronic periodontitis are inflammatory diseases leading to an increase in the number of inflammasomes. To date, no published studies have reported on mutations in the Mediterranean fever (MEFV) gene in patients with chronic periodontitis, although the roles of MEFV gene mutations in FMF and FMF-associated amyloidosis (FMF-A) are well known. Therefore, the aim of this study was to evaluate the frequencies of MEFV gene mutations and serum amyloid A (SAA) and high-sensitivity C-reactive protein (hs-CRP) levels in patients with chronic periodontitis, FMF and FMF-A.

**MATERIAL AND METHODS:** The study population included 122 patients with FMF and 128 subjects who were systemically healthy. Clinical periodontal parameters, including the plaque index, gingival index, probing pocket depth, clinical attachment level and percentage of bleeding on probing were recorded. Blood samples were obtained from patients with FMF and systemically healthy controls, and all mutations located on exons 2 and 10 of the MEFV gene were analyzed by DNA Sanger Sequencing, which is the gold standard. SAA and high-sensitive CRP levels were also assessed.

**RESULTS:** Mean gingival index, percentage of bleeding on probing, probing pocket depth and clinical attachment level, and the levels of SAA and hs-CRP were higher in the FMF-A group than those in the FMF and control groups. The two most relevant mutations in patients with FMF were heterozygous M694V (46.2%), and heterozygous R202Q (32.7%). The frequencies of the homozygous M694V and R202Q mutations in the FMF-A group were 53.8% and 46.1%, respectively. The complex R202Q/M694V homozygous state led to an increased risk of chronic periodontitis (odds ratio: 3.6), and FMF-A (odds ratio: 7.6).

**CONCLUSION:** This is the first study to report the R202Q mutation in patients with periodontitis. Furthermore, the MEFV gene-mediated inflammatory pathway increased serum acute phase reactants, and the changes in the R202Q and M694V could play a role in inflammatory-genetic diseases, such as FMF, FMF-associated amyloidosis and chronic periodontitis.

DOI: 10.1111/jre.12467

PMID: 28590056 [Indexed for MEDLINE]

734. Z Rheumatol. 2018 Feb;77(1):28-39. doi: 10.1007/s00393-017-0330-4.

[Safety and efficacy of off-label use of biologic therapies in patients with inflammatory rheumatic diseases refractory to standard of care therapy : Data from a nationwide German registry (GRAID2)].

[Article in German]

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**BACKGROUND:** The German Registry of Autoimmune Diseases 2 (GRAID2) is a retrospective, non-interventional, multicenter registry study collecting data from patients with inflammatory, mainly rheumatic diseases refractory to standard of care therapy and treated with an off-label biologic therapy. The retrospective documentation comprised case history, diagnosis, course of disease (including safety and global efficacy). The objective was to evaluate the global clinical outcome and safety of off-label biologic therapy in clinical practice.

**RESULTS:** Data from 311 patients with an overall observation period of 338.5 patient-years were collected. The mean patients age was 47.8 years with 56.9% females. The most frequently documented diagnoses comprised rejection prophylaxis/therapy after renal transplantation (NTX, 18.3%), ANCA-vasculitides

(17.4%), systemic lupus erythematosus (SLE, 10.3%), autoinflammatory fever syndromes (8.4%), autoimmune myositis (7.4%) and pemphigus (5.8%). Documented biologic therapies included rituximab (RTX, 70.1%), tocilizumab (TCZ, 9.3%), infliximab (IFX, 7.1%), anakinra (ANK, 5.5%), adalimumab (ADA, 3.5%), etanercept (ETA, 2.3%) and certolizumab (CTZ, 0.6%). After initiation of off-label biologic treatment, tolerability was assessed by the physicians as "very good"/"good" in 95.5%. Altogether, 275 adverse events were documented and of these, 104 were classified as serious adverse events and occurred in 62 patients. In 19 of these patients severe infections (30.6%) were documented, resulting in a rate of 5.6 severe infections per 100 patient years. A total of six deaths were documented, while five of these cases were rated as not related to the biologics treatment. Notably, the use of RTX in patients with small vessel vasculitides and of TCZ in patients with large vessel vasculitides prior to their approval support their relevance in clinical management of patients with severe diseases.

**CONCLUSION:** The results of this registry together with data of GRAID1 provide evidence that use of off-label biologic therapies in patients with inflammatory rheumatic diseases refractory to conventional treatment did not result in any new safety signal already known for these compounds or subsequently shown by clinical trials in certain entities.

DOI: 10.1007/s00393-017-0330-4

PMID: 28589389

735. Z Rheumatol. 2018 Feb;77(1):46-54. doi: 10.1007/s00393-017-0329-x.

[Efficacy and safety analysis of off-label treatment with biologics in autoinflammatory diseases : Experiences from a German registry (GRAID2)].

[Article in German]

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**OBJECTIVE:** To evaluate the safety and efficacy of therapy with biologics in patients with autoinflammatory diseases (AIF) or macrophage activating syndrome (MAS) in a real-life setting in Germany.

**METHODS:** The German Register of Autoimmune Diseases 2 (GRAID2) is a retrospective, non-interventional, multicenter registry collecting data from all patients with inflammatory rheumatic diseases refractory to conventional therapy and treated with initial off-label biologics between August 2006 and December 2013. Patients with MAS could be included without prior treatment with a biologic agent.

**RESULTS:** Data from 26 patients with AIF and 5 with MAS were collected. Of the AIF patients 13 (50%) were diagnosed with adult onset Still's disease (AOSD), 6 (23%) with familial Mediterranean fever (FMF), 4 (15.4%) with tumor necrosis factor-associated periodic syndrome (TRAPS), 1 (3.8%) patient with cryopyrin-associated periodic syndrome (CAPS) and 2 (8%) with undifferentiated fever syndromes. The 5 MAS patients suffered from rheumatoid arthritis (RA) with chronic myeloid leukemia, systemic lupus erythematosus and in 2 cases AOSD. In 1 patient a chronic neurological disease was documented without further differentiation. All patients with TRAPS were primarily treated with etanercept and all CAPS patients with canakinumab. The AOSD and FMF patients were treated with anakinra as the first line off-label biologic in 6 out of 13 and 5 out of 6 cases, respectively. The MAS patients responded very well or well to therapy in 40% and 60% had a moderate response. There were no non-responders. Within the group of AIF patients the physicians documented a very effective or effective treatment in 38.5%, a moderate response in 30.8% and no response in 30.7%. The tolerance was very good in 5 out of 5 of the MAS and in 92% of the AIF patients.

**CONCLUSION:** The data of this retrospective register provide indications for an effective and safe treatment with off-label biologic medication in patients with AIF and MAS in daily practice.

DOI: 10.1007/s00393-017-0329-x

PMID: 28589388

736. Clin Case Rep. 2017 Apr 18;5(6):833-840. doi: 10.1002/ccr3.904. eCollection 2017 Jun.

Coupling clinical exome sequencing with functional characterization studies to diagnose a patient with familial Mediterranean fever and MED13L haploinsufficiency syndromes.

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Clinicians should consider that clinical exome sequencing provides the unique potential to disentangle complex phenotypes into multiple genetic etiologies. Further, functional studies on variants of uncertain significance are necessary to arrive at an accurate diagnosis for the patient.

DOI: 10.1002/ccr3.904

PMCID: PMC5458005

PMID: 28588821

737. Front Pharmacol. 2017 May 23;8:293. doi: 10.3389/fphar.2017.00293. eCollection 2017.

## A Brief History of IL-1 and IL-1 Ra in Rheumatology.

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The history of what, in 1979, was called interleukin-1 (IL-1), orchestrator of leukocyte inter-communication, began many years before then, initially by the observation of fever induction via the endogenous pyrogen (EP) (1974) and then in rheumatology on the role in tissue destruction in rheumatoid diseases via the induction of collagenase and PGE2 in human synovial cells by a mononuclear cell factor (MCF) (1977). Since then, the family has exploded to presently 11 members as well as many membrane-bound and soluble receptor forms. The discovery of a natural Interleukin-1 receptor antagonist (IL-1Ra) in human biological fluids has highlighted the importance of IL-1 and IL-1Ra in human diseases. Evidence delineating its role in autoinflammatory syndromes and the elucidation of the macromolecular complex referred to as "inflammasome" have been instrumental to our understanding of the link with IL-1. At present, the IL-1blockade as therapeutic approach is crucial for many hereditary autoinflammatory diseases, as well as for adult-onset Still's disease, crystal-induced arthropathies, certain skin diseases including neutrophil-triggered skin diseases, Behçet's disease and deficiency of IL-1Ra and other rare fever syndromes. Its role is only marginally important in rheumatoid arthritis and is still under debate with regard to osteoarthritis, type 2 diabetes mellitus, cardiovascular diseases and cancer. This brief historical review focuses on some aspects of IL-1, mainly IL-1 $\beta$  and IL-1Ra, in rheumatology. There are many excellent reviews focusing on the IL-1 family in general or with regard to specific diseases or biological discoveries.

DOI: 10.3389/fphar.2017.00293

PMCID: PMC5440542

PMID: 28588495

738. Front Pharmacol. 2017 May 22;8:278. doi: 10.3389/fphar.2017.00278. eCollection 2017.

## Potential of IL-1, IL-18 and Inflammasome Inhibition for the Treatment of Inflammatory Skin Diseases.

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In 2002, intracellular protein complexes known as the inflammasomes were discovered and were shown to have a crucial role in the sensing of intracellular pathogen- and danger-associated molecular patterns (PAMPs and DAMPs). Activation of the inflammasomes results in the processing and subsequent secretion of the pro-inflammatory cytokines IL-1 $\beta$  and IL-18. Several autoinflammatory disorders such as cryopyrin-associated periodic syndromes and Familial Mediterranean Fever have been associated with mutations of genes encoding inflammasome components. Moreover, the importance of IL-1 has been reported for an increasing number of autoinflammatory skin diseases including but not limited to deficiency of IL-1 receptor antagonist, mevalonate kinase deficiency and PAPA syndrome. Recent findings have revealed that excessive IL-1 release induced by harmful stimuli likely contributes to the pathogenesis of common dermatological diseases such as acne vulgaris or seborrheic dermatitis. A key pathogenic feature of these diseases is IL-1 $\beta$ -induced neutrophil recruitment to the skin. IL-1 $\beta$  blockade may therefore represent a promising therapeutic approach. Several case reports and clinical trials have demonstrated the efficacy of IL-1 inhibition in the treatment of these skin disorders. Next to the recombinant IL-1 receptor antagonist (IL-1Ra) Anakinra and the soluble decoy Rilonacept, the anti-IL-1 $\alpha$  monoclonal antibody MABp1 and anti-IL-1 $\beta$  Canakinumab but also Gevokizumab, LY2189102 and P2D7KK, offer valid alternatives to target IL-1. Although less thoroughly investigated, an involvement of IL-18 in the development of cutaneous inflammatory disorders is also suspected. The present review describes the role of IL-1 in diseases with skin involvement and gives an overview of the relevant studies discussing the therapeutic potential of modulating the secretion and activity of IL-1 and IL-18 in such diseases.

DOI: 10.3389/fphar.2017.00278

PMCID: PMC5438978

PMID: 28588486

739. Expert Rev Clin Pharmacol. 2017 Aug;10(8):855-864. doi: 10.1080/17512433.2017.1338946. Epub 2017 Jun 20.

Pharmacological treatment options for cryopyrin-associated periodic syndromes.

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**INTRODUCTION:** Cryopyrin-associated periodic syndromes (CAPS) are rare monogenic autoinflammatory diseases, comprising a spectrum of phenotypes of varying severity. CAPS are associated with gain-of-function mutations in the NLRP3 inflammasome, a multiprotein complex critical for the activation of IL-1 $\beta$ , and are characterized by episodes of fever, urticaria-like rash, musculoskeletal, ocular, and neurological symptoms. Areas covered: Accounting for the pivotal role of IL-1 $\beta$  in the pathogenesis of CAPS, three therapeutic options, all blocking the action of IL-1 $\beta$ , are currently approved: anakinra, a recombinant IL-1 receptor antagonist, the IL-1 trap rilonacept and canakinumab, a monoclonal anti-IL-1 $\beta$  antibody. All agents reduce or even resolve clinical symptoms, biochemical activity markers and improve quality of life in CAPS. This review also covers pharmacokinetic, pharmacodynamic and safety aspects of the approved drugs and the potential utility of IL-1 $\beta$  blockers in a wide range of other conditions with an autoinflammatory component. Expert commentary: Due to the success story of current pharmaceuticals, the therapeutic options in CAPS are not expected to expand in the near future. Prospective observational studies are needed to confirm long-term efficacy and sustained benefit. New IL-1 $\beta$  blockers will likely address unmet clinical needs in other autoinflammatory conditions.

DOI: 10.1080/17512433.2017.1338946

PMID: 28586272 [Indexed for MEDLINE]

740. J Pak Med Assoc. 2017 Jun;67(6):945-947.

Canakinumab treatment in four children with colchicine resistant familial mediterranean fever.

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Familial Mediterranean Fever (FMF) is an autosomal recessive and autoinflammatory disease, characterized with inflammation of serous membranes such as peritoneum, pleura, synovium with fever and pain. Colchicine is the main treatment of FMF, but 5-10 % of patients are unresponsive to colchicine. We report using anti-interleukin-1 agents anakinra and canakinumab in four colchicine-resistant patients who were successfully treated. Three of the patients were siblings.

PMID: 28585601

741. J Biol Chem. 2017 Jul 28;292(30):12691-12701. doi: 10.1074/jbc.M116.769695. Epub 2017 Jun 5.

NLRC3 protein inhibits inflammation by disrupting NALP3 inflammasome assembly via competition with the adaptor protein ASC for pro-caspase-1 binding.

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Inflammasomes are multiprotein complexes that sense pathogen-associated and danger-associated molecular patterns and induce inflammation in cells. The NALP3



inflammasome is tightly regulated by recently discovered control mechanisms, but other modulators still remain to be characterized. NLR family CARD-containing 3 (NLRC3) protein, a caspase recruitment domain (CARD)-containing member of the nucleotide oligomerization domain-like receptor (NLR) family, was found to down-regulate the NF- $\kappa$ B pathway and stimulator of interferon genes (STING)-dependent cytokine secretion. However, the effect of NLRC3 on the NALP3 inflammasome or other inflammasomes is still unknown. We hypothesized that NLRC3 might inhibit NALP3 inflammasome complex assembly. Toward this end, we tested whether NLRC3 overexpression or knockdown influences NALP3 activity in human monocyte and HEK293FT cells when the complex is ectopically reconstituted. We found that NLRC3 indeed decreases NALP3-induced IL-1 $\beta$  maturation and secretion, pro-caspase-1 cleavage, and speck formation by apoptosis-associated speck-like protein containing a CARD (ASC) protein in response to NALP3 activators. We also show that endogenous NLRC3 interacts with both ASC and pro-caspase-1 but not with NALP3, disrupts ASC speck formation through its CARD, and impairs the ASC and pro-caspase-1 interaction. Moreover, the NLRC3 CARD alone could dampen IL-1 $\beta$  secretion and ASC speck formation induced by NALP3 mutants associated with autoinflammatory diseases. In conclusion, we show here that, besides its role in the inhibition of the NF- $\kappa$ B pathway, NLRC3 interferes with the assembly and activity of the NALP3 inflammasome complex by competing with ASC for pro-caspase-1 binding.

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DOI: 10.1074/jbc.M116.769695

PMCID: PMC5535042

PMID: 28584053 [Indexed for MEDLINE]

742. Gastroenterology. 2017 Jul;153(1):19-20. doi: 10.1053/j.gastro.2017.01.020. Epub 2017 Jun 2.

Febrile Attacks With a Refractory Colonic Lesion.

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DOI: 10.1053/j.gastro.2017.01.020  
PMID: 28583842 [Indexed for MEDLINE]

743. Reumatol Clin. 2017 Jun 2. pii: S1699-258X(17)30099-2. doi: 10.1016/j.reuma.2017.04.008. [Epub ahead of print]

Periodic fever: From Still's disease to Muckle-Wells syndrome.

[Article in English, Spanish]

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Muckle-Wells syndrome is a systemic autoinflammatory disease included in the group of hereditary periodic febrile syndromes. We report the case of a patient with this rare disease to call the attention to the singularity of this condition, its low incidence, its atypical presentation and the subsequent delay in the diagnosis, which is reached when late and devastating consequences have taken place. In this case, the first-line therapy, anti-interleukin 1 (IL-1), failed to control the disease. Nevertheless, the IL-6 inhibitor, tocilizumab, proved effective, achieving the total remission of nephrotic syndrome associated with AA secondary amyloidosis, changing the bleak prognosis of this disease.

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DOI: 10.1016/j.reuma.2017.04.008  
PMID: 28583784

744. Int J Neurosci. 2018 Jan;128(1):10-14. doi: 10.1080/00207454.2017.1338697. Epub 2017 Jun 22.

Does familial Mediterranean fever affect cognitive function in children?  
Electrophysiological preliminary study.

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**OBJECTIVES:** Familial Mediterranean fever (FMF) is a periodic autoinflammatory disease with subclinical inflammation occurring between attacks. The aim of the study was to prospectively evaluate the cognitive function of children diagnosed with FMF that were under colchicine therapy and compare them with healthy controls through electrophysiologically event-related potentials (ERPs) study.

**METHODS:** Twelve children with FMF and 12 healthy controls were included in the study. During the electroencephalography recordings, all participants were instructed to discriminate rare stimuli (target stimuli) from frequent stimuli (standard stimuli) by pressing a button on a mouse immediately following the target stimulus. P300, the cognitive component of ERP, was obtained in response to target stimuli and its amplitude and latency were measured.

**RESULTS:** The amplitude of the P300 of the FMF patients was higher and the latencies of the P300 of the FMF patients were shorter than the amplitudes and latencies of control patients, respectively. The difference between the groups was statistically significant for amplitude but not for latency.

**CONCLUSIONS:** Cognitive processing reflecting allocation of attention and visual processing speed seems not to be negatively affected in FMF patients with homozygous M694V mutations undergoing colchicine treatment. As this study is unique in its evaluation of the cognitive function of children with FMF, these

findings may be helpful for counseling families and patients affected by the condition.

DOI: 10.1080/00207454.2017.1338697

PMID: 28581880 [Indexed for MEDLINE]

745. Nat Commun. 2017 Jun 5;8:15677. doi: 10.1038/ncomms15677.

Ndfip1 restricts mTORC1 signalling and glycolysis in regulatory T cells to prevent autoinflammatory disease.

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Foxp3<sup>+</sup> T regulatory (Treg) cells suppress immune cell activation and establish normal immune homeostasis. How Treg cells maintain their identity is not completely understood. Here we show that Ndfip1, a coactivator of Nedd4-family E3 ubiquitin ligases, is required for Treg cell stability and function. Ndfip1 deletion in Treg cells results in autoinflammatory disease. Ndfip1-deficient Treg cells are highly proliferative and are more likely to lose Foxp3 expression to become IL-4-producing TH2 effector cells. Proteomic analyses indicate altered metabolic signature of Ndfip1-deficient Treg cells and metabolic profiling reveals elevated glycolysis and increased mTORC1 signalling. Ndfip1 restricts Treg cell metabolism and IL-4 production via distinct mechanisms, as IL-4 deficiency does not prevent hyperproliferation or elevated mTORC1 signalling in Ndfip1-deficient Treg cells. Thus, Ndfip1 preserves Treg lineage stability and

immune homeostasis by preventing the expansion of highly proliferative and metabolically active Treg cells and by preventing pathological secretion of IL-4 from Treg cells.

DOI: 10.1038/ncomms15677

PMCID: PMC5465375

PMID: 28580955 [Indexed for MEDLINE]

746. Clin Rev Allergy Immunol. 2018 Jun;54(3):454-479. doi: 10.1007/s12016-017-8613-8.

Geoepidemiology and Immunologic Features of Autoinflammatory Diseases: a Comprehensive Review.

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The knowledge on systemic autoinflammatory disorders (SAID) is expanding rapidly and new signalling pathways are being decrypted. The concept of autoinflammation has been proposed since 1999, to define a group of diseases with abnormal innate immunity activation. Since then, more than 30 monogenic SAID have been described. In this review, we first describe inflammasomopathies and SAID related to the interleukin-1 pathway. Recent insights into the pathogenesis of familial Mediterranean fever and the function of Pyrin are detailed. In addition, complex

or polygenic SAID, such as Still's disease or PFAPA syndrome, are also discussed. Then, major players driving autoinflammation, such as type-1 interferonopathies (including the recently described haploinsufficiency in A20 and otulipenia), TNF-associated periodic syndromes, defects in ubiquitination, and SAID with overlapping features of autoimmunity or immunodeficiency. Discoveries of the pathogenic role of mosaicism, intronic defects coupled to the likelihood to identify digenic or polygenic diseases are providing new challenges for physicians and geneticists. This comprehensive review depicts the various SAID, presenting them according to their predominant pathophysiological mechanism, with a particular emphasis on recent findings. Epidemiologic data are also presented. Finally, we propose a practical diagnostic approach to the most common monogenic SAID, based on the most characteristic clinical presentation of these disorders.

DOI: 10.1007/s12016-017-8613-8

PMID: 28578473 [Indexed for MEDLINE]

747. Arthritis Rheumatol. 2017 Sep;69(9):1914. doi: 10.1002/art.40167. Epub 2017 Jul 21.

Important Issues Concerning the Double-Blind Study of Anakinra in Familial Mediterranean Fever: Comment on the Article by Ben-Zvi et al.

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DOI: 10.1002/art.40167

PMID: 28575543

748. Clin Rheumatol. 2017 Nov;36(11):2589-2594. doi: 10.1007/s10067-017-3701-y. Epub 2017 Jun 1.

Frequency of familial Mediterranean fever (MEFV) gene mutations in patients with biopsy-proven primary glomerulonephritis.

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Primary glomerulopathies are those disorders that affect glomerular structure, function, or both in the absence of a multisystem disorder. We aimed to evaluate the frequency of MEFV gene mutation to show possible coexistence of FMF in patients diagnosed with biopsy-proven primary glomerulonephritis (GN). A total of 64 patients with biopsy-proven primary GN were included in the study. MEFV gene mutations examined retrospectively. The mean age of patients was  $39.6 \pm 13.4$  (range 18-69), 35 of patients were female and 29 of patients were male. Of the 64 patients, 17 were mesangial proliferative glomerulonephritis (MsPGN), 15 were IgA nephropathy (IgAN), 12 were membranous glomerulonephritis (MGN), 11 were focal segmental glomerulosclerosis (FSGS), three were membranous proliferative glomerulonephritis (MPGN), three were immune complex glomerulonephritis (ICGN), two were minimal change disease (MCD), and one was IgM nephropathy (IgMN). MEFV gene mutation was detected in 35.9% (23) of these patients. The most frequently detected mutations were E148Q and M694V. Twelve cases (18.75% of GN patients) with MEFV gene mutation were diagnosed as FMF phenotype I. The frequency of MEFV gene mutation was detected at a high rate of 35.9%. Further studies with larger populations are needed to clarify the importance of these mutations on clinical progression of glomerulonephritis.

DOI: 10.1007/s10067-017-3701-y

PMID: 28573371 [Indexed for MEDLINE]

Myocarditis in auto-immune or auto-inflammatory diseases.

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Myocarditis is a major cause of heart disease in young patients and a common precursor of heart failure due to dilated cardiomyopathy. Some auto-immune and/or auto-inflammatory diseases may be accompanied by myocarditis, such as sarcoidosis, Behçet's disease, eosinophilic granulomatosis with polyangiitis, myositis, and systemic lupus erythematosus. However, data concerning myocarditis in such auto-immune and/or auto-inflammatory diseases are sparse. New therapeutic strategies should better target the modulation of the immune system, depending on the phase of the disease and the type of underlying auto-immune and/or auto-inflammatory disease.

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DOI: 10.1016/j.autrev.2017.05.021

PMID: 28572050 [Indexed for MEDLINE]

750. Int J Rheum Dis. 2018 Oct;21(10):1849-1856. doi: 10.1111/1756-185X.13104. Epub 2017 May 31.

Incidence of sleep disturbances in patients with familial Mediterranean fever and the relation of sleep quality with disease activity.



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**AIM:** To evaluate the sleep quality and the relation of sleep quality with depression, anxiety, fatigue and disease activity in adult patients with familial Mediterranean fever (FMF).

**METHOD:** One hundred and seventy-four FMF patients and 84 age-sex matched healthy individuals were included in this study. The Pittsburgh Sleep Quality Index (PSQI), Multidimensional Assessment of Fatigue (MAF) and the Hospital Anxiety and Depression Index (HADS) were used to assess sleep quality, fatigue, depression and anxiety, respectively.

**RESULT:** FMF patients had significantly higher depression, anxiety, fatigue and PSQI scores than healthy controls. As the severity of the disease increased, scores of total PSQI and its domains increased. Patients with total PSQI score higher than 5 had statistically significantly higher erythrocyte sedimentation rates (ESR), serum C-reactive protein and serum amyloid levels during attacks, more attack numbers in last 3 months and worse fatigue, depression scores. Total PSQI score was positively correlated with inflammatory markers during attacks, attack numbers in the last 3 months and fatigue score. Logistic regression models identified disease duration, ESR during attacks, fatigue, attack numbers in the last 3 months as predictors of poor sleep quality.

**CONCLUSION:** Poor sleep quality is common in adult FMF patients. Anxiety, depression and fatigue are more frequent in FMF patients than healthy

individuals. Poor sleep quality is associated with inflammatory marker levels during attacks, fatigue and attack numbers in the last 3 months.

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DOI: 10.1111/1756-185X.13104

PMID: 28560764

751. Orphanet J Rare Dis. 2017 May 30;12(1):105. doi: 10.1186/s13023-017-0642-0.

Tocilizumab in the treatment of twelve cases with aa amyloidosis secondary to familial mediterranean fever.

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**BACKGROUND:** There is no established treatment of AA amyloidosis, a long-term complication of various chronic inflammatory diseases associated with increased mortality, such as familial Mediterranean fever (FMF). Recently there are few reports pointing out that tocilizumab(TCZ), an anti IL-6 agent may be effective in AA amyloidosis resistant to conventional treatments. We report our data on the effect of TCZ in patients with FMF complicated with AA amyloidosis.

**METHODS:** FMF patients with histologically proven AA amyloidosis, treated with TCZ (8 mg/kg per month) were followed monthly and the changes in creatinine, creatinine clearance, the amount of 24-hour urinary protein, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were noted throughout the treatment period. Adverse effects of the treatment were closely monitored.

**RESULTS:** TCZ was given to 12 patients (6 F, 6 M) who also continued to receive colchicine ( $1.9 \pm 0.4$  mg/day). Coexisting diseases were ankylosing spondylitis(4) and Crohn's disease(1). The mean age was  $35.2 \pm 10.0$  years and the mean follow-up on TCZ was  $17.5 \pm 14.7$  months. The renal functions remained stable (mean creatinine from  $1.1 \pm 0.9$  mg/dl to  $1.0 \pm 0.6$  mg/dl), while a significant decrease

in acute phase response (the mean CRP from  $18.1 \pm 19.5$  mg/L to  $5.8 \pm 7.1$  mg/L and ESR from  $48.7 \pm 31.0$  mm/h to  $28.7 \pm 28.3$  mm/h) was observed and the mean 24-hour urinary protein excretion reduced from  $6537.6 \pm 6526.0$  mg/dl to  $4745.5 \pm 5462.7$  mg/dl. Two patients whose renal functions were impaired prior to TCZ therapy improved significantly on this regimen. No infusion reaction was observed. None of the patients experienced any FMF attack under TCZ treatment with the exception of 2, one of whom had less frequent attacks while the other had episodes of erysipelas-like erythema. CONCLUSION: Tocilizumab improved the acute phase response and the renal function in this group of patients and was generally well tolerated. Besides improving the renal function TCZ seemed to control the recurrence of FMF attacks too. Further studies are warranted to test the efficacy and safety of TCZ in AA amyloidosis secondary to FMF as well as other inflammatory conditions.

DOI: 10.1186/s13023-017-0642-0

PMCID: PMC5450086

PMID: 28558744 [Indexed for MEDLINE]

752. Curr Opin Rheumatol. 2017 Sep;29(5):493-499. doi: 10.1097/BOR.0000000000000418.

Unraveling the pathogenesis of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis through genetic, immunologic, and microbiologic discoveries: an update.

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PURPOSE OF REVIEW: Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is considered the most common periodic fever syndrome of childhood. Although it was first described three decades ago, the pathogenesis has been poorly understood. Recent studies on the heritability and immunology of the disorder have begun to shed light into the mechanisms of this autoinflammatory disorder. This review will focus on the pathogenesis of PFAPA,

especially as it pertains to the genetic susceptibility, tonsillar immunology, and the role of the microbiome.

RECENT FINDINGS: Recent literature provides insights into the heritability, potential genetic modifiers, and the immunologic and microbiological profile of the tonsils in this syndrome.

SUMMARY: Evidence is mounting that PFAPA is inherited as a complex genetic disease. Furthermore, tonsillectomy is curative in the majority of patients, including those who do not meet the complete clinical criteria for PFAPA. The tonsils in PFAPA patients may exhibit unique immunologic and microbiological features. The goal of this review is to outline these new developments.

DOI: 10.1097/BOR.0000000000000418

PMID: 28557837 [Indexed for MEDLINE]

753. J Ocul Pharmacol Ther. 2017 Sep;33(7):549-555. doi: 10.1089/jop.2017.0034. Epub 2017 May 30.

Systemic Steroid Sparing Effect of Intravitreal Dexamethasone Implant in Chronic Noninfectious Uveitic Macular Edema.

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**PURPOSE:** To evaluate the effectiveness and the systemic corticosteroid sparing effect of a single intravitreal dexamethasone (DEX) implant in patients with chronic noninfectious uveitic macular edema (UME).

**METHODS:** Data from 22 eyes treated with DEX implant for UME related to systemic or ocular-confined noninfectious diseases were retrospectively analyzed.

**RESULTS:** The mean systemic prednisone (or equivalent) dosage significantly decreased at 3- and 6-month follow-up evaluations compared to baseline ( $P = 0.002$  and  $P = 0.01$ , respectively). Compared to baseline, central macular thickness values significantly decreased at 1-, 3-, and 6-month evaluations after the implantation ( $P < 0.0001$ ). The mean best corrected visual acuity (BCVA) value gradually improved at 1-, 3-, and 6-month visits compared to baseline ( $P = 0.009$ ,  $P = 0.0004$ , and  $P = 0.0001$ , respectively). At fluorescein angiography, active retinal vasculitis was identified in 11 (50%) eyes at baseline, 3 (13.6%) eyes at 1- and 3-month follow-up, and in 2 (9.1%) eyes at the last visit. Regarding side effects, 3/22 (13.6%) eyes presented a newly recognized intraocular hypertension at 1-month follow-up; however, intraocular pressure reverted to normal values within the 6-month follow-up in all cases.

**CONCLUSIONS:** Treatment with intravitreal DEX implant in noninfectious uveitis allowed a significant corticosteroid sparing effect, a significant improvement in BCVA, and a prompt resolution of UME and vasculitis. No safety issues were observed.

DOI: 10.1089/jop.2017.0034

PMID: 28557602 [Indexed for MEDLINE]

754. J Autoimmun. 2017 Aug;82:47-61. doi: 10.1016/j.jaut.2017.05.003. Epub 2017 May 24.

The molecular signature of murine T cell homeostatic proliferation reveals both inflammatory and immune inhibition patterns.

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T lymphocyte homeostatic proliferation, driven by the engagement of T cell antigen receptor with self-peptide/major histocompatibility complexes, and signaling through the common  $\gamma$ -chain-containing cytokine receptors, is critical for the maintenance of the T cell compartment and is regulated by the Fas death receptor (Fas, CD95). In the absence of Fas, Fas-deficient lymphoproliferation spontaneous mutation (lpr) mice accumulate homeostatically expanded T cells. The functional consequences of sequential rounds of homeostatic expansion are not well defined. We thus examined the gene expression profiles of murine wild-type and Fas-deficient lpr CD8<sup>+</sup> T cell subsets that have undergone different amounts of homeostatic proliferation as defined by their level of CD44 expression, and the CD4-CD8-TCR $\alpha\beta$ <sup>+</sup> T cell subset that results from extensive homeostatic expansion of CD8<sup>+</sup> T cells. Our studies show that recurrent T cell homeostatic proliferation results in global gene expression changes, including the progressive upregulation of both cytolytic proteins such as Fas-Ligand and granzyme B as well as inhibitory proteins such as programmed cell death protein 1 (PD-1) and lymphocyte activating 3 (Lag3). These findings provide an explanation for how augmented T cell homeostatic expansion could lead to the frequently observed clinical paradox of simultaneous autoinflammatory and immunodeficiency syndromes and provide further insight into the regulatory programs that control chronically stimulated T cells.

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DOI: 10.1016/j.jaut.2017.05.003

PMCID: PMC5902411

PMID: 28551033 [Indexed for MEDLINE]

755. J Clin Lab Anal. 2018 Feb;32(2). doi: 10.1002/jcla.22259. Epub 2017 May 22.

MTHFR gene C677T and A1298C variants are associated with FMF risk in a Turkish

cohort.

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**BACKGROUND:** Methylenetetrahydrofolate reductase (MTHFR) is a crucial enzyme in homocysteine (Hcy) metabolism. We aimed to evaluate a possible relationship between MTHFR gene C677T (rs 1801133), A1298C (rs 1801131) variants and susceptibility to FMF in a Turkish cohort.

**MATERIAL-METHODS:** This case-control study included 198 Turkish FMF patients and 100 healthy subjects as controls. MTHFR C677T and A1298C were analyzed by polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) methods.

**RESULTS:** The genotype distribution and allele frequency of the MTHFR C677T were statistically different between the patients and the control group ( $P=.006$ ,  $P=.001$ , respectively). The frequency of the TT genotype and T allele of MTHFR C677T was significantly higher in the patients than in the controls. The genotype distribution of MTHFR A1298C variant did not show any statistically significant difference between the patients and the controls ( $P>.05$ ). The patients had statistically different frequencies in allele C of MTHFR A1298C variant compared with the control ( $P=.032$ ). We also examined the risk associated with inheriting the combined genotypes for the two MTHFR variants. According to these results, individuals who were CC homozygous at C677T locus and AA homozygous at A1298C locus have a lower risk of developing FMF ( $P=.002$ ). Individuals who were TT homozygous at C677T locus and AC heterozygous at A1298C locus have higher risk of developing FMF ( $P=.033$ ).

**CONCLUSION:** Our findings clearly showed there was an association the MTHFR C677T/A1298C variants and susceptibility to FMF in the Turkish sample.

DOI: 10.1002/jcla.22259

PMID: 28543752 [Indexed for MEDLINE]

756. Immunology. 2017 Oct;152(2):243-254. doi: 10.1111/imm.12761. Epub 2017 Jun 19.

CD40-mediated signalling influences trafficking, T-cell receptor expression, and T-cell pathogenesis, in the NOD model of type 1 diabetes.

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CD40 plays a critical role in the pathogenesis of type 1 diabetes (T1D). The mechanism of action, however, is undetermined, probably because CD40 expression has been grossly underestimated. CD40 is expressed on numerous cell types that now include T cells and pancreatic  $\beta$  cells. CD40<sup>+</sup> CD4<sup>+</sup> cells [T helper type 40 (TH40)] prove highly pathogenic in NOD mice and in translational human T1D studies. We generated BDC2.5.CD40<sup>-/-</sup> and re-derived NOD.CD154<sup>-/-</sup> mice to better understand the CD40 mechanism of action. Fully functional CD40 expression is required not only for T1D development but also for insulinitis. In NOD mice, TH40 cell expansion in pancreatic lymph nodes occurs before insulinitis and demonstrates an activated phenotype compared with conventional CD4<sup>+</sup> cells, apparently regardless of antigen specificity. TH40 T-cell receptor (TCR) usage demonstrates increases in several V $\alpha$  and V $\beta$  species, particularly V $\alpha$ 3.2<sup>+</sup> that arise early and are sustained throughout disease development. TH40 cells isolated from diabetic pancreas demonstrate a relatively broad TCR repertoire rather than restricted clonal expansions. The expansion of the V $\alpha$ /V $\beta$  species associated with diabetes depends upon CD40 signalling; NOD.CD154<sup>-/-</sup> mice do not expand the same TCR species. Finally, CD40-mediated signals significantly increase pro-inflammatory Th1- and Th17-associated cytokines whereas CD28 co-stimulus alternatively promotes regulatory cytokines.



DOI: 10.1111/imm.12761

PMCID: PMC5588813

PMID: 28542921 [Indexed for MEDLINE]

757. Reumatologia. 2017;55(2):94-99. doi: 10.5114/reum.2017.67605. Epub 2017 Apr 28.

The human body as an energetic hybrid? New perspectives for chronic disease treatment?

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Inflammatory response is accompanied by changes in cellular energy metabolism. Proinflammatory mediators like plasma C-reactive protein, IL-6, plasminogen activator inhibitor-1, TNF- $\alpha$  or monocyte chemoattractant protein-1 released in the site of inflammation activates immune cells and increase energy consumption. Increased demand for energy creates local hypoxia and lead in consequence to mitochondrial dysfunction. Metabolism of cells is switched to anaerobic glycolysis. Mitochondria continuously generate free radicals that what result in imbalance that causes oxidative stress, which results in oxidative damage. Chronic energy imbalance promotes oxidative stress, aging, and neurodegeneration and is associated with numerous disorders like Alzheimer's disease, multiple sclerosis, Parkinson's disease or Huntington's disease. It is also believed that oxidative stress and the formation of free radicals play an important role in the pathogenesis of rheumatoid diseases including especially rheumatoid arthritis. Pharmacological control of energy metabolism disturbances may be valuable therapeutic strategy of treatment of this disorders. In recent review we sum up knowledge related to energy disturbances and discuss phenomena such as zombies or hibernation which may indicate the potential targets for regulation of energy metabolism.

DOI: 10.5114/reum.2017.67605

PMCID: PMC5442301

PMID: 28539682

Conflict of interest statement: The authors declare no conflict of interest.

758. Nihon Rinsho Meneki Gakkai Kaishi. 2017;40(1):21-27. doi: 10.2177/jsci.40.21.

A retrospective analysis of 7 cases of familial mediterranean fever.

[Article in Japanese]

Ogita C(1), Matsui K(1), Kisida D(2), Yazaki M(2), Nakamura A(2), Kaku S(1), Makino H(1), Tadokoro R(1), Azuma K(1), Tsuboi K(1), Tani M(1), Tamura M(1), Yoshikawa T(1), Morimoto M(1), Nishioka A(1), Sekiguchi M(1), Azuma N(1), Kitano M(1), Tsunoda S(3), Sawai H(3), Sano H(1).

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**BACKGROUND:** Familial mediterranean fever (FMF) is a single inherited autoinflammatory disease characterized by periodic fever with relatively short duration of 1 to 3 days and sterile serositis. Although the prevalence rate is highest in the Mediterranean coastal area, a large number of cases have been reported recently by genetic analysis by identification of MEFV (Mediterranean fever) which is responsible gene in Japan too. In outpatient department of rheumatology, diagnosis and treatment of FMF is performed in cases where fever and abdominal pain attack are repeated for a short period of time.

**PATIENTS AND METHODS:** We examined cases in which symptoms considered periodic seizures were repeated, excluding autoimmune diseases, infectious diseases, and malignant tumors. In both cases, genetic analysis is performed as auxiliary diagnosis.

RESULTS: Seven cases satisfied the Tel-Hashomer criteria criteria and MEFV gene mutation was detected. Everyone was a female, and half had seizure symptoms at menstruation. Even though there is a difference in the amount of colchicine to be used, either one is effective.

CONCLUSION: In cases of periodic symptoms or cases called periodic fever, exclusion diagnosis is carried out, there is a need to suspect FMF, determine the effect of colchicine, and perform genetic analysis.

DOI: 10.2177/jsci.40.21

PMID: 28539550 [Indexed for MEDLINE]

759. Semin Cutan Med Surg. 2017 Jun;36(2):55-57. doi: 10.12788/j.sder.2017.018.

Comorbidities of hidradenitis suppurativa.

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Hidradenitis suppurativa (HS) is an inflammatory skin disorder with many associated comorbidities, including obesity, metabolic syndrome, smoking, depression, arthritis, autoinflammatory syndromes, inflammatory bowel disease, and genetic syndromes. In addition, HS patients can suffer from a variety of diseases related to the chronic inflammatory nature of their HS such as cardiovascular disease and anemia. An understanding of these comorbidities and associations is essential for the management of HS, and routine screening for these entities should be considered in all HS patients.

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DOI: 10.12788/j.sder.2017.018

PMID: 28538744 [Indexed for MEDLINE]

760. Clin Rheumatol. 2017 Jul;36(7):1687-1690. doi: 10.1007/s10067-017-3688-4. Epub 2017 May 23.

Efficacy and safety of anakinra in tumor necrosis factor receptor-associated periodic syndrome (TRAPS) complicated by severe renal failure: a report after long-term follow-up and review of the literature.

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Tumor necrosis factor receptor-associated periodic syndrome (TRAPS), caused by mutations in the TNFRSF1A gene, is the most frequent autosomal dominant autoinflammatory disease displaying a relevant risk of reactive AA amyloidosis, if left untreated. Our report deals with one adult with TRAPS complicated by amyloidosis-related renal failure, treated with the recombinant human interleukin-1 receptor antagonist anakinra at a higher than conventional dosage. This treatment did not present any adverse event and led remarkably to the disappearance of all TRAPS-related manifestations and prompt decrease of laboratory abnormalities, including proteinuria. A review of the medical literature has been also considered to evaluate efficacy and safety of interleukin-1 inhibition in patients with TRAPS.

DOI: 10.1007/s10067-017-3688-4

PMID: 28536823 [Indexed for MEDLINE]

761. J Neural Transm (Vienna). 2018 May;125(5):781-795. doi: 10.1007/s00702-017-1732-9. Epub 2017 May 22.

The IL-1 $\beta$  phenomena in neuroinflammatory diseases.

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It is becoming increasingly clear that neuroinflammation has a causal role in the pathogenesis of central nervous system (CNS)-related diseases, and therefore therapeutic strategies targeting the regulation or availability of inflammatory mediators can be used to prevent or mitigate pathology. Interestingly, the proinflammatory cytokine, interleukin-1 beta (IL-1 $\beta$ ), has been implicated in perpetuating immune responses and contributing to disease severity in a variety of CNS diseases ranging from multiple sclerosis, neurodegenerative diseases, traumatic brain injury, and diabetic retinopathy. Moreover, pharmacological blockade of IL-1 signaling has shown to be beneficial in some autoimmune and autoinflammatory diseases, making IL-1 $\beta$  a promising therapeutic target in neuroinflammatory conditions. This review highlights recent advances of our understanding on the multifaceted roles of IL-1 $\beta$  in neuroinflammatory diseases.

DOI: 10.1007/s00702-017-1732-9

PMCID: PMC5699978 [Available on 2019-05-01]

PMID: 28534174

762. F1000Res. 2017 Mar 23;6:310. doi: 10.12688/f1000research.11025.1. eCollection 2017.

Case Report: Behçet's disease accompanied with vitiligo.

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Recently, a few case reports and clinical studies have been published that explore the association of Behçet's Disease (BD) and vitiligo, with conflicting results. Genetic and immunological properties of BD and presence of autoantibodies support autoimmunity, but clinical features suggest autoinflammatory diseases. BD is thought to be a cornerstone between autoimmune and autoinflammatory diseases. On the other hand, vitiligo has been accepted as an autoimmune disease with associations of other autoimmune disorders and there is a possible role of autoimmunity in pathogenesis of the disease. Significant advances have been made understanding the pathogenesis and genetics of BD. However, it is worth presenting rare clinical variants for improving the clinical understanding of BD. Herein, we are presenting a case with diagnosis of both Behçet's disease and vitiligo in same patient, which is a rare occurrence. Discussion and demonstrating the association of these two diseases may give rise to understanding similar and different aspects of autoimmunity and autoinflammatory pathogenesis of both diseases.

DOI: 10.12688/f1000research.11025.1

PMCID: PMC5428486

PMID: 28529705

Conflict of interest statement: Competing interests: No competing interests were disclosed.

763. Clin Rheumatol. 2017 Jul;36(7):1459-1469. doi: 10.1007/s10067-017-3672-z. Epub 2017 May 20.

IL-6 blockade in the management of non-infectious uveitis.

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Several pathogenetic studies have paved the way for a newer more rational therapeutic approach to non-infectious uveitis, and treatment of different forms of immune-driven uveitis has drastically evolved in recent years after the advent of biotechnological drugs. Tumor necrosis factor- $\alpha$  targeted therapies, the first-line recommended biologics in uveitis, have certainly led to remarkable results in patients with non-infectious uveitis. Nevertheless, the decision-making process turns out to be extremely difficult in anti-tumor necrosis factor or multidrug-resistant cases. Interleukin (IL)-6 holds a critical role in the pathogenic pathways of uveitis, due to its extended and protean range of effects. On this background, manipulation of IL-6 inflammatory cascade has unraveled encouraging outcomes. For instance, rising evidence has been achieved regarding the successful use of tocilizumab, the humanized monoclonal antibody targeted against the IL-6 receptor, in treating uveitis related to juvenile idiopathic arthritis or Behçet's disease. Similar findings have also been reported for uveitis associated with systemic disorders, such as rheumatoid arthritis or multicentric Castleman disease, but also for idiopathic uveitis, the rare birdshot chorioretinopathy, and even in cases complicated by macular edema. This work provides a digest of all current experiences and evidences concerning IL-6 blockade, as suggested by the medical literature, proving its potential role in the management of non-infectious uveitis.

DOI: 10.1007/s10067-017-3672-z  
PMID: 28528519 [Indexed for MEDLINE]

764. Curr Cardiol Rep. 2017 Jul;19(7):60. doi: 10.1007/s11886-017-0866-6.

New Insights into Pericarditis: Mechanisms of Injury and Therapeutic Targets.

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**PURPOSE OF REVIEW:** This review article aims to provide a contemporary insight into the pathophysiological mechanisms of and therapeutic targets for pericarditis, drawing distinction between autoinflammatory and autoimmune pericarditis.

**RECENT FINDINGS:** Recent research has focused on the distinction between autoinflammatory and autoimmune pericarditis. In autoinflammatory pericarditis, viruses can activate the sensor molecule of the inflammasome, which results in downstream release of cytokines, such as interleukin-1, that recruit neutrophils and macrophages to the site of injury. Conversely, in autoimmune pericarditis, a type I interferon signature predominates, and pericardial manifestations coincide with the severity of the underlying systemic autoimmune disease. In addition, autoimmune pericarditis can also develop after cardiac injury syndromes. With either type of pericarditis, imaging can help stage the inflammatory state.

Prominent pericardial delayed hyperenhancement on magnetic resonance imaging suggests ongoing inflammation whereas calcium on computed tomography suggests a completed inflammatory cascade. In patients with ongoing pericarditis, treatments that converge on the inflammasome, such as colchicine and anakinra, have proved effective in recurrent autoinflammatory pericarditis, though further clinical trials with anakinra are warranted. An improved understanding of the pathophysiological mechanisms of pericarditis helps unravel effective therapeutic targets for this condition.



DOI: 10.1007/s11886-017-0866-6

PMID: 28528454 [Indexed for MEDLINE]

765. Clin Exp Immunol. 2017 Sep;189(3):383-391. doi: 10.1111/cei.12989. Epub 2017 Jun 23.

T helper type 1-related molecules as well as interleukin-15 are hyperexpressed in the skin lesions of patients with pyoderma gangrenosum.

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Pyoderma gangrenosum (PG) is a rare, immune-mediated skin disease classified into the group of neutrophilic dermatoses. Although a number of studies confirmed the central role of innate immunity, only few studies have investigated the possible contributing role of acquired immunity. In particular, no reports concerning T helper type 1 (Th1) and Th2 cells are available as yet. Therefore, 15 patients with PG, five with Sweet's syndrome (SS) and nine skin specimens from healthy controls (HC) were investigated, evaluating the expression of Th1-related markers interleukin (IL)-12, interferon (IFN)- $\gamma$ , C-X-C motif chemokine receptor 3 (CXCR3) and C-C motif chemokine receptor 5 (CCR5), of the Th2-related molecules IL-4, IL-5, IL-13 and CCR3, of the co-stimulatory axis CD40/CD40 ligand, of IL-15 and the natural killer (NK) cell marker CD56 in skin lesions by immunohistochemistry. Patients with PG and SS showed a higher expression of Th1 markers than HC. Conversely, IL-5- and CCR3-expressing cells were less numerous in PG skin lesions compared to SS ( $P = 0.0157$  and  $< 0.0001$ , respectively). Both CD40 and CD40L were expressed more in PG than in SS and HC ( $P < 0.0001$  for both). Finally, the number of IL-15+ and CD56+ cells was higher in the skin of patients with PG than in those of SS and HC ( $P < 0.0001$  for both). Our results suggest that Th2 cells are down-regulated in PG. At the same time, over-expression of the co-stimulatory

axis CD40/CD40L amplifies the impairment of the Th1/Th2 balance. Both these findings might explain the most aggressive behaviour of PG in comparison to SS. Moreover, over-expression of IL-15+ and CD56+ cells may suggest a possible role of NK cells in the pathogenesis of the disease.

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DOI: 10.1111/cei.12989

PMCID: PMC5543499

PMID: 28518224 [Indexed for MEDLINE]

766. Rheumatol Int. 2018 Jan;38(1):129-136. doi: 10.1007/s00296-017-3740-3. Epub 2017 May 17.

Clinical, imaging and genotypical features of three deceased and five surviving cases with ADA2 deficiency.

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Deficiency of adenosine deaminase type 2 (DADA2) is a rare form of autoinflammatory disorder with limited reported cases. In this paper, we have presented the clinico-immunological, radiological and genetic characteristics of five surviving and three deceased childhood-onset DADA2 patients. We aimed to compare surviving and deceased patients in terms of clinical features and treatment modalities. Moreover, we have evaluated the causes of death in our DADA2 subjects together with the previously reported cases. Demographic features, clinical characteristics, imaging findings, mutations and pharmacological

treatments of DADA2 subjects were noted from patient records of pediatric and adult rheumatology clinics in a retrospective and longitudinal nature. Eight patients from seven families were enrolled. While five of them were surviving, three of them had died due to various reasons. Median age of the patients at disease onset and diagnosis was 7 years (range 0.5-13 years) and 14 years (range 5-27 years), respectively. The main clinical manifestations were cutaneous findings (7/8), recurrent low-grade fever (6/8), neurological involvement (6/8) and gastrointestinal involvement (5/8). All patients had increased acute phase reactants at presentation and also during the disease flares. Until the diagnosis of DADA2 was confirmed, five patients have been followed-up with the diagnosis of PAN: two patients both with PAN and FMF, and one patient with CAPS and vasculitis. Demographic, clinical, neurological features and genetic mutations did not differ in surviving and deceased DADA2 patients. Deceased and surviving subjects differed in terms of treatment modalities after the diagnosis of DADA2. Anti-TNF alpha treatment has been initiated in five surviving patients as soon as the diagnosis of DADA2 was established. However, three patients who have died were not able to use sufficient doses of anti-TNF alpha treatment; in one case due to reluctance of patient and in two cases due to establishment of the definite diagnosis by genetic analysis at the same time with the last fatal DADA2 episode. Despite limited number of patients, this case series for the first time compares the phenotypic, genotypic and medication differences between surviving and deceased DADA2 patients. Anti-TNF alpha treatment seems to be efficient and lifesaving in DADA2 patients.

DOI: 10.1007/s00296-017-3740-3

PMID: 28516235 [Indexed for MEDLINE]

767. CEN Case Rep. 2016 May;5(1):43-47. doi: 10.1007/s13730-015-0188-8. Epub 2015 Jul 20.

Familial Mediterranean Fever developing in a Japanese kidney transplant recipient.

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Familial Mediterranean Fever (FMF) is an auto-inflammatory disease characterized by periodic febrile episodes and sterile polyserositis and is extremely rare in Asian populations. Here, we report a case of FMF in a 61-year-old Japanese man who received a kidney transplant 31 years ago but had to re-start hemodialysis. Although kidney function had been stable since his initial transplant, serum creatinine levels had been increasing over the 2 years prior to his presentation at our hospital, and a periodic fever developed at the same time. Uremic symptoms were observed, and hemodialysis was re-started, prompting the patient to choose to undergo a second kidney transplantation. We re-checked his medical history and conducted further physical examinations. Given that the patient had previously undergone an operation for olecranon bursitis in which pericardial effusion had been identified, we considered the possibility of FMF and conducted a genetic test, which identified the E202Q heterozygous mutation in the MEFV gene. The patient was therefore diagnosed with variant FMF. To our knowledge, this is the first report of a Japanese kidney transplant recipient being diagnosed as an FMF variant. We describe the relationship of FMF and kidney transplantation in terms of prognosis and important points to note for treatment.

DOI: 10.1007/s13730-015-0188-8

PMCID: PMC5411659

PMID: 28509164

768. J Rheumatol. 2017 Aug;44(8):1142-1150. doi: 10.3899/jrheum.161354. Epub 2017 May 15.

Elevated Expression of the NLRP3 Inflammasome and Its Correlation with Disease Activity in Adult-onset Still Disease.

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**OBJECTIVE:** The dysregulation of the NLRP3 (NLR containing a pyrin domain) inflammasome is involved in autoinflammatory diseases. Adult-onset Still disease (AOSD) is regarded as an autoinflammatory disease. However, the pathogenic involvement of NLRP3 inflammasome in AOSD remains unclear and NLRP3 activators in AOSD are currently unknown.

**METHODS:** The mRNA expression of NLRP3 inflammasome signaling in peripheral blood mononuclear cells (PBMC) from 34 patients with AOSD and 14 healthy subjects was determined using quantitative-PCR (qPCR). The changes in mRNA and protein levels of NLRP3 inflammasome signaling in PBMC treated with the potential activator

[imiquimod (IMQ)] or inhibitor of NLRP3 were evaluated using qPCR and immunoblotting, respectively. The supernatant levels of interleukin (IL)-1 $\beta$  and IL-18 were determined by ELISA.

**RESULTS:** Significantly higher mRNA levels of NLRP3 inflammasome signaling were observed in patients with AOSD compared with healthy controls. NLRP3 expressions were positively correlated with disease activity in patients with AOSD. IMQ (an effective Toll-like receptor 7 ligand; 10  $\mu$ g/ml and 25  $\mu$ g/ml) stimulation of PBMC from patients with AOSD induced dose-dependent increases of mRNA expression of NLRP3 (mean  $\pm$  standard error of the mean,  $2.06 \pm 0.46$  and  $6.05 \pm 1.84$ , respectively), caspase-1 ( $1.81 \pm 0.23$  and  $4.25 \pm 0.48$ ), IL-1 $\beta$  ( $5.68 \pm 1.51$  and  $12.13 \pm 3.71$ ), and IL-18 ( $2.32 \pm 0.37$  and  $4.81 \pm 0.51$ ) compared with controls (all  $p < 0.005$ ). IMQ stimulation of PBMC from patients similarly induced greater increases in protein expressions of NLRP3 inflammasome compared with controls. The protein expressions of NLRP3, IL-1 $\beta$ , and IL-18 on PBMC significantly decreased after treatment with NLRP3 inhibitor in patients with AOSD.

**CONCLUSION:** Increased expression of NLRP3 inflammasome and its positive correlation with disease activity in AOSD suggest its involvement in disease pathogenesis. IMQ upregulated expressions of NLRP3 inflammasome signaling, and IMQ might be an activator of NLRP3 inflammasome in AOSD.

DOI: 10.3899/jrheum.161354

PMID: 28507179 [Indexed for MEDLINE]

769. J Clin Immunol. 2017 Jul;37(5):445-451. doi: 10.1007/s10875-017-0399-1. Epub 2017 May 15.

Deficiency of Interleukin-1 Receptor Antagonist (DIRA): Report of the First Indian Patient and a Novel Deletion Affecting IL1RN.

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**PURPOSE:** Deficiency of interleukin-1 receptor antagonist (DIRA) is a rare life-threatening autoinflammatory disease caused by autosomal recessive mutations in IL1RN. DIRA presents clinically with early onset generalized pustulosis, multifocal osteomyelitis, and elevation of acute phase reactants. We evaluated and treated an antibiotic-unresponsive patient with presumed DIRA with recombinant IL-1Ra (anakinra). The patient developed anaphylaxis to anakinra and was subsequently desensitized.

**METHODS:** Genetic analysis of IL1RN was undertaken and treatment with anakinra was initiated.

**RESULTS:** A 5-month-old Indian girl born to healthy non-consanguineous parents presented at the third week of life with irritability, sterile multifocal osteomyelitis including ribs and clavicles, a mild pustular rash, and elevated acute phase reactants. SNP array of the patient's genomic DNA revealed a previously unrecognized homozygous deletion of approximately 22.5 Kb. PCR and Sanger sequencing of the borders of the deleted area allowed identification of the breakpoints of the deletion, thus confirming a homozygous 22,216 bp deletion that spans the first four exons of IL1RN. Due to a clinical suspicion of DIRA, anakinra was initiated which resulted in an anaphylactic reaction that triggered desensitization with subsequent marked and sustained clinical and laboratory improvement.

**CONCLUSION:** We report a novel DIRA-causing homozygous deletion affecting IL1RN in an Indian patient. The mutation likely is a founder mutation; the design of breakpoint-specific primers will enable genetic screening in Indian patients suspected of DIRA. The patient developed anaphylaxis to anakinra, was desensitized, and is in clinical remission on continued treatment.

DOI: [10.1007/s10875-017-0399-1](https://doi.org/10.1007/s10875-017-0399-1)

PMID: 28503715 [Indexed for MEDLINE]



770. J Invest Dermatol. 2017 Sep;137(9):2019-2021. doi: 10.1016/j.jid.2017.04.024. Epub 2017 May 10.

Hidradenitis Suppurativa Is Associated with Familial Mediterranean Fever-A Population-Based Study.

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DOI: 10.1016/j.jid.2017.04.024

PMID: 28499757 [Indexed for MEDLINE]

771. Paediatr Drugs. 2017 Aug;19(4):303-311. doi: 10.1007/s40272-017-0232-6.

Monogenic Periodic Fever Syndromes: Treatment Options for the Pediatric Patient.

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Autoinflammatory diseases are disorders of the innate immune system characterized

by uncontrolled inflammation. The most commonly encountered autoinflammatory diseases are the hereditary periodic fever syndromes, which present with fever and other features of the skin, serosal membranes, and musculoskeletal system. The main inherited (monogenic) periodic fever syndromes are familial Mediterranean fever (FMF), cryopyrin-associated periodic syndrome (CAPS), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), and hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD). Recent advances in our understanding of the molecular and pathophysiological basis of autoinflammatory diseases have provided new treatment strategies. Patients with periodic fever syndromes have clearly benefited from anti-interleukin (IL)-1 treatment. Colchicine is still the mainstay of FMF therapy, but IL-1 blockade is also effective if colchicine fails. Early diagnosis and effective treatment can prevent irreversible organ damage. The scope of pathogenic mutations and more targeted therapy for better management of these rare diseases remains to be defined.

DOI: 10.1007/s40272-017-0232-6

PMID: 28497352 [Indexed for MEDLINE]

772. BioDrugs. 2017 Jun;31(3):207-221. doi: 10.1007/s40259-017-0224-7.

Interleukin-1 Blockade: An Update on Emerging Indications.

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Interleukin (IL)-1 is a pro-inflammatory cytokine that induces local and systemic inflammation aimed to eliminate microorganisms and tissue damage. However, an increasing number of clinical conditions have been identified in which IL-1 production is considered inappropriate and IL-1 is part of the disease etiology. In autoinflammatory diseases, gout, Schnitzler's syndrome, and adult-onset Still's disease, high levels of inappropriate IL-1 production have been shown to be a key process in the etiology of the disease. In these conditions, blocking IL-1 has proven very effective in clinical studies. In other diseases, IL-1 has shown to be present in disease process but is not the central driving force of inflammation. In these conditions, including type 1 and 2 diabetes mellitus, acute coronary syndrome, amyotrophic lateral sclerosis, and several neoplastic diseases, the benefits of IL-1 blockade are minimal or absent.

DOI: 10.1007/s40259-017-0224-7

PMID: 28497222 [Indexed for MEDLINE]

773. Front Immunol. 2017 Apr 27;8:497. doi: 10.3389/fimmu.2017.00497. eCollection 2017.

Toward an Inclusive, Congruent, and Precise Definition of Autoinflammatory Diseases.

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Autoinflammatory disease was introduced as a concept in 1999, demarcating an entirely new group of diseases in clinical, immunological, and conceptual terms. During recent years, the preconditions for the definition of autoinflammatory conditions have changed. This includes the recent discovery of a number of monogenic autoinflammatory conditions with complex phenotypes that combine autoinflammation with defects of the adaptive and/or innate immune system,

resulting in the occurrence of infection, autoimmunity, and/or uncontrolled hyperinflammation in addition to autoinflammation. Further, there are strong indications that classical IL-1-driven autoinflammatory diseases are associated with activation of adaptive immunity. As suggested by this development, we are of the opinion that an all-encompassing definition of autoinflammatory diseases should regard autoinflammatory conditions and innate dysregulation as inseparable and integral parts of the immune system as a whole. Hence, in this article, we try to advance the conceptual understanding of autoinflammatory disease by, proposing a modification of the definition by Daniel Kastner et al., which allows for a congruent and precise description of conditions that expand the immunological spectrum of autoinflammatory disease.

DOI: 10.3389/fimmu.2017.00497

PMCID: PMC5406409

PMID: 28496446

774. Front Immunol. 2017 Apr 27;8:476. doi: 10.3389/fimmu.2017.00476. eCollection 2017.

Higher Levels of Secretory IgA Are Associated with Low Disease Activity Index in Patients with Reactive Arthritis and Undifferentiated Spondyloarthritis.

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**INTRODUCTION:** Both reactive arthritis (ReA) and undifferentiated spondyloarthritis (uSpA) belong to the group of autoinflammatory diseases called spondyloarthritis (SpA). Hypotheses have been proposed about a relationship

between the intestinal mucosa and inflammation of joint tissues. The role of immunoglobulin IgA or secretory immunoglobulin A (SIgA) in the inflammatory and/or clinical activity of patients with SpA remains poorly understood.

**OBJECTIVE:** To evaluate the status of total IgA and SIgA, and the association among the levels of SIgA, IgA, IgA anti-*Chlamydia trachomatis*, and anti-*Shigella* spp. with the disease activity measures, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, was compared in a cohort of patients with ReA and uSpA and healthy subjects.

**METHODS:** This was a cross-sectional study. The serum concentrations of SIgA, IgA anti-*C. trachomatis*, anti-*Shigella* spp., and total IgA were measured. Disease activity was measured in each patient by means of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS). Statistical analysis did include as bivariate evaluation, comparisons by Student's t-test, Kruskal-Wallis test, and U Mann-Whitney test, with a multivariate evaluation by principal components analysis (PCA). A correlation analysis was carried out using the Pearson correlation coefficient and a linear regression models. All analysis were made using Stata version 11.2® for Windows, R V3.3.21. Statistical significance was defined a p-value <0.05.

**RESULTS:** In all, 46 patients (78.2% men; mean age,  $34.8 \pm 12.3$  years) and 53 controls (41% men; mean age,  $32 \pm 11.4$  years) were included in the study. The mean serum levels of SIgA were higher in SpA patients than in healthy subjects ( $p < 0.001$ ). Only SIgA levels correlated with disease activity: BASDAI ( $r = -0.42$ ,  $p = 0.0046$ ), ASDAS-CRP ( $r = -0.37$ ,  $p = 0.014$ ), and ASDAS-ESR ( $r = -0.45$ ,  $p = 0.0021$ ). The negative correlation between SIgA and all activity indices was higher in HLA-B27-positive patients (BASDAI  $r = -0.70$ ,  $p = 0.0009$ , ASDAS-CRP  $r = -0.58$ ,  $p = 0.0093$ , and ASDAS-ESR  $r = -0.57$ ,  $p = 0.0083$ ). The PCA showed three factors: the first component was constituted by variables referred as clinical activity measures, the second did include the serological activity markers, and the last component was compounded by age and symptoms time.

**CONCLUSION:** Elevated serum levels of SIgA were found to be related with low disease activity in patients with ReA and uSpA.

DOI: 10.3389/fimmu.2017.00476

PMCID: PMC5406393

PMID: 28496443

Probable DRESS syndrome induced by IL-1 inhibitors.

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Comment on

Orphanet J Rare Dis. 2015 Feb 15;10 :19.

Interleukin (IL)-1 inhibitors have been increasingly used for treating autoinflammatory diseases during the last 10 years, but the spectrum of their possible side effects is not yet fully known. Here, we bring physicians' attention to a new severe complication of IL-1 inhibitors, manifesting as a probable drug reaction with eosinophilia and systemic symptoms (DRESS) in two patients.

DOI: 10.1186/s13023-017-0645-x

PMCID: PMC5425965

PMID: 28494771 [Indexed for MEDLINE]

776. Br J Pain. 2017 May;11(2):97-101. doi: 10.1177/2049463717701393. Epub 2017 Mar 22.

Fibromyalgia in Behçet's disease: a narrative review.

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**INTRODUCTION:** Fibromyalgia is characterised by chronic widespread pain and tenderness. It has often been reported to occur concomitantly with chronic rheumatological conditions. Behçet's disease is a chronic relapsing, multisystem, autoinflammatory disease. There is only limited understanding of a potential relationship between fibromyalgia and Behçet's disease.

**AIM:** Given the potential detrimental influence of pain on the outcome of chronic disease, the aim of this narrative review is to gain an understanding of the incidence and presentation of fibromyalgia in Behçet's disease.

**METHODS:** Electronic databases Scopus, Medline, PubMed and UpToDate were searched.

**RESULTS:** A total of 269 studies were identified, and limitations and exclusion/inclusion criteria were applied to ensure accurate and comparable selection of studies; four studies were selected. All cases were assessed for the presence of fibromyalgia according to the 1990 or 2010 diagnostic criteria of the American College of Rheumatology, with Behçet's disease diagnosed according to the International Study Group (ISG) for Behçet's disease criteria. A higher prevalence of fibromyalgia (5.7-37.1%) was reported in Behçet's disease compared to that of the general population (2.9-4.7%).

**DISCUSSION:** While an increased prevalence of fibromyalgia was found in patients with Behçet's disease, this needs to be considered within the context of limited available evidence. The potential impact of these conditions on the disease activity of each other is not clear and may require a prospective study.

**CONCLUSION:** Fibromyalgia appears to be more prevalent in those with Behçet's disease than would be expected in the overall population. Significance: This review provides some evidence that fibromyalgia is more prevalent in those with

Behçet's disease. To ensure appropriate patient treatment choices, it is important that both conditions are diagnosed where they co-exist.

DOI: 10.1177/2049463717701393

PMCID: PMC5405975

PMID: 28491302

Conflict of interest statement: Conflict of interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

777. Nat Rev Rheumatol. 2017 Jun;13(6):381-386. doi: 10.1038/nrrheum.2017.68. Epub 2017 May 11.

The changing face of polyarteritis nodosa and necrotizing vasculitis.

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Polyarteritis nodosa (PAN) is a vasculitic disease characterized primarily by necrotizing vasculitis - inflammatory lesions in blood vessels that lead to vessel wall necrosis. Our understanding of PAN and necrotizing vasculitis has evolved over time. In addition to PAN, necrotizing vasculitis is now a recognized feature of a broad range of diseases with different aetiopathogenesis. For example, necrotizing vasculitis associated with hepatitis B virus infection has a different aetiopathogenesis to PAN and is now classified as a separate disease. Additionally, although 'classic' PAN is not an inherited disease, mutations in specific genes, such as ADA2 (also known as CECR1), can result in a necrotizing vasculopathy similar to PAN. The literature also suggests that the course of PAN differs in childhood-onset disease and in cases confined to the skin (so-called cutaneous PAN). Dissecting PAN and other autoinflammatory diseases with PAN-like features has enabled more-specific therapies and might also help us better understand the pathogenesis of these devastating conditions.

DOI: 10.1038/nrrheum.2017.68



PMID: 28490787 [Indexed for MEDLINE]

778. Rheumatology (Oxford). 2017 Sep 1;56(9):1627-1628. doi: 10.1093/rheumatology/kex180.

Successful use of tocilizumab in two cases of severe autoinflammatory disease with a single copy of the Mediterranean fever gene.

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DOI: 10.1093/rheumatology/kex180

PMID: 28486679 [Indexed for MEDLINE]

779. Rheumatology (Oxford). 2018 Jan 1;57(1):41-48. doi: 10.1093/rheumatology/kex066.

Chronic recurrent multifocal osteomyelitis in children and adults: current understanding and areas for development.

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Since the first descriptions of chronic recurrent multifocal osteomyelitis in the 1970s, there have been numerous case reports in the literature; both unusual case reports and case series from all over the world. Our understanding of the pathogenesis has significantly changed, with it now being regarded as an autoinflammatory condition. Treatment options have also expanded, but little

progress has been made in developing the evidence for treatments. Advancing gene studies have provided a mouse model, but the quest for a single gene to match the phenotype has been elusive. Early cohorts of patients have grown up into adults, allowing prospective data to inform the expected outcomes.

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DOI: 10.1093/rheumatology/kex066  
PMID: 28486628 [Indexed for MEDLINE]

780. Gene. 2017 Aug 30;626:9-13. doi: 10.1016/j.gene.2017.05.013. Epub 2017 May 5.

MEFV mutations and their relation to major clinical symptoms of Familial Mediterranean Fever.

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Familial Mediterranean fever is a common hereditary disease in Turkey. To date, different mutational spectrum of MEFV gene was observed in studies carried out in different regions of Turkey but in most of these studies association of clinical symptoms of FMF to mutant genotypes have not been investigated in details. Here we report the MEFV gene variations in exons 2, 3, 5 and 10 and their relations to major clinical symptoms of FMF in 514 unrelated (245 males and 269 females) Turkish patients. MEFV mutations were found in 45% (n=230) of patients and 55% (n=284) of patients did not have any mutations. One hundred and thirty-seven (60%) patients were heterozygous, 57 (24.7%) patients were compound heterozygous, 33 (14%) patients were homozygous and 3 (1.3%) patients were having a complex

genotype. Allele frequencies of MEFV mutations were M694V (48%), E148Q (18%), M680I (15%), V726A (12.5%), P369S (3.3%), R761H (0.9%), K695R (0.9%), E148V (0.9%) and A744S (0.5%). Abdominal pain (76%) and fever (58%) were two most seen complications among patients followed by arthritis (28%) and chest pain (19%). Almost all major clinical symptoms of FMF were higher in patients with one or more M694V or M680I mutant allele. In contrast, patients having E148Q or V726A mutant allele showed fewer clinical FMF symptoms. Patients with P369S have higher abdominal pain, chest pain and fever than expected. Arthritis was high in K695R heterozygous genotype. One hundred and eighteen patients were carrying more than one polymorphic allele. The most common polymorphism was R202Q (13%). In addition, a novel heterozygous polymorphism at 564th nucleotide (C>T) of exon2 were found in 2 patients.

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DOI: 10.1016/j.gene.2017.05.013

PMID: 28483595 [Indexed for MEDLINE]

781. Zhonghua Er Ke Za Zhi. 2017 May 4;55(5):383-387. doi: 10.3760/cma.j.issn.0578-1310.2017.05.015.

[Three cases with familial Mediterranean fever misdiagnosed as juvenile idiopathic arthritis].

[Article in Chinese; Abstract available in Chinese from the publisher]

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Objective: To explore the key points of diagnosis and treatment of familial Mediterranean fever(FMF). Method: The clinical data of 3 cases with FMF misdiagnosed as Juvenile idiopathic arthritis(JIA)seen from January 2014 to June 2016 in Peking Union Medical College Hospital were retrospectively collected. The clinical manifestations, gene mutation characteristics, treatment and prognosis were also evaluated. Result: Two cases were male and 1 was female. The mean age

of onset was 17 months (3 months to 36 months), while the average age of diagnosis was 6 years and 8 months (24 months to 11 years). All the 3 cases presented with periodic fever, red rash and arthritis. Two of them suffered from anemia, 2 of them showed lymphadenopathy, and 1 of them presented with hepatosplenomegaly. All of the 3 cases were diagnosed as JIA by excluding infectious diseases and neoplastic diseases and responding poorly to anti-infection treatment, but they benefitted little from glucocorticoids and a variety of immunosuppressive therapy. The mutations of MEFV gene were found in 3 cases by gene detection, and all of them were complex heterozygous mutations. Four reported pathogenic mutations were found: R202Q, E148Q, L110P, P369S. All the 3 cases are currently receiving oral colchicine (in accordance with the initial dose of children under the age of 5 recommended  $\leq 0.5$  mg/d, 5 to 10 years old children 0.5-1.0 mg/d, 10 years old children and older children 1.0-1.5 mg / d) , and the symptoms were significantly improved. Conclusion: The familial Mediterranean fever can be characterized by repeated remittent fever, red rash, arthritis, and is easy to be confused with JIA in clinical manifestation. In this paper, 3 cases were diagnosed as complex heterozygous MEFV gene mutation by gene analysis. During the 6 months follow-up, all of the 3 patients responded well to colchicine.

**Publisher:** **目的：** 探讨家族性地中海热患儿的诊断治疗要点。**方法：**

回顾性分析北京协和医院儿科2014年1月—2016年6月收治的3例误诊为幼年型特发性关节炎(JIA)的家族性地中海热患儿的病历资料，探讨其临床表现、基因突变特点、治疗及预后情况。**结果：**

3例中男2例，女1例。平均发病月龄17月龄(3~36月龄)，平均确诊年龄为6岁8月龄(24月龄~11岁)。临床表现周期性弛张热、分布于全身的红色斑疹及关节炎3例，贫血2例，淋巴结肿大2例，肝脾肿大1例。3例患儿曾经在常规抗感染无效、除外了感染性疾病及肿瘤性疾病后被诊断为JIA，但接受糖皮质激素及多种免疫抑制剂治疗效果不佳。

经基因检测3例均存在MEFV基因突变，且均为复合杂合突变。发现的4种突变：R202Q、E148Q、L110P、P369S均为已报道的致病突变。3例患儿目前均接受口

服秋水仙碱(按照起始剂量推荐5岁以下儿童为 $\leq 0.5$  mg/d、5~10岁儿童为0.5~1.0 mg/d、10岁以上儿童和成人为1.0~1.5

mg/d)治疗，症状较治疗前明显改善。结论：

家族性地中海热可以表现为反复弛张高热、全身红色斑疹、关节炎，在临床表现上容易与JIA相混淆，仅依靠临床表现鉴别有难度。3例均为MEFV基因复合杂合突变。予秋水仙碱

口服后随访半年以上，症状均有明显缓解。

DOI: 10.3760/cma.j.issn.0578-1310.2017.05.015

PMID: 28482392 [Indexed for MEDLINE]

782. BMC Genomics. 2017 May 4;18(1):348. doi: 10.1186/s12864-017-3737-z.

Whole genome sequencing identifies missense mutation in MTBP in Shar-Pei affected with Autoinflammatory Disease (SPAID).

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BACKGROUND: Autoinflammatory diseases in dogs are characterized by complex disease processes with varying clinical signs. In Shar-Pei, signs of inflammation including fever and arthritis are known to be related with a breed-specific predisposition for Shar-Pei Autoinflammatory Disease (SPAID).

RESULTS: Clinical and histopathological examinations of two severely SPAID-affected Shar-Pei revealed signs of inflammation including fever, arthritis, and perivascular and diffuse dermatitis in both dogs. A multifocal accumulation of amyloid in different organs was found in one SPAID-affected case. Whole genome sequencing resulted in 37 variants, which were homozygous mutant private mutations in SPAID-affected Shar-Pei. Nine SNVs with predicted damaging effects and three INDELs were further investigated in 102 Shar-Pei affected with

SPAID, 62 unaffected Shar-Pei and 162 controls from 11 different dog breeds. The results showed the missense variant MTBP:g.19383758G > A in MTBP to be highly associated with SPAID in Shar-Pei. In the region of this gene a large ROH (runs of homozygosity) region could be detected exclusively in the two investigated SPAID-affected Shar-Pei compared to control dog breeds. No further SPAID-associated variant with predicted high or moderate effects could be found in genes identified in ROH regions. This MTBP variant was predicted to affect the MDN2-binding protein domain and consequently promote proinflammatory reactions. In the investigated group of Shar-Pei older than six years all dogs with the mutant genotype A/A were SPAID-affected whereas SPAID-unaffected dogs harbored the homozygous wildtype (G/G). Shar-Pei with a heterozygous genotype (G/A) were shown to have a 2.13-fold higher risk for disease development, which gave evidence for an incomplete dominant mode of inheritance.

**CONCLUSIONS:** The results of this study give strong evidence for a variant in MTBP related with proinflammatory processes via MTBP-MDM2 pathway. Thus, these results enable a reliable detection of SPAID in Shar-Pei dogs.

DOI: 10.1186/s12864-017-3737-z

PMCID: PMC5418765

PMID: 28472921 [Indexed for MEDLINE]

783. Melanoma Res. 2017 Aug;27(4):377-379. doi: 10.1097/CMR.0000000000000354.

Hemophagocytic lymphohistiocytosis in patients with metastatic malignant melanoma.

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Hemophagocytic lymphohistiocytosis (HLH) is an autoinflammatory disease that classically occurs because of infections, autoinflammatory, or autoimmune diseases, hematologic cancers, and rarely because of solid tumor. We report a rare case of HLH attributed to metastatic malignant melanoma treated without corticosteroid and with a nonfatal outcome thanks to specific therapies:

etoposide for HLH and a selective inhibitor of mutated forms of BRAF kinase associated with a MEK inhibitor for melanoma.

DOI: 10.1097/CMR.0000000000000354

PMID: 28471834 [Indexed for MEDLINE]

784. World J Pediatr. 2017 Aug;13(4):341-345. doi: 10.1007/s12519-017-0032-7. Epub 2017 Apr 29.

Acute hemorrhagic edema of infancy: the experience of a large tertiary pediatric center in Israel.

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**BACKGROUND:** Acute hemorrhagic edema of infancy (AHEI) is a rare leukocytoclastic vasculitis of the small vessels occurring at a young age and considered as a benign self-limited disease. Due to its low prevalence, there are limited data on the presentation and complications of this disease.

**METHODS:** All computerized files of children who were hospitalized at a tertiary pediatric center due to AHEI over a 10 year period were reviewed. Clinical, laboratory and histopathological data were collected.

**RESULTS:** Twenty-six patients were included in our study, accounting for 0.7 cases per 1000 admissions of children aged 2 years or less. Mean age was 12.9 months. More than two thirds of the children had preceding symptoms compatible with a viral infection. Upon admission, all patients presented with typical findings of a rash and edema. Edema was most profound over the lower extremities (73%). Concomitant viral or bacterial infections were found in six children. Skin biopsy was performed in six patients revealing leukocytoclastic vasculitis. Thirteen children (50%) had systemic involvement including joint involvement (n=9), gastrointestinal hemorrhage (n=4), microscopic hematuria (n=1) and compartment

syndrome of the limb (n=1). The latter was diagnosed in a patient with familial Mediterranean fever.

CONCLUSIONS: Our largest data series highlighted what is known regarding clinical and histological findings in children with AHEI. However, contrary to what was previously reported, we found a higher rate of systemic involvement. Although AHEI is a rare entity, pediatricians should be familiar with its presentation, management and our reported complications.

DOI: 10.1007/s12519-017-0032-7

PMID: 28470578 [Indexed for MEDLINE]

785. Front Immunol. 2017 Apr 19;8:399. doi: 10.3389/fimmu.2017.00399. eCollection 2017.

NF- $\kappa$ B Pathway in Autoinflammatory Diseases: Dysregulation of Protein Modifications by Ubiquitin Defines a New Category of Autoinflammatory Diseases.

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Autoinflammatory diseases are caused by defects in genes that regulate the innate immunity. Recently, the scope of autoinflammation has been broadened to include diseases that result from dysregulations in protein modifications by the highly conserved ubiquitin (Ub) peptides. Thus far these diseases consist of linear ubiquitin chain assembly complex (LUBAC) and OTULIN deficiencies, and haploinsufficiency of A20. The LUBAC is critical for linear ubiquitination of key signaling molecules in immune response pathways, while deubiquitinase enzymes, OTULIN and TNFAIP3/A20, reverse the effects of ubiquitination by hydrolyzing linear (Met1) and Lys63 (K63) Ub moieties, respectively, from conjugated proteins. Consequently, OTULIN or A20-deficient cells have an excess of Met1 or K63 Ub chains on NEMO, RIPK1, and other target substrates, which lead to constitutive activation of the NF- $\kappa$ B pathway. Mutant cells produce elevated levels of many proinflammatory cytokines and respond to therapy with cytokine inhibitors. Patients with an impairment in LUBAC stability have compromised NF- $\kappa$ B responses in non-immune cells such as fibroblasts, while their monocytes are



hyperresponsive to IL-1 $\beta$ . Discoveries of germline mutations in enzymes that regulate protein modifications by Ub define a new category of autoinflammatory diseases caused by upregulations in the NF- $\kappa$ B signaling. The primary aim of this review is to summarize the latest developments in our understanding of the etiology of autoinflammation.

DOI: 10.3389/fimmu.2017.00399

PMCID: PMC5395695

PMID: 28469620

786. J Clin Med. 2017 May 2;6(5). pii: E49. doi: 10.3390/jcm6050049.

Serum Profiles of Cytokines in Behcet's Disease.

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**Introduction:** Behcet's disease (BD) is a chronic systemic autoinflammatory vasculitis which is handled by the variety of proteins like cytokines. Therefore, cytokines are considered as one of the prototypic factors during inflammatory responses of BD. Consequently, the present study was designed for evaluation of cytokine profiles in Iranian BD cases, including those with and without uveitis.

**Materials and Method:** All cases were divided into three groups based on ophthalmologic exam results: BD with uveitis, BD without uveitis, and recovered uveitis BD. Cases with a history of BD recovery were placed in the group of recovered uveitis. The patients with infectious uveitis as well as other collagen vascular diseases and patients who have used biologics to treat ocular immune-mediated diseases were excluded. Finally, after venous blood sampling, levels of cytokines were quantified and statistical approaches were performed for measurements. **Results:** Enrolled cases were divided to 26 patients with active uveitis, 25 patients with recovered uveitis and 24 patients without uveitis and interestingly, just IL-2 was the only cytokine that showed statistical difference in patients with BD uveitis in comparison with other groups (pvalue = 0.02). The pair wise comparison showed a significant difference between the patients with and without uveitis groups (pvalue = 0.004) as well as patients with uveitis and recovered uveitis groups (pvalue = 0.002). **Discussion:** Significant elevation of IL-2 in patients with uveitis (in comparison with recovered or without uveitis cases) demonstrates that it may be one of the main proteins that enroll in the pathophysiology of BD uveitis and may be considered as a new target for refractory disease therapies. Studies with larger samples can help to obtain more accurate conclusions.

DOI: 10.3390/jcm6050049

PMCID: PMC5447940

PMID: 28468317

787. Cell Mol Biol (Noisy-le-grand). 2017 Mar 31;63(3):26-28. doi: 10.14715/cmb/2017.63.3.5.

Familial Mediterranean Fever: Observations from a pilot gene expression microarray analysis study.

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Familial Mediterranean Fever (FMF) is an autosomal recessive autoinflammatory disease affecting people of Mediterranean ancestry. The disease is caused by mutations in the MEFV gene located on chromosome 16p13.3. The aim of this pilot study was to assess global gene expression and identify genes and pathways involved in FMF that could be downstream to MEFV mutations or could be novel involved. EDTA blood samples were collected from 14 patients showing FMF-like symptoms and age-matched to 7 controls showing healthy conditions. Microarray was used to assess global gene expression and identify genes and pathways involved in FMF. When we compared individuals with MEFV mutations (homozygous and heterozygous) to control group, probe sets of receptor proteins HLA-DQA1 and HLA-DQB1 were significantly over expressed by 5 folds among the patients group. Despite its limitations, this pilot study could strongly suggest that the role of HLA be investigated in the pathogenesis of MEFV mutation and as a potential moderator explaining penetrance and variation in symptoms among patient groups.

DOI: 10.14715/cmb/2017.63.3.5

PMID: 28466819 [Indexed for MEDLINE]

788. Allergol Immunopathol (Madr). 2017 Nov - Dec;45(6):549-552. doi: 10.1016/j.aller.2016.12.006. Epub 2017 Apr 29.

Is there any difference regarding atopy between children with familial Mediterranean fever and healthy controls?

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**INTRODUCTION:** There are only a few studies regarding the prevalence of atopy in Familial Mediterranean fever (FMF) patients, and their results are conflicting.

**METHODS:** In this study children with the diagnosis of FMF were evaluated for the presence of atopy by comparing with controls. One hundred and eighteen children diagnosed as FMF and 50 healthy age and sex matched controls were enrolled. They were evaluated for the presence of rhinitis, atopic dermatitis, urticaria and asthma. Laboratory assessment was done by measuring IgA, IgM, IgG, IgE levels, total eosinophil count and by performing skin prick test (SPT) panels for common allergens to children with FMF and healthy controls.

**RESULTS:** One hundred and eighteen children (61girls and 57 boys) diagnosed as FMF with a median age of  $120\pm47$  months (range 36-204 months) were compared with 50 healthy controls (31 girls and 19 boys) having a median age of  $126\pm37$  (range 48-192 months). The mean percentage of total eosinophil count of patients was similar to that of the control group. The mean level of IgE was significantly higher in children with FMF than controls ( $136\pm268$ ,  $87\pm201$ , respectively;  $p$  values  $<0.05$ ). The percentage of skin prick test positivity was similar for both patients and controls (13% and 8.2%, respectively;  $p>0.05$ ). The prevalences of atopic dermatitis, allergic rhinitis, and asthma in the patient group were 5.08%, 28.8%, and 15.25%, respectively, while the control group had the prevalences of 0%, 36%, and 14% respectively.

**CONCLUSION:** Children with FMF did not show an increase of atopic dermatitis, allergic rhinitis and asthma with respect to controls.

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DOI: 10.1016/j.aller.2016.12.006

PMID: 28465037 [Indexed for MEDLINE]

789. Nephrol Ther. 2017 Jun;13(4):258-264. doi: 10.1016/j.nephro.2017.03.001. Epub 2017 Apr 24.

[AA amyloidosis].

[Article in French]

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AA amyloidosis remains one of the three main types of systemic amyloidosis with AL and ATTR. Its incidence has been however decreasing recently in Western countries. Chronic inflammatory diseases are currently the first cause of AA amyloidosis, including rheumatoid arthritis, spondyloarthritis and autoinflammatory diseases. Castleman's disease is a specific cause of AA amyloidosis that can be cured by surgery. A chronic inflammatory response is required to develop amyloidosis. Other genetic and environmental factors are also involved. The first clinical manifestation is a chronic glomerular nephropathy, which can be detected by urine examination and serum creatinine measure. Immunohistochemistry is mandatory to confirm the clinical diagnosis of AA amyloidosis and to avoid misdiagnosis. Long-term prognosis remains poor on chronic dialysis in case of clinical gut involvement. Current treatment is based on the control of the inflammatory response. Specific treatment aimed at inhibiting amyloid formation targeting serum amyloid P component and heparan sulphate are currently evaluated.

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DOI: 10.1016/j.nephro.2017.03.001

790. J Res Med Sci. 2017 Mar 15;22:35. doi: 10.4103/1735-1995.202140. eCollection 2017.

Assessment of neutrophil to lymphocyte ratio and mean platelet volume in pediatric familial Mediterranean fever patients.

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**BACKGROUND:** Blood neutrophil to lymphocyte ratio (NLR) and mean platelet volume (MPV) both have been used as a simple marker of inflammation in many disorders. Here, we aimed to investigate the relationship between NLR, MPV, and familial Mediterranean fever (FMF).

**MATERIALS AND METHODS:** In this retrospective study, the files of FMF patients in pediatric rheumatology outpatient clinic were reviewed. There were 160 participants (68.4%) in the FMF patient group and 74 participants (31.6%) in the control group. Ninety of patients were in attack-free period, and 70 were in attack period.

**RESULTS:** The highest values of NLR were found in the patients at attack period. Patients in attack-free period and the participants in control group had similar levels of NLR ( $1.71 \pm 0.83$  and  $1.91 \pm 1.86$  respectively) ( $P = 0.457$ ), and they had lower ratios than the patients did at attack period ( $4.10 \pm 3.11$ ) ( $P < 0.001$  for both). There was no significant difference between MPV values of attack patients ( $8.35 \pm 4.91$ ) and attack-free patients ( $8.43 \pm 1.15$ ) ( $P = 0.074$ ). MPV values of attack patients and attack-free patients were significantly higher than control group ( $7.99 \pm 0.81$ ) ( $P < 0.001$  for both).

**CONCLUSION:** NLR ratio may indicate FMF attack period. Since there was no significant difference between attack-free patients and control groups, NLR ratio cannot be used as a subclinical inflammation marker. However, NLR could be a useful predictor of inflammation in FMF patients. On the other hand, since our attack and attack-free patients have similar MPV values and both had greater MPV values than control group, we suggest that MPV may be used to show subclinical inflammation.

DOI: 10.4103/1735-1995.202140

PMCID: PMC5390538

PMID: 28461821

Conflict of interest statement: There are no conflicts of interest.

791. J Rheumatol. 2017 Jul;44(7):1058-1065. doi: 10.3899/jrheum.161255. Epub 2017 May 1.

Treatment Response and Longterm Outcomes in Children with Chronic Nonbacterial Osteomyelitis.

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**OBJECTIVE:** The autoinflammatory bone disorder chronic nonbacterial osteomyelitis (CNO) covers a wide clinical spectrum, ranging from mild self-limited presentations to chronically active or recurrent courses, which are then referred to as chronic recurrent multifocal osteomyelitis (CRMO). Little is known about treatment options and longterm outcomes. We investigated treatment responses and outcomes in children with CNO.

**METHODS:** A retrospective chart review was conducted in a tertiary referral center, covering 2004-2015. Disease activity was measured at 0, 3, 6, 12, and 24 months after treatment initiation, and at the last recorded visit.

**RESULTS:** Fifty-six patients with CNO were identified; 44 had multifocal CNO. Fifty percent of patients relapsed after a median of 2.4 years, and as few as 40% remained relapse-free after 5 years. Nonsteroidal antiinflammatory drugs were used as first-line treatment in 55 patients, inducing remission after 3 months in all individuals with relapse rates of 50% after 2 years. Further treatment included corticosteroids (n = 23), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) inhibitors (n = 7), and bisphosphonates (n = 8). While 47% of patients with CNO relapsed within 1 year after corticosteroid therapy, favorable outcomes were achieved with TNF- $\alpha$  inhibitors or bisphosphonates (pamidronate).

**CONCLUSION:** CNO is a chronic disease with favorable outcomes within the first year, but high relapse rates in longterm followup. Particularly, patients with CRMO with long-lasting, uncontrolled inflammation were at risk for the development of arthritis. Our findings underscore the importance of a timely diagnosis and treatment initiation. Prospective studies are warranted to establish evidence-based diagnostic and therapeutic approaches to CNO.

DOI: 10.3899/jrheum.161255

PMID: 28461645 [Indexed for MEDLINE]



Epub 2017 Apr 29.

Reply.

Canna SW(1), Girard C(2), Malle L(3), de Jesus A(3), Romberg N(4), Kelsen J(4), Surrey LF(4), Russo P(4), Sleight A(5), Schiffrin E(5), Gabay C(2), Goldbach-Mansky R(3), Behrens EM(4).

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DOI: 10.1016/j.jaci.2017.03.016

PMID: 28460789

793. Expert Rev Clin Immunol. 2017 Jun;13(6):513-523. doi: 10.1080/1744666X.2017.1324783.

Canakinumab for the treatment of TNF-receptor associated periodic syndrome.

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**INTRODUCTION:** TNF-receptor-associated periodic syndrome is an autoinflammatory disorder caused by mutations in TNF receptor superfamily 1A gene. The molecular pathogenesis of TRAPS remains unclear; it is known that a key role is played by mutations in TNFRSF1A that induce the hypersecretion of pro-inflammatory

cytokines as well as IL-1 $\beta$ , resulting in uncontrolled inflammatory reactions. Furthermore, TNFRSF1A gene mutations result in intracellular stress ultimately leading to increased production of interleukin-1 $\beta$ , but the exact mechanism referred to in the connection between TNFRSF1A mutation and increased release of IL-1 $\beta$ , is still under study. This explains why IL-1 inhibition treatment can be effective in treating TRAPS patients. The purpose of this review is to discuss the safety and efficacy of canakinumab, a high-affinity human monoclonal anti IL-1 $\beta$  antibody. Areas covered: The data obtained from case reports, case series, Phase II study and a phase III randomized, double-blind, placebo controlled trial have been analyzed. Efficacy and safety profiles of canakinumab are discussed. Expert commentary: Was discussed an overview of treatment options in TRAPS patients. The understanding of pathogenesis of TNF-receptor-associated periodic syndrome led to realize why TRAPS patients respond to IL-1 inhibition. Canakinumab became approved for the treatment in TRAPS patients very recently.

DOI: 10.1080/1744666X.2017.1324783

PMID: 28454496 [Indexed for MEDLINE]

794. J Biol Chem. 2017 Jun 9;292(23):9680-9689. doi: 10.1074/jbc.M117.789180. Epub 2017 Apr 26.

The Behçet's disease-associated variant of the aminopeptidase ERAP1 shapes a low-affinity HLA-B\*51 peptidome by differential subpeptidome processing.

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A low-activity variant of endoplasmic reticulum aminopeptidase 1 (ERAP1), Hap10, is associated with the autoinflammatory disorder Behçet's disease (BD) in epistasis with HLA-B\*51, which is the main risk factor for this disorder. The role of Hap10 in BD pathogenesis is unknown. We sought to define the effects of Hap10 on the HLA-B\*51 peptidome and to distinguish these effects from those due to HLA-B\*51 polymorphisms unrelated to disease. The peptidome of the BD-associated HLA-B\*51:08 subtype expressed in a Hap10-positive cell line was isolated, characterized by mass spectrometry, and compared with the HLA-B\*51:01 peptidome from cells expressing more active ERAP1 allotypes. We additionally performed synthetic peptide digestions with recombinant ERAP1 variants and estimated peptide-binding affinity with standard algorithms. In the BD-associated ERAP1 context of B\*51:08, longer peptides were generated; of the two major HLA-B\*51 subpeptidomes with Pro-2 and Ala-2, the former one was significantly reduced, and the latter was increased and showed more ERAP1-susceptible N-terminal residues. These effects were readily explained by the low activity of Hap10 and the differential susceptibility of X-Pro and X-Ala bonds to ERAP1 trimming and together resulted in a significantly altered peptidome with lower affinity. The differences due to ERAP1 were clearly distinguished from those due to HLA-B\*51 subtype polymorphism, which affected residue frequencies at internal positions of the peptide ligands. The alterations in the nature and affinity of HLA-B\*51-peptide complexes probably affect T-cell and natural killer cell recognition, providing a sound basis for the joint association of ERAP1 and HLA-B\*51 with BD.

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DOI: 10.1074/jbc.M117.789180

PMCID: PMC5465491

PMID: 28446606 [Indexed for MEDLINE]

795. Gene. 2017 Aug 5;623:29-32. doi: 10.1016/j.gene.2017.04.037. Epub 2017 Apr 23.

Fas and Fas ligand gene polymorphisms in Turkish patients with Familial Mediterranean Fever.

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Familial Mediterranean Fever (FMF) is an autosomal recessive autoinflammatory disorder characterized by recurrent fever, serositis, abdominal pain, arthritis, arthralgia and erysipelas like erythema. Fas and Fas ligand molecules play a central role in the apoptosis signaling of various cell types including neutrophils. Neutrophils are the major cell population involved in acute inflammation in patients with FMF and the role of Fas and Fas ligand molecules in this cells of FMF patients may be crucial. Therefore, in the present study, we aimed to investigate whether the Fas cell surface receptor gene (FAS); NM\_000043.5: c.-671A>G (rs1800682, Mval) and Fas ligand gene (FASLG), NM\_000639.2: c.-844C>T (rs763110, BsrD1) functional polymorphisms in patients with FMF and their relation to the main clinical features of the disease. The polymorphisms in the promoter regions of FAS c.-671A>G and FASLG c.-844C>T were investigated in 97 non-related FMF patients and 70 non-related healthy controls by using PCR-RFLP technique. The frequencies of FAS c.-671AG genotype and G allele were not significantly different between FMF patients and healthy subjects. The frequency of FASLG -844TC genotype was found significantly different between the patients with FMF and healthy controls whereas T or C allele frequency was not significantly different between the groups. Haplotype frequencies of the studied polymorphisms were also not significantly different between FMF patients and controls. There were no correlations between the studied FAS c.-671A>G and FASLG c.-844C>T polymorphisms and the main clinical features of FMF such as fever, arthritis, abdominal and chest pain, arthralgia and erysipelas-like erythema. Our findings suggest that FAS c.-671AG genotype or G allele and FASLG c.-844 allele are not to be a risk factor, whereas FASLG c.-844TC genotype may be protective in the studied Turkish population. According to our results we may suggest that although not statistically significant, higher frequencies of FASLG c.-844CC genotype in FMF patients may be related to delayed apoptosis of neutrophils and

ultimately cause neutrophilic inflammation by increasing FASLG expression.

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DOI: 10.1016/j.gene.2017.04.037

PMID: 28442396 [Indexed for MEDLINE]

796. *Actas Dermosifiliogr.* 2017 Sep;108(7):609-619. doi: 10.1016/j.ad.2016.12.021. Epub 2017 Apr 23.

Autoinflammatory Diseases in Pediatric Dermatology-Part 1: Urticaria-like Syndromes, Pustular Syndromes, and Mucocutaneous Ulceration Syndromes.

[Article in English, Spanish]

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Monogenic autoinflammatory diseases are a heterogeneous emergent group of conditions that are currently under intensive study. We review the etiopathogenesis of these syndromes and their principal manifestations. Our aim is to propose a classification system based on the clinicopathologic features of typical skin lesions for routine clinical use in dermatology. Our focus is on diagnosis in pediatric practice given that this is the period when the signs and symptoms of these syndromes first appear. In Part 1 we discuss the course of urticaria-like syndromes, which include cryopyrin-associated periodic conditions and hereditary periodic fever syndromes. Pustular syndromes are also covered in this part. Finally, we review the range of therapies available as well as the genetic mutations associated with these autoinflammatory diseases.

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DOI: 10.1016/j.ad.2016.12.021

PMID: 28442130 [Indexed for MEDLINE]

797. Allergy Asthma Proc. 2017 May 1;38(3):231-235. doi: 10.2500/aap.2017.38.4039.

A 30-year-old woman with chronic hives, intermittent fevers, and joint pain.

Cook KA, Lynch MT, Weis PJ, White AA.

Comment in

Allergy Asthma Proc. 2017 May 1;38(3):167-169.

Chronic urticaria with concomitant systemic symptoms may be seen in several rheumatologic and autoinflammatory conditions. Although most of these conditions tend to improve with corticosteroids, symptoms often recur with dose tapering. The appearance of the rash in addition to the symptom pattern and laboratory data must be considered to differentiate potential causes. We presented a unique case of chronic urticaria with fevers and arthralgias. A diagnosis was made, and the patient had rapid improvement with targeted therapy.

DOI: 10.2500/aap.2017.38.4039

PMID: 28441994 [Indexed for MEDLINE]

798. Med Ultrason. 2017 Apr 22;19(2):224-227. doi: 10.11152/mu-889.

Ultrasonographic findings in hyperimmunoglobulin D syndrome: a case report.

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Hyperimmunoglobulin D syndrome due to mevalonate kinase deficiency is a rare autoinflammatory disease with digestive tract involvement. We report an 11-year female child who has presented since the age of 1 year, bouts of fever, rash, joint swelling, pulmonary consolidation, lymph node involvement and hepatosplenomegaly. Hyperimmunoglobulin D and increased urinary mevalonic acid were detected. The ultrasonographic features of hepatosplenomegaly ranged from increment in size to pseudotumoral involvement, with hypoechogenic masses without apparent wall. Abdominal CT during a disease flare showed hypodense, hypoenhancing nodular lesions, suggesting metastases. Nevertheless, a thorough search for malignancy was negative and the masses disappeared after the flare. Mevalonate kinase deficiency may add to the causes of hepatosplenic and pulmonary inflammatory pseudotumors.

DOI: 10.11152/mu-889

PMID: 28440359 [Indexed for MEDLINE]

799. Actas Dermosifiliogr. 2017 Sep;108(7):620-629. doi: 10.1016/j.ad.2016.12.022.  
Epub 2017 Apr 21.

Autoinflammatory Diseases in Pediatric Dermatology-Part 2: Histiocytic,  
Macrophage Activation, and Vasculitis Syndromes.

[Article in English, Spanish]

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The discovery of new autoinflammatory syndromes and novel mutations has advanced at breakneck speed in recent years. Part 2 of this review focuses on vasculitis syndromes and the group of histiocytic and macrophage activation syndromes. We also include a table showing the mutations associated with these autoinflammatory syndromes and treatment alternatives.

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DOI: 10.1016/j.ad.2016.12.022

PMID: 28438265 [Indexed for MEDLINE]

800. Microbiome. 2017 Apr 24;5(1):46. doi: 10.1186/s40168-017-0263-9.

Microbiota-activated CD103<sup>+</sup> DCs stemming from microbiota adaptation specifically drive  $\gamma\delta$ T17 proliferation and activation.

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BACKGROUND: IL-17-producing  $\gamma\delta$ T cells ( $\gamma\delta$ T17) promote autoinflammatory diseases



and cancers. Yet,  $\gamma\delta T17$  peripheral regulation has not been thoroughly explored especially in the context of microbiota-host interaction. The potent antigen-presenting CD103+ dendritic cell (DC) is a key immune player in close contact with both  $\gamma\delta T17$  cells and microbiota. This study presents a novel cellular network among microbiota, CD103+ DCs, and  $\gamma\delta T17$  cells.

**METHODS:** Immunophenotyping of IL-17r<sup>-/-</sup> mice and IL-17r<sup>-/-</sup> IRF8<sup>-/-</sup> mice were performed by ex vivo immunostaining and flow cytometric analysis. We observed striking microbiome differences in the oral cavity and gut of IL-17r<sup>-/-</sup> mice by sequencing 16S rRNA gene (v1-v3 region) and analyzed using QIIME 1.9.0 software platform. Principal coordinate analysis of unweighted UniFrac distance matrix showed differential clustering for WT and IL-17r<sup>-/-</sup> mice.

**RESULTS:** We found drastic homeostatic expansion of  $\gamma\delta T17$  in all major tissues, most prominently in cervical lymph nodes (cLNs) with monoclonal expansion of V $\gamma$ 6  $\gamma\delta T17$  in IL-17r<sup>-/-</sup> mice. Ki-67 staining and in vitro CFSE assays showed cellular proliferation due to cell-to-cell contact stimulation with microbiota-activated CD103+ DCs. A newly developed double knockout mice model for IL-17r and CD103+ DCs (IL-17r<sup>-/-</sup>IRF8<sup>-/-</sup>) showed a specific reduction in V $\gamma$ 6  $\gamma\delta T17$ . V $\gamma$ 6  $\gamma\delta T17$  expansion is inhibited in germ-free mice and antibiotic-treated specific pathogen-free (SPF) mice. Microbiota transfer using cohousing of IL-17r<sup>-/-</sup> mice with wildtype mice induces  $\gamma\delta T17$  expansion in the wildtype mice with increased activated CD103+ DCs in cLNs. However, microbiota transfer using fecal transplant through oral gavage to bypass the oral cavity showed no difference in colon or systemic  $\gamma\delta T17$  expansion.

**CONCLUSIONS:** These findings reveal for the first time that  $\gamma\delta T17$  cells are regulated by microbiota dysbiosis through cell-to-cell contact with activated CD103+ DCs leading to drastic systemic, monoclonal expansion. Microbiota dysbiosis, as indicated by drastic bacterial population changes at the phylum and genus levels especially in the oral cavity, was discovered in mice lacking IL-17r. This network could be very important in regulating both microbiota and immune players. This critical regulatory pathway for  $\gamma\delta T17$  could play a major role in IL-17-driven inflammatory diseases and needs further investigation to determine specific targets for future therapeutic intervention.

DOI: 10.1186/s40168-017-0263-9

PMCID: PMC5404689

PMID: 28438184 [Indexed for MEDLINE]

# Novel mutation identified in severe early-onset tumor necrosis factor receptor-associated periodic syndrome: a case report.

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**BACKGROUND:** Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS) is the second most common heritable autoinflammatory disease, typically presenting in pre-school aged children with fever episodes lasting 1-3 weeks.

Systemic symptoms can include rash, myalgia, ocular inflammation, and serositis.

**CASE PRESENTATION:** Here we report an unusual presentation of TRAPS in a 7 month old girl who presented with only persistent fever. She was initially diagnosed with incomplete Kawasaki Disease and received IVIG and infliximab; however, her fevers quickly recurred. Subsequent testing revealed a urinary tract infection, but she did not improve despite appropriate therapy. As fever continued, she developed significant abdominal distension with imaging concerning for appendicitis, followed by hyperthermia and hemodynamic instability. Given her protracted clinical course and maternal history of a poorly defined inflammatory condition, an autoinflammatory disease was considered. Therapy with anakinra was initiated, resulting in rapid resolution of fever and normalization of inflammatory markers. She was found to have a previously unreported mutation, Thr90Pro, in the TNFRSF1A gene associated with TRAPS. This novel mutation was also confirmed in the patient's mother and maternal uncle.

**CONCLUSIONS:** This report reviews a severe case of TRAPS in infancy associated with a novel mutation, Thr90Pro, in the TNFRSF1A gene, and emphasizes that autoinflammatory disease should be considered in the differential of infants with fever of unknown origin.

DOI: 10.1186/s12887-017-0856-2

PMCID: PMC5399385

PMID: 28427379 [Indexed for MEDLINE]

802. Turk J Med Sci. 2017 Apr 18;47(2):463-469. doi: 10.3906/sag-1602-88.

Effect of familial Mediterranean fever on sexual and reproductive health in women.

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**BACKGROUND/AIM:** The aim of this study was to investigate the relationship between familial Mediterranean fever and female sexual dysfunction and premenstrual syndrome.

**MATERIALS AND METHODS:** This study included 36 patients with familial Mediterranean fever and 33 healthy volunteers. Familial Mediterranean fever was diagnosed according to the Tel Hashomer criteria and familial Mediterranean fever mutations were identified in all of the patients. The patients and healthy volunteers were compared in terms of anxiety, depression, sexual dysfunction, and premenstrual syndrome, and a model was created that describes the relationships among these variables.

**RESULTS:** We found statistically significant differences between the groups in terms of anxiety, premenstrual syndrome, and Golombok Rust Inventory of Sexual Satisfaction frequency and vaginismus subscale scores. There was no difference in depression scores between the groups.

**CONCLUSION:** Familial Mediterranean fever is a rheumatic disease that predisposes patients to sexual dysfunction and premenstrual syndrome, which emerges as direct and indirect psychological factors.

DOI: 10.3906/sag-1602-88

PMID: 28425232 [Indexed for MEDLINE]

803. Front Immunol. 2017 Apr 5;8:392. doi: 10.3389/fimmu.2017.00392. eCollection 2017.

Clinical Overlapping in Autoinflammatory Diseases: The Role of Gene Duplication.

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DOI: 10.3389/fimmu.2017.00392

PMCID: PMC5380662

PMID: 28424701

804. PLoS One. 2017 Apr 19;12(4):e0175153. doi: 10.1371/journal.pone.0175153. eCollection 2017.

Th17 micro-milieu regulates NLRP1-dependent caspase-5 activity in skin autoinflammation.

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IL-1 $\beta$  is a potent player in cutaneous inflammation and central for the development of a Th17 micro-milieu in autoinflammatory diseases including psoriasis. Its production is controlled at the transcriptional level and by subsequent posttranslational processing via inflammatory caspases. In this study, we detected inflammatory caspase-5 active in epidermal keratinocytes and in psoriatic skin lesions. Further, interferon- $\gamma$  and interleukin-17A synergistically induced caspase-5 expression in cultured keratinocytes, which was dependent on the antimicrobial peptide psoriasin (S100A7). However, diseases-relevant triggers for caspase-5 activity and IL-1 $\beta$  production remain unknown. Recently, extranuclear DNA has been identified as danger-signals abundant in the psoriatic epidermis. Here, we could demonstrate that cytosolic double-stranded (ds) DNA transfected into keratinocytes triggered the activation of caspase-5 and the release of IL-1 $\beta$ . Further, interleukin-17A promoted caspase-5 function via facilitation of the NLRP1-inflammasome. Anti-inflammatory vitamin D interfered with the IL-1 $\beta$  release and suppressed caspase-5 in keratinocytes and in psoriatic skin lesions. Our data link the disease-intrinsic danger signals psoriasin (S100A7) and dsDNA for NLRP1-dependent caspase-5 activity in psoriasis providing potential therapeutic targets in Th17-mediated skin autoinflammation.

DOI: 10.1371/journal.pone.0175153

PMCID: PMC5396864

PMID: 28422993 [Indexed for MEDLINE]

805. Swiss Med Wkly. 2017 Apr 18;147:w14424. doi: 10.4414/smw.2017.14424. eCollection 2017.

Prions, prionoid complexes and amyloids: the bad, the good and something in between.

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Prions are infectious agents causing transmissible spongiform encephalopathies in humans and animals. These protein-based particles template conformational changes in a host-encoded prion protein to an insoluble self-like conformation. Prions are also present in yeast, where they support protein-based epigenetic inheritance. There is emerging evidence that prion-like (prionoid) particles can support a variety of pathological and beneficial functions. The recent data on the prionoid spread of other pathological amyloids are discussed in light of differences between prions and prion-like aggregates. On the other hand, prion-like action has also been found to support important functions such as memory, and amyloids were shown to have a variety of physiological roles from storage to scaffolding in simple organisms and in humans. Higher-order protein complexes play important roles in signalling. Many death-fold domains can polymerise upon nucleation to enhance sensitivity and induce a robust response. Although these polymers are structurally different from amyloids, some of them are characterised by prionoid activities, such as intercellular spread. The initial activation of these complexes is vital for organismal health, whereas prolonged activation leading to unresolved inflammation underlies autoinflammatory and other diseases. Prionoid complexes play important roles far beyond prion diseases and neurodegeneration.

DOI: 10.4414/smw.2017.14424

PMID: 28421568 [Indexed for MEDLINE]

806. Front Immunol. 2017 Apr 4;8:345. doi: 10.3389/fimmu.2017.00345. eCollection 2017.

Dysregulated IL-1 $\beta$  Secretion in Autoinflammatory Diseases: A Matter of Stress?

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Infectious and sterile inflammation is induced by activation of innate immune cells. Triggering of toll-like receptors by pathogen-associated molecular pattern or damage-associated molecular pattern (PAMP or DAMP) molecules generates reactive oxygen species that in turn induce production and activation of pro-inflammatory cytokines such as IL-1 $\beta$ . Recent evidence indicates that cell stress due to common events, like starvation, enhanced metabolic demand, cold or heat, not only potentiates inflammation but may also directly trigger it in the absence of PAMPs or DAMPs. Stress-mediated inflammation is also a common feature of many hereditary disorders, due to the proteotoxic effects of mutant proteins. We propose that harmful mutant proteins can induce dysregulated IL-1 $\beta$  production and inflammation through different pathways depending on the cell type involved. When expressed in professional inflammatory cells, stress induced by the mutant protein activates in a cell-autonomous way the onset of inflammation and mediates its aberrant development, resulting in the explosive responses that hallmark autoinflammatory diseases. When expressed in non-immune cells, the mutant protein may cause the release of transcellular stress signals that trigger and propagate inflammation.

DOI: 10.3389/fimmu.2017.00345

PMCID: PMC5378711

PMID: 28421072

807. Front Immunol. 2017 Apr 3;8:344. doi: 10.3389/fimmu.2017.00344. eCollection 2017.

Monogenic Autoinflammatory Diseases with Mendelian Inheritance: Genes, Mutations, and Genotype/Phenotype Correlations.

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Autoinflammatory diseases (AIDs) are a genetically heterogeneous group of diseases caused by mutations of genes encoding proteins, which play a pivotal

role in the regulation of the inflammatory response. In the pathogenesis of AIDs, the role of the genetic background is triggered by environmental factors through the modulation of the innate immune system. Monogenic AIDs are characterized by Mendelian inheritance and are caused by highly penetrant genetic variants in single genes. During the last years, remarkable progress has been made in the identification of disease-associated genes by using new technologies, such as next-generation sequencing, which has allowed the genetic characterization in undiagnosed patients and in sporadic cases by means of targeted resequencing of a gene panel and whole exome sequencing. In this review, we delineate the genetics of the monogenic AIDs, report the role of the most common gene mutations, and describe the evidences of the most sound genotype/phenotype correlations in AID.

DOI: 10.3389/fimmu.2017.00344

PMCID: PMC5376573

PMID: 28421071

808. Semin Arthritis Rheum. 2017 Aug;47(1):115-120. doi: 10.1016/j.semarthrit.2017.03.006. Epub 2017 Mar 20.

Colchicine resistance and intolerance in familial mediterranean fever: Definition, causes, and alternative treatments.

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**BACKGROUND:** Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory syndrome characterized by recurrent serositis or arthritis attacks and, in some patients, chronic subclinical inflammation that predisposes to secondary amyloidosis. Colchicine is the gold standard of treatment, which reduces attack frequency and amyloidosis risk. However, up to 5% of patients are considered



resistant or inadequately respond to colchicine, and some others cannot tolerate the side effects of effective doses of colchicine (colchicine intolerant).

**METHODS:** We examine how the definition of colchicine resistance has evolved along with various characteristics of colchicine that may help explain unresponsiveness to the drug.

**RESULTS:** Key factors in assessing colchicine resistance include attack frequency and severity, levels of acute phase reactants, colchicine dosage and composition, and treatment compliance. Promising clinical results have been obtained with biologics targeting interleukin-1 in colchicine-resistant or -intolerant patients with FMF.

**CONCLUSIONS:** These results underscore the need to identify patients who are not optimally managed with colchicine and who might therefore benefit from additional biologic therapies.

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DOI: 10.1016/j.semarthrit.2017.03.006

PMID: 28413100 [Indexed for MEDLINE]

809. *Pediatr Dev Pathol.* 2017 Nov-Dec;20(6):498-505. doi: 10.1177/1093526616686890. Epub 2017 Mar 15.

Novel NLRC4 Mutation Causes a Syndrome of Perinatal Autoinflammation With Hemophagocytic Lymphohistiocytosis, Hepatosplenomegaly, Fetal Thrombotic Vasculopathy, and Congenital Anemia and Ascites.

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Autoinflammatory diseases are caused by pathologic activation of the innate immune system. Primary hemophagocytic lymphohistiocytosis (HLH) is an aggressive syndrome of excessive immune activation caused by monogenic mutations resulting in cytotoxic cell defects and subsequent failure to eliminate activated macrophages. Secondary HLH is often diagnosed in cases without a known Mendelian inheritance. However, some cases of "secondary" HLH have been shown to harbor mutations with partial dysfunction of the cytotoxic system. Recently, macrophage intrinsic abnormalities caused by NLRC4 inflammasome mutations have been linked to autoinflammation and recurrent macrophage activation syndromes resembling a primary HLH. We report a case of a former 28-week preterm infant with congenital anemia, ascites, and a heavy edematous placenta with fetal thrombotic vasculopathy, who developed hepatosplenomegaly and unexplained systemic inflammation with laboratory features of HLH in the early postnatal course and died at 2 months of age. Postmortem examination confirmed the hepatosplenomegaly with marked sinusoidal hemophagocytosis, along with striking hemophagocytosis in the bone marrow and lymph nodes. There was extensive acute and chronic ischemic bowel disease with matted bowel loops, fibrous adhesions, and patchy necrotizing enterocolitis features. Whole exome sequencing analysis demonstrated a novel mosaic heterozygous NLRC4 512 C> T (p.Ser171Phe) de novo mutation predicated to cause a dominant, gain-of-function mutation resulting in a constitutively active protein. The assembly of NLRC4-containing inflammasomes via an induced self-propagation mechanism likely enables a perpetuating process of systemic macrophage activation, presumed to be initiated in utero in this patient.

DOI: 10.1177/1093526616686890

PMID: 28403691

810. Clin Rheumatol. 2017 Sep;36(9):2063-2069. doi: 10.1007/s10067-017-3627-4. Epub 2017 Apr 11.

Long-term efficacy and safety of golimumab in the treatment of multirefractory Behçet's disease.

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Erratum in

Clin Rheumatol. 2018 Sep 22;.

Our aim was to retrospectively assess the role of golimumab as a treatment choice in patients with Behçet's disease (BD). Seventeen patients diagnosed with BD according to the international criteria were consecutively enrolled; the BD Current Activity Form (BDCAF) was used to evaluate disease activity. After having collected clinical data from patients, statistical analysis was performed to identify differences between the start of therapy and last visit; significance was defined as  $p < 0.05$ . The mean duration of golimumab treatment was  $18.47 \pm 20.8$  months. At the time of data enrollment, 12/17 (70.6%) patients were still on golimumab therapy. The mean time required to obtained clinical response was  $4.9 \pm 5.7$  weeks. At 3 months evaluation, golimumab was able to control BD-related manifestations in 16/17 (94.1%) cases; the BDCAF values were significantly decreased at the last follow-up compared to those assessed at the start of golimumab ( $p = 0.002$ ). The BDCAF improvement was significantly higher among patients co-administered with DMARDs than those undergoing golimumab as monotherapy ( $p = 0.048$ ). At the last follow-up visit, corticosteroids had been discontinued in 10 (58.8%) patients, while the corticosteroid dosage was

significantly lower at the last follow-up visit compared to the start of therapy in those patients already on corticosteroids at the end of the study ( $p = 0.001$ ). Golimumab is a promising and safe treatment opportunity in BD patients with different systemic involvement, inducing a prompt resolution of clinical manifestations, a meaningful improvement of BDCAF score, and a significant corticosteroid-sparing effect. However, golimumab co-administered with DMARDs has provided better results than in patients undergoing monotherapy.

DOI: 10.1007/s10067-017-3627-4

PMID: 28401434 [Indexed for MEDLINE]

811. Paediatr Drugs. 2017 Jun;19(3):165-172. doi: 10.1007/s40272-017-0226-4.

An Update on the Pathogenesis and Treatment of Chronic Recurrent Multifocal Osteomyelitis in Children.

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Chronic recurrent multifocal osteomyelitis (CRMO), also known as chronic non-bacterial osteomyelitis (CNO), is a rare inflammatory disorder that primarily affects children. It is characterized by pain, local bone expansion, and radiological findings suggestive of osteomyelitis, usually at multiple sites. CRMO predominantly affects the metaphyses of long bones, but involvement of the clavicle or mandible are suggestive of the diagnosis. CRMO is a diagnosis of exclusion, and its pathogenesis remains unknown. Differential diagnosis includes infection, malignancies, benign bone tumors, metabolic disorders, and other autoinflammatory disorders. Biopsy of the bone lesion is not often required but could be necessary in unclear cases, especially for differentiation from bone

neoplasia. Non-steroidal anti-inflammatory drugs (NSAIDs) are the first-line treatment. Alternative therapies have been used, including corticosteroids, methotrexate, bisphosphonates, and tumor necrosis factor (TNF)- $\alpha$  inhibitors. No guidelines have been established regarding diagnosis and treatment options. This manuscript gives an overview of the most recent findings on the pathogenesis of CRMO and clinical approaches for patients with the condition.

DOI: 10.1007/s40272-017-0226-4

PMID: 28401420 [Indexed for MEDLINE]

812. Front Pharmacol. 2017 Mar 28;8:163. doi: 10.3389/fphar.2017.00163. eCollection 2017.

IL-1 Inhibition May Have an Important Role in Treating Refractory Kawasaki Disease.

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Kawasaki disease (KD) is an acute inflammatory vasculitis occurring in young children before 5 years and representing at this age, the main cause of acquired heart disease. A single infusion of 2 g/kg of intravenous immunoglobulins along with aspirin has reduced the frequency of coronary artery aneurysms from 25 to 5%. However, 10-20% of patients do not respond to standard treatment and have an increased risk of cardiac complications and death. The development of more potent therapeutic approaches of KD is an urgent need. Phenotypical and immunological similarities between KD and systemic juvenile idiopathic arthritis led to the hypothesis that KD could be considered as an autoinflammatory disease. New insights regarding KD's pathogenesis have merged from the combination of genetic and transcriptomic data revealing the key role of interleukin-1 (IL-1) signaling in the pathogenesis of the vasculitis. Once activated, IL-1 $\alpha$  and IL-1 $\beta$  trigger a local proinflammatory environment-inducing vasodilatation and attracting monocytes and neutrophils to sites causing tissue damage and stress. Both IL-1 $\alpha$  and IL-1 $\beta$  have been shown to induce myocarditis and aneurysm formation in

Lactobacillus casei cell-wall extract mouse model of KD; both being successfully improved with IL-1 blockade treatment such as anakinra. Treatment failure in patients with the high-risk inositol-triphosphate 3-kinase C genotype was associated with highest basal and stimulated intracellular calcium levels, increased cellular production of IL-1 $\beta$ , and IL-18, and higher circulating levels of both cytokines. Three clinical trials of IL-1 blockade enrolling KD patients are currently being conducted in Western Europe and in USA, they could change KD outcome.

DOI: 10.3389/fphar.2017.00163

PMCID: PMC5368266

PMID: 28400731

813. Front Immunol. 2017 Mar 27;8:299. doi: 10.3389/fimmu.2017.00299. eCollection 2017.

Disease Phenotype and Outcome Depending on the Age at Disease Onset in Patients Carrying the R92Q Low-Penetrance Variant in TNFRSF1A Gene.

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**BACKGROUND:** Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is an autosomal-dominant autoinflammatory disease caused by mutations in the

TNFRSF1A gene. R92Q, a low-penetrance variant, is usually associated with a milder TRAPS phenotype than structural or pathogenic mutations. No studies differentiating R92Q-related disease in patients with pediatric and adult onset have been performed to date.

**OBJECTIVE:** To analyze clinical features and disease outcomes in patients diagnosed with TRAPS associated with R92Q variant and to investigate differences between patients with pediatric and adult disease onset.

**METHODS:** A retrospective review of patients with R92Q-related disease from four reference centers for autoinflammatory diseases was performed. Clinical and laboratory features, family history of autoinflammatory diseases, treatments received, and outcomes during follow-up were recorded and separately analyzed in pediatric and adult patients. Our results were included in the analysis with other reported pediatric and adult R92Q-related disease series.

**RESULTS:** Our series encompassed 18 patients (9 females and 9 males) with R92Q variant. In 61% of patients, disease onset occurred during infancy and in 39%, during adulthood, with a median diagnostic delay of 5 years and a follow-up of 5.4 years. A positive family history of autoinflammatory disease was detected in 28% of patients. All patients presented with febrile recurrent episodes. Other common symptoms included arthralgia/arthritis (61%), myalgia (39%), asthenia/fatigue (44%), abdominal pain (39%), headache (33%), odynophagia (33%), skin rash (28%), and chest pain (22%). During attacks, 80% of patients increased acute phase reactants levels. No patient had developed amyloidosis during the study period. At the end of follow-up, 28% of patients were asymptomatic and treatment free, 50% were receiving non-steroidal anti-inflammatory drugs or glucocorticoids on demand, and 22% were being treated with biologic agents. When differences between pediatric and adult patients were globally analyzed, adults tended to have longer attacks duration and presented more frequently with chest pain and headache, while abdominal pain, vomiting, cervical adenitis, and pharyngitis predominated in pediatric patients. No differences in outcomes and treatment requirements were observed in both age groups.

**CONCLUSION:** This study has contributed to characterize R92Q-related disease by identifying trends in disease phenotypes depending on the age at disease onset.

DOI: 10.3389/fimmu.2017.00299

PMCID: PMC5366323

PMID: 28396659

## Effect of Familial Mediterranean Fever on Ivf Outcome: A Retrospective Case Series.

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Although the in vitro fertilization-intra-cytoplasmic sperm injection (IVF-ICSI) has been utilized widely, the management in patients with an autoimmune disease is still a challenge. The aim of this study was to demonstrate IVF-ICSI outcomes in infertile women with familial Mediterranean fever (FMF). Patient data were collected from the cases registered from January 2006 until January 2014. A total of 6152 assisted reproductive technology (ART) cycles were analyzed retrospectively in the Ankara Zekai Tahir Burak Women's Health Education and Research Hospital. Ten infertile women with FMF were included in the study. Baseline clinical and laboratory characteristics were collected and perinatal outcomes evaluated. The mean age (years), duration of infertility (years) and body mass index (kg/m<sup>2</sup>) were 29.9±5.3, 5.7±5.3 and 27.9±5.7, respectively. The mean baseline follicle-stimulating hormone (FSH; IU/L), estradiol (E<sub>2</sub>; pg/mL) and antral follicle count were 7.0±2.4, 48.1±15.8 and 7.9±2.9, respectively. The distribution of ovarian response was heterogeneous. Fourteen cycles in ten patients were evaluated. Embryo transfer could be achieved in only ten cycles. Three out of ten patients became pregnant. No adverse perinatal outcome was observed. Our findings indicate that FMF might have no impact on ART cycles.

DOI: 10.20471/acc.2016.55.02.11

PMID: 28394112 [Indexed for MEDLINE]



Skin microbiome and mast cells.

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Microbiotas in the skin have high levels of diversity at the species level, but low phylum-level diversity. The human skin microbiota is composed predominantly of Gram-positive bacteria especially Actinobacteria, which are the dominant bacterial phylum on the skin. Lipoteichoic acid (LTA) is a major constituent of the cell wall of Gram-positive bacteria and is therefore abundant in the skin microbiome. Recent studies have shown that LTA, and other bacterial products, permeates the whole skin and comes into contact with epidermal and dermal cells, including mast cells (MCs), with the potential of stimulating MC toll-like receptors (TLRs). MCs express a variety of pattern recognition receptors, including TLRs, on their cell surface in order to detect bacteria. Recent publications suggest that the skin microbiome has influence on MC migration, localization and maturation in the skin. Germ free (no microbiome) animals possess an underdeveloped immune system and immature MCs. Despite much research done on skin microbiota and many papers describing skin interaction with "the good microbiota", there is still controversy regarding how mast cells, communicate with surface bacteria. The present review intends to quell the controversy by illuminating the communication mechanism between bacteria and MCs.

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DOI: 10.1016/j.trsl.2017.03.003

PMCID: PMC5538027

PMID: 28390799 [Indexed for MEDLINE]

816. Z Rheumatol. 2017 May;76(4):322-327. doi: 10.1007/s00393-017-0285-5.

[Familial chilblain lupus : Type 1 interferonopathy with model character].

[Article in German]

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Familial chilblain lupus belongs to the group of type 1 interferonopathies and is particularly characterized by typical skin manifestations and ischemia of the acra. There are various mutations that can lead to this autosomal dominant disease. A mutation in the TREX-1 gene has been most frequently found; however, families with mutations in the SAMHD1 gene and recently in the gene which codes for the stimulator of interferon genes (STING) protein were also described. A common feature of these genetic defects is that they are all involved in the process of detection of intracellular free DNA, which as a result leads to increased production of type 1 interferons and the induced gene products. This then leads to autoinflammation and autoimmunity, which is characteristic for the disease. The activation of interferon-induced genes is controlled by the JAK-STAT system; therefore, JAK inhibitors were successfully used in several cases to treat type 1 interferonopathies. Experience with this treatment modality is continuously growing.

DOI: 10.1007/s00393-017-0285-5

PMID: 28389709 [Indexed for MEDLINE]

817. Immunol Invest. 2017 May;46(4):419-432. doi: 10.1080/08820139.2017.1288240. Epub 2017 Apr 7.

Natural Killer Cell Subsets and Their Functional Activity in Behçet's Disease.

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**BACKGROUND:** Behçet's disease (BD) is a rare, chronic autoinflammatory disorder of unknown origin. Natural killer (NK) cells are one of the major immunoregulatory cell groups of the innate immune system, but their role in BD pathogenesis is not well documented.

**OBJECTIVES:** We aimed to investigate the role of NK cell subsets and their cytokine secretion and cytotoxic activity in patients with BD.

**PATIENTS AND METHODS:** The study group consisted of BD patients who had only mucocutaneous involvement, and they were compared with healthy subjects. BD patients were divided into two groups according to their frequencies of oral ulcerations. NK cell cytotoxicity was determined using CD107a expression and a CFSE-based cytotoxicity test. Expression of NK cell receptors and surface markers and the intracellular IL-5, IL-10, IL-17, and IFN- $\gamma$  levels in CD16<sup>+</sup> NK cells were assessed by flow cytometry.

**RESULTS:** Although the cytokine secretion pattern was different, no difference was obtained in cytotoxic activity, expression of activatory receptors, or degranulation of NK cells.

**CONCLUSION:** Increases in NK1/NK2 ratio and CD16<sup>+</sup>IFN- $\gamma$ <sup>+</sup> NK1 cells might support the idea of a biased IFN- $\gamma$  dominant immune response in the mucocutaneous involvement of BD pathogenesis. Although the cytokine secretion pattern was different, no difference was obtained in cytotoxic activity, expression of activatory receptors, or degranulation of NK cells.

DOI: 10.1080/08820139.2017.1288240

PMID: 28388249 [Indexed for MEDLINE]

818. Int Immunol. 2017 Nov 1;29(9):393-400. doi: 10.1093/intimm/dxx020.

A clinical update on inflammasomopathies.

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Inflammasomes are important elements of the innate immune defense. The most common autoinflammatory syndromes, as well a number of rare ones, are due to hereditary defects in the inflammasomes, hence are called inflammasomopathies. The recent clinical advances in these diseases will be reviewed, with special emphasis on reflecting the international collaborative work in the field. Recent recommendations for familial Mediterranean fever, cryopyrin-associated periodic syndromes and hyper-IgD syndrome/mevalonate kinase deficiency will be presented and diagnostics tests, treatment alternatives and follow-up recommendations will be summarized. The other rare inflammasomopathies will be briefly discussed based on clinical features; these diseases are pyogenic arthritis, pyoderma gangrenosum and acne, NLRC4-related macrophage-activation syndrome of enterocolitis, mutations in NLRP12 that cause hereditary periodic fever syndromes (familial cold inflammatory syndrome 2) and NLRP1-associated autoinflammation with arthritis and dyskeratosis.

Published by Oxford University Press on behalf of The Japanese Society for Immunology 2017.

DOI: 10.1093/intimm/dxx020

PMID: 28387826 [Indexed for MEDLINE]

819. Front Immunol. 2017 Mar 23;8:253. doi: 10.3389/fimmu.2017.00253. eCollection 2017.

Familial Mediterranean Fever: Recent Developments in Pathogenesis and New Recommendations for Management.

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Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory

disease (AID) affecting mainly the ethnic groups originating from Mediterranean basin. The disease is characterized by self-limited inflammatory attacks of fever and polyserositis along with elevated acute phase reactants. FMF is inherited autosomal recessively; however, a significant proportion of heterozygotes also express the phenotype. FMF is caused by mutations in the MEFV gene coding for pyrin, which is a component of inflammasome functioning in inflammatory response and production of interleukin-1 $\beta$  (IL-1 $\beta$ ). Recent studies have shown that pyrin recognizes bacterial modifications in Rho GTPases, which results in inflammasome activation and increase in IL-1 $\beta$ . Pyrin does not directly recognize Rho modification but probably affected by Rho effector kinase, which is a downstream event in the actin cytoskeleton pathway. Recently, an international group of experts has published the recommendations for the management of FMF. Colchicine is the mainstay of FMF treatment, and its regular use prevents attacks and controls subclinical inflammation in the majority of patients. Furthermore, it decreases the long-term risk of amyloidosis. However, a minority of FMF patients fail to response or tolerate colchicine treatment. Anti-interleukin-1 drugs could be considered in these patients. One should keep in mind the possibility of non-compliance in colchicine-non-responders. Although FMF is a relatively well-described AID and almost 20 years has passed since the discovery of the MEFV gene, there are still a number of unsolved problems about it such as the exact mechanism of the disease, symptomatic heterozygotes and their treatment, and the optimal management of colchicine resistance.

DOI: 10.3389/fimmu.2017.00253

PMCID: PMC5362626

PMID: 28386255

820. J Pediatric Infect Dis Soc. 2018 May 15;7(2):119-123. doi: 10.1093/jpids/pix016.

Using the Electronic Medical Record to Correlate Kawasaki Disease Phenotypes With Clinical Outcomes.

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**Background:** We sought to systematically standardize the documentation of clinical and laboratory features in Kawasaki disease (KD) on the day of initial treatment and correlate the presentation with clinical outcomes.

**Methods:** Kawasaki disease features and classification were documented by the attending physician using a standardized documentation tool on the day of treatment for KD, including confidence in the KD diagnosis on a 4-point scale. Incomplete KD was further classified using American Heart Association (AHA) criteria (sufficient or insufficient) and baseline echocardiogram data. We prospectively recorded intravenous immunoglobulin (IVIG) resistance, coronary artery abnormalities (CAAs), periungual peeling, and retrospectively identified subsequent diagnoses of autoimmune/inflammatory disease.

**Results:** From November 2012 to October, 2015, 162 patients were treated for KD: 105 with complete KD (Group 1), 7 with incomplete KD based on CAAs on day of KD diagnosis (Group 2), 23 with incomplete KD meeting AHA criteria (Group 3), and 27 with incomplete KD and insufficient AHA criteria (Group 4). Group 4 patients had lower baseline median C-reactive protein levels (Group 4 median 4.65 mg/dL [interquartile range {IQR}, 2.3-13.6] vs Group 1 median 8.0 mg/dL [IQR, 4.5-17], Group 2 median 13.9 mg/dL [IQR, 1.4-18.2], Group 3 median 13.3 mg/dL [IQR, 4.9-20.2]), and no coronary abnormalities developed, although 11% had IVIG resistance. Group 4 had higher rates of subsequent autoimmune/inflammatory conditions diagnosed (11.1% in Group 4 vs <5% for all others,  $P = .02$ ).

**Conclusions:** Standardized documentation and classification of KD features may be useful to correlate with clinical outcomes, including subsequent diagnosis of autoimmune/autoinflammatory disease. Among patients with incomplete KD who did not meet AHA criteria and had a normal baseline echocardiogram, the IVIG resistance rate may have been related to a lower likelihood of an accurate diagnosis of KD.

DOI: 10.1093/jpids/pix016

PMID: 28383697 [Indexed for MEDLINE]

## Genetic and Epigenetic Determinants in Autoinflammatory Diseases.

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The concept of autoinflammation has evolved over the past 20 years, beginning with the discovery that mutations in the Mediterranean Fever (MEFV) gene were causative of Familial Mediterranean Fever. Currently, autoinflammatory diseases comprise a wide range of disorders with the common features of recurrent fever attacks, prevalence of hyperreactive innate immune cells, and signs of inflammation that can be systemic or organ specific in the absence of pathogenic infection or autoimmunity. Innate immune cells from the myeloid compartment are the main effectors of uncontrolled inflammation that is caused in great extent by the overproduction of inflammatory cytokines such as IL-1 $\beta$  and IL-18. Defects in several signaling pathways that control innate immune defense, particularly the hyperreactivity of one or more inflammasomes, are at the core of pathologic autoinflammatory phenotypes. Although many of the autoinflammatory syndromes are known to be monogenic, some of them are genetically complex and are impacted by environmental factors. Recently, epigenetic dysregulation has surfaced as an additional contributor to pathogenesis. In the present review, we discuss data that are currently available to describe the contribution of epigenetic mechanisms in autoinflammatory diseases.

DOI: 10.3389/fimmu.2017.00318

PMCID: PMC5360705

PMID: 28382039

822. *Pediatr Rheumatol Online J.* 2017 Apr 5;15(1):19. doi: 10.1186/s12969-017-0152-6.

Munchausen by proxy syndrome mimicking systemic autoinflammatory disease: case report and review of the literature.

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**BACKGROUND:** Systemic autoinflammatory diseases (SAIDs) represent a growing number of monogenic, polygenic or multifactorial disorders that are often difficult to diagnose.

**CASE PRESENTATION:** Here we report a patient who was initially erroneously diagnosed and treated for SAID. Symptoms consisted of recurrent fever, erythematous and/or blistering skin lesions, angioedema, susceptibility to bleeding, external ear infections and reversible anisocoria in the absence of laboratory evidence of systemic inflammation. After two and a half years of extensive diagnostic work-up and multiple empirical therapies, a final diagnosis of Munchausen by proxy syndrome (MBPS) was established.

**CONCLUSIONS:** The diagnosis of SAID needs to be carefully reassessed if measurable systemic inflammation is missing, and MBPS should be included in the differential diagnosis.

DOI: 10.1186/s12969-017-0152-6

PMCID: PMC5382472

PMID: 28381287 [Indexed for MEDLINE]

823. Z Rheumatol. 2017 May;76(4):295-302. doi: 10.1007/s00393-017-0300-x.

[Genetic methods for analysis of autoinflammatory diseases].

[Article in German]

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Over the past years the phenotypic and genetic spectrum of autoinflammatory diseases has continuously increased. Moreover, several monogenic autoinflammatory disorders have now been identified where febrile episodes are not among the leading symptoms and which can be accompanied by autoimmune phenomena and susceptibility to infections. Autoinflammatory conditions that are characterized by uncontrolled activity of cytokines, such as interleukin-1 beta (IL1 $\beta$ ), tumor necrosis factor alpha (TNF- $\alpha$ ) and type 1 interferons (1-IFN), are amenable to specific therapeutic interventions. Thus, identification of the underlying genetic cause is important. During diagnostic work-up, genetic testing of a patient with autoinflammation should be carried out depending on the clinical presentation. If a distinct disorder is suspected, sequencing of the causative gene should be performed. Genetic tests using next generation sequencing (NGS), such as panel sequencing, exome sequencing and array comparative genomic hybridization (CGH) can be carried out if symptoms cannot be assigned to a specific disease entity.

DOI: 10.1007/s00393-017-0300-x

PMID: 28378116 [Indexed for MEDLINE]

824. Clin Exp Rheumatol. 2017 May-Jun;35 Suppl 104(2):13-14. Epub 2017 Apr 4.

Circulating intercellular adhesion molecule 1 (sICAM-1) in tumour necrosis factor receptor-associated periodic syndrome (TRAPS).

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PMID: 28375838 [Indexed for MEDLINE]

825. FEBS J. 2017 Aug;284(15):2363-2374. doi: 10.1111/febs.14076. Epub 2017 Apr 26.

Inflammasome activation by nucleic acids and nucleosomes in sterile inflammation...  
or is it sterile?

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Inflammasomes are multiprotein complexes that form in the cytoplasm in response to cellular damage and cytosolic pathogen-associated molecules during infection. These complexes play important roles in initiating innate and adaptive immune responses to infectious disease. In addition, inflammasomes are now recognized as important mediators of sterile inflammation in various autoimmune and autoinflammatory diseases. Interestingly, microbiota and infection play critical roles in the development of 'sterile inflammation'. Herein, we highlight recent advances in our understanding of the role for inflammasomes in nucleic acid-, nucleosome-, and histone-driven sterile inflammation and discuss knowledge gaps

and areas of potential future research.

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DOI: 10.1111/febs.14076

PMCID: PMC5683406

PMID: 28374568 [Indexed for MEDLINE]

826. Arch Rheumatol. 2017 Apr 5;32(3):244-249. doi: 10.5606/ArchRheumatol.2017.6071. eCollection 2017 Sep.

Deteriorated Systolic Blood Pressure Recovery and Heart Rate Recovery After Graded Exercise in Children With Familial Mediterranean Fever.

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**Objectives:** This study aims to investigate if cardiac involvement may occur in children with familial Mediterranean fever (FMF) without cardiovascular symptoms by using heart rate recovery (HRR) and systolic blood pressure recovery (SBPR) parameters.

**Patients and methods:** A total of 50 FMF patients (26 males, 24 females; mean age  $151 \pm 33.4$  month; range 60 to 216 month) and 30 healthy controls (18 males, 12 females; mean age  $143 \pm 43.9$  month; range 84 to 228 month) were included in the study. All patients were evaluated by echocardiography. All patients underwent a maximal graded exercise stress test. HRR and SBPR parameters were calculated.

**Results:** There was a significant decrease in HRR1 value in FMF group ( $p=0.03$ ). SBPR1 and SBPR2 values were higher in FMF group compared to control group ( $0.96 \pm 0.12$  vs  $0.88 \pm 0.12$  and  $0.95 \pm 0.09$  vs  $0.91 \pm 0.11$ , respectively); and the high

SBPR1 value was statistically significant ( $p=0.02$ ). FMF presence had a negative correlation with HRR1 ( $r= -0.26$ ,  $p=0.03$ ) and a positive correlation with SBPR1 ( $r=0.29$ ,  $p=0.02$ ). There was a negative correlation of M694V homozygous mutation with HRR1 and HRR2 values ( $r= -0.43$ ,  $p=0.004$ ,  $r=-0.42$ ,  $p=0.005$ ).

Conclusion: Cardiac involvement may occur in FMF patients without cardiovascular symptoms. Impaired SBPR and decreased HRR response may indicate increased cardiovascular risk in these patients despite normal exercise stress test results.

DOI: 10.5606/ArchRheumatol.2017.6071

PMCID: PMC6190945

PMID: 30375532

Conflict of interest statement: Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

827. Acta Reumatol Port. 2017 Jan-Mar;42(1):88-90.

Tofacitinib suppresses disease activity and febrile attacks in a patient with coexisting rheumatoid arthritis and familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is the most common hereditary auto-inflammatory (periodic fever) syndrome, and usually successfully treated with colchicine. However, nearly 5-10% of FMF cases are resistant or intolerant to colchicine and treatment options are highly restricted in these cases.

Biologics including anakinra, canakinumab, rilonacept, etanercept, infliximab, interferon-alpha, and tocilizumab are shown to have efficacy to control FMF attacks. Tofacitinib, a Janus kinase (JAK) inhibitor, is an orally administered non-biologic disease modifying anti-rheumatic drug for the treatment of rheumatoid arthritis (RA). Herein we report a female patient with coexisting RA and colchicine resistant FMF whose FMF attacks and disease activity were completely controlled after treatment with tofacitinib, a small-molecule JAK3

inhibitor.

PMID: 28371574 [Indexed for MEDLINE]

828. Rep Biochem Mol Biol. 2017 Apr;5(2):117-120.

Genetic Analysis of Southwestern Iranian Patients with Familial Mediterranean Fever.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is an autosomal recessive genetic disorder characterized by recurrent episodes of self-limited fever and serosal tissues inflammation.

**METHODS:** To evaluate clinical symptoms and common genetic mutations in southwestern Iranian patients with FMF, 20 unrelated patients were enrolled in this study based on clinical criteria. A panel of 12 common MEFV gene mutations was tested.

**RESULTS:** The most frequent clinical presentations of the patients were fever, colicky abdominal pain and arthritis. Eighteen patients responded completely to colchicine therapy. MEFV gene mutations were detected in only 40% of the patients. The most common mutation was E148Q, detected in five patients (25%). The V726A, M694V and P369S mutations were each observed in one patient.

**CONCLUSIONS:** Although none of the 12 mutations we included in our test panel was detected in 60% of our patients, all of them had FMF symptoms and responded well to colchicine. MEFV full gene sequencing analysis in these patients may lead to finding new mutations in southwestern Iranian FMF patients which would be helpful in designing a local diagnostic kit.

PMCID: PMC5346280

PMID: 28367474

829. Expert Rev Clin Immunol. 2017 May;13(5):393-404. doi: 10.1080/1744666X.2017.1313116. Epub 2017 Apr 10.

Canakinumab for the treatment of familial Mediterranean fever.

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Erratum in

Expert Rev Clin Immunol. 2017 May;13(5):viii.

**INTRODUCTION:** Familial Mediterranean fever (FMF) is the most frequent of all hereditary autoinflammatory syndromes. It is characterized by recurrent attacks of fever and serositis. If not treated it may be complicated with AA amyloidosis. It is caused by mutations in the MEFV gene that encodes pyrin which is involved in the regulation of IL-1 $\beta$ . The mainstay of treatment is colchicine, however a subset of patients requires an alternative treatment either due to inadequate response or intolerance. The accumulating data indicates that anti IL-1 drugs are effective in treating colchicine resistant FMF cases and improving their quality of life. Areas covered: This review focuses on canakinumab, a fully human anti IL-1 $\beta$  antibody, treatment in FMF. Expert commentary: Canakinumab became the first approved therapy by the Food and Drug Administration for FMF very recently, which highlights its importance as the alternative treatment in FMF.

DOI: 10.1080/1744666X.2017.1313116

PMID: 28362189 [Indexed for MEDLINE]

830. Curr Rheumatol Rep. 2017 Apr;19(4):18. doi: 10.1007/s11926-017-0645-9.

Chronic Recurrent Multifocal Osteomyelitis and Related Diseases-Update on

Pathogenesis.

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**PURPOSE OF REVIEW:** We focus on recent advances in the understanding of the genetic, molecular, immunologic, and environmental factors implicated in the pathogenesis of autoinflammatory bone diseases including the syndromic and non-syndromic forms of chronic recurrent multifocal osteomyelitis (CRMO).

**RECENT FINDINGS:** Evidence implicating the IL-1 pathway in the pathogenesis of the Mendelian forms of CRMO is growing. LIPIN2 can regulate the NLRP3 inflammasome by affecting P2X7 receptor activation, and intracellular cholesterol can modulate P2X7R currents. Work in a mouse model of CRMO demonstrates that dietary manipulation can alter the microbiome and protect these mice from the development of sterile osteomyelitis in vivo. Although the genetic and immunologic basis of non-syndromic CRMO remains only partially understood, the IL-1 pathway is central to the pathogenesis in the syndromic autoinflammatory bone disorders. Recent work implicates lipids and the microbiome in sterile osteomyelitis.

DOI: 10.1007/s11926-017-0645-9

PMCID: PMC5545929

PMID: 28361334 [Indexed for MEDLINE]

831. Mol Genet Genomic Med. 2017 Jan 14;5(2):110-116. doi: 10.1002/mgg3.229. eCollection 2017 Mar.

Clinical dose effect and functional consequences of R92Q in two families presenting with a TRAPS/PFAPA-like phenotype.

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**BACKGROUND:** TNF receptor-associated syndrome (TRAPS) is a dominantly inherited autoinflammatory condition caused by mutations in the TNFRSF1A gene. The mechanism underlying the variable expressivity of the common variant R92Q (rs4149584; c.362G>A; p.Arg121Gln) is unclear and is of critical importance for patient care and genetic counseling. This study evaluated the impact of the number of R92Q mutations in two unique unrelated families.

**METHODS:** Two patients with undefined but clear autoinflammatory symptoms were referred for genetic diagnosis. Blood samples were collected from the available family members to screen autoinflammatory genes and assess key steps of the TNFR1-mediated signaling pathway using flow cytometry and ex vivo culture.

**RESULTS:** R92Q homozygosity was demonstrated for the two probands. In family 1, the segregation analysis revealed TRAPS-like symptoms in all carriers, with a more severe presentation in the proband, whereas in family 2, the heterozygous parents were totally asymptomatic, suggesting recessive transmission. Functional studies revealed a nonclassical pathogenesis of TRAPS in the two probands and suggested a compensatory mechanism without clear dose effect.

**CONCLUSION:** We observed for the first time a possible clinical dose effect of R92Q. This work highlights the importance of familial studies to reconcile the contradictory reports published on the pathogenicity of this variant.

DOI: 10.1002/mgg3.229

PMCID: PMC5370222

PMID: 28361096



832. Am J Cardiovasc Drugs. 2017 Oct;17(5):347-360. doi: 10.1007/s40256-017-0226-3.

Teaching an Old Dog New Tricks: Colchicine in Cardiovascular Medicine.

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Colchicine is one of the oldest known drugs that remains part of the current pharmacopeia. Recent studies have examined the efficacy of colchicine in cardiology with promising results. We conducted a search of electronic databases for studies on colchicine in cardiovascular medicine published through October 2016. As the utilization of colchicine in the management of cardiac conditions grows, it is paramount that internists and cardiologists are familiarized with its benefits and risks. We present a comprehensive review of the role of colchicine in the management of cardiovascular diseases with a strong emphasis on side effects and potential drug interactions.

DOI: 10.1007/s40256-017-0226-3

PMID: 28353024 [Indexed for MEDLINE]

833. Int J Dermatol. 2017 Aug;56(8):811-818. doi: 10.1111/ijd.13603. Epub 2017 Mar 27.

Autoinflammatory syndromes associated with hidradenitis suppurativa and/or acne.

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Autoinflammatory syndromes associated with hidradenitis suppurativa (HS) and/or acne are rare but potentially debilitating disorders if not diagnosed and treated correctly. They share a common pathogenesis involving a dysregulated innate immune system with abnormal interleukin (IL)-1 signaling leading to sterile neutrophilic inflammation. The clinical features are recurrent episodes of fever, painful arthritis, and skin lesions consistent with HS, acne, and pyoderma gangrenosum (PG) accompanied by elevated systemic inflammatory markers in blood. So far, several clinically different syndromes have been reported in the literature including pyoderma gangrenosum, acne, and pyogenic arthritis (PAPA), pyoderma gangrenosum, acne, and hidradenitis suppurativa (PASH), pyoderma gangrenosum, acne, and spondyloarthritis (PASS), pyoderma gangrenosum, acne, pyogenic arthritis, and hidradenitis suppurativa (PAPASH), psoriatic arthritis, pyoderma gangrenosum, acne, and hidradenitis suppurativa (PsAPASH), and pyoderma gangrenosum, acne, and ulcerative colitis (PAC). The rarity of the syndromes complicates the establishment of evidence-based treatment guidelines. Furthermore, treatment can be challenging due to lack of response to standard treatment modalities. Therefore, it is important to increase the awareness about these diseases in order to optimize disease management and ultimately improve the quality of life of patients.

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DOI: 10.1111/ijd.13603

PMID: 28345207 [Indexed for MEDLINE]

834. Wiad Lek. 2017;70(1):144-147.

Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (pfapa) syndrome in children.

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**INTRODUCTION:** Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome refers to a group of primary immunodeficiencies, namely autoinflammatory diseases. Most pediatricians and otolaryngologists do not suspect PFAPA syndrome when treating recurrent pharyngitis (according to Ukrainian classification - tonsillitis) and stomatitis. Therefore, patients with a given syndrome receive unnecessary treatment (antibiotic therapy or antiviral drugs) and the diagnosis is made late. The aim of the research was to provide pediatricians, family physicians and otolaryngologists with information on the importance of early diagnosis of PFAPA syndrome.

**MATERIALS AND METHODS:** The analysis of the prevalence and diagnosis of PFAPA syndrome in Ukraine and worldwide has been made as well as a late diagnosis of PFAPA syndrome in a child living in Ivano-Frankivsk, Ukraine has been described (case report).

**RESULTS:** The Case report 7-year-old boy, who grows and develops normally. The symptoms of pharyngitis including high body temperature ( $>40^{\circ}\text{C}$ ), sore throat and white spots on the tonsils appeared for the first time at the age of two years. The boy received antibacterial drugs about 10 times a year. During a four-year period of recurrent episodes of the disease antimicrobial susceptibility testing to determine susceptibility of the oropharyngeal flora to the antibiotics were continuously performed, different blood tests for herpes viruses, Epstein-Barr virus infection and cytomegalovirus in particular were made using the enzyme immunoassay (EIA) and polymerase chain reaction (PCR) in addition to long-term treatment.

**CONCLUSIONS:** An example of late diagnosing PFAPA syndrome (four years after the onset of first symptoms) resulting in regular examinations, medical manoeuvres, outpatient and inpatient treatment, use of antibiotic therapy including intravenous injections on a monthly basis has been studied.

PMID: 28343210 [Indexed for MEDLINE]

835. J Allergy Clin Immunol. 2017 Nov;140(5):1378-1387.e13. doi: 10.1016/j.jaci.2017.02.021. Epub 2017 Mar 23.

Regulated in development and DNA damage responses 1 (REDD1) links stress with IL-1 $\beta$ -mediated familial Mediterranean fever attack through autophagy-driven neutrophil extracellular traps.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is an IL-1 $\beta$ -dependent autoinflammatory disease caused by mutations of Mediterranean fever (MEFV) encoding pyrin and characterized by inflammatory attacks induced by physical or psychological stress.

**OBJECTIVE:** We investigated the underlying mechanism that links stress-induced inflammatory attacks with neutrophil activation and release of IL-1 $\beta$ -bearing neutrophil extracellular traps (NETs) in patients with FMF.

**METHODS:** RNA sequencing was performed in peripheral neutrophils from 3 patients with FMF isolated both during attacks and remission, 8 patients in remission, and 8 healthy subjects. NET formation and proteins were analyzed by using confocal immunofluorescence microscopy, immunoblotting, myeloperoxidase-DNA complex ELISA, and flow cytometry. Samples from patients with Still's disease and bacterial

infections were used also.

**RESULTS:** The stress-related protein regulated in development and DNA damage responses 1 (REDD1) is significantly overexpressed during FMF attacks.

Neutrophils from patients with FMF during remission are resistant to autophagy-mediated NET release, which can be overcome through REDD1 induction. Stress-related mediators (eg, epinephrine) decrease this threshold, leading to autophagy-driven NET release, whereas the synchronous inflammatory environment of FMF attack leads to intracellular production of IL-1 $\beta$  and its release through NETs. REDD1 in autolysosomes colocalizes with pyrin and nucleotide-binding domain, leucine-rich repeat/pyrin domain-containing 3. Mutated pyrin prohibits this colocalization, leading to higher IL-1 $\beta$  levels on NETs.

**CONCLUSIONS:** This study provides a link between stress and initiation of inflammatory attacks in patients with FMF. REDD1 emerges as a regulator of neutrophil function upstream to pyrin, is involved in NET release and regulation of IL-1 $\beta$ , and might constitute an important piece in the IL-1 $\beta$ -mediated inflammation puzzle.

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DOI: 10.1016/j.jaci.2017.02.021

PMID: 28342915 [Indexed for MEDLINE]

836. J Cutan Pathol. 2017 Jun;44(6):591-595. doi: 10.1111/cup.12935. Epub 2017 Apr 18.

Clinical and histopathological features of cutaneous manifestations of adult-onset Still disease.

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Adult-onset Still disease (AOSD) is a rare autoinflammatory syndrome

characterized by recurring fevers, arthralgia, and consistent laboratory abnormalities that include leukocytosis and hyperferritinemia. Skin findings accompany the disease in nearly 90% of the cases. Early reports described evanescent, pruritic, salmon-pink or urticarial lesions, referred to as the typical eruption of AOSD. Histopathologic findings consist of superficial perivascular dermatitis with varying number of interstitial neutrophils. Later reports described a more persistent rash that tended to be photodistributed, hyperpigmented, often in a linear configuration, sometimes in a rippled pattern, referred to as the atypical eruption of AOSD. The presence of individual necrotic keratinocytes in the upper spinous layer has been the consistent histopathologic finding. The persistent rash may not represent an atypical presentation of AOSD as recent reports indicate a high prevalence of the rash. Emerging data also suggest that patients with persistent eruption have a worse prognosis. The recognition of the clinical and histopathological findings of skin eruptions of AOSD may facilitate an earlier diagnosis, potentially improving disease outcome. Herein, clinical and histopathological features of cutaneous manifestation of AOSD in 2 Asian women are highlighted accompanied by a relevant review of the disease.

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DOI: 10.1111/cup.12935

PMID: 28342280 [Indexed for MEDLINE]

837. Immunol Lett. 2017 May;185:74-78. doi: 10.1016/j.imlet.2017.03.001. Epub 2017 Mar 21.

Serum vitamin D level in Egyptian children with Familial Mediterranean fever.

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**BACKGROUND:** The aim of the study is to measure plasma vitamin D levels in a group of Egyptian children with familial Mediterranean fever (FMF) compared to healthy children.

**METHODS:** The study enrolled 52 children with FMF and 40 apparently healthy controls. Serum vitamin D level was measured by enzyme-linked immunosorbent assay.

**RESULTS:** The mean serum vitamin D level was significantly lower in children with FMF than control group ( $12.3 \pm 3.4$  and  $21.2 \pm 3.5$  ng/mL, respectively,  $p < 0.001$ ).

Vitamin D level was significantly lower in female patients than males ( $11.3 \pm 2.9$ ,  $13.2 \pm 3.6$ , respectively  $p = 0.04$ ). No statistically significant relations were detected between vitamin D level and different clinical, laboratory and genetic variables.

**CONCLUSION:** Vitamin D levels were lower in Egyptian FMF children than healthy controls. There is a speculation that vitamin D deficiency in FMF patients may be related to inflammation. Further studies with larger number of patients before and after Vitamin D, therapy may be needed. Supplementation with high doses of vitamin D seems appropriate for children with FMF.

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DOI: 10.1016/j.imlet.2017.03.001

PMID: 28341008 [Indexed for MEDLINE]

# Is There a Long-Term Risk for Donors With Heterozygous MEFV Mutation After Kidney Donation?

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**BACKGROUND:** Familial Mediterranean fever (FMF) is an autosomal-recessive autoinflammatory disorder manifested severely by systemic amyloidosis. It has been hypothesized that heterozygous carriers may also have susceptibility to certain symptoms or even diseases. Because the living kidney donors of patients with FMF are generally relatives of the kidney recipients, there is a high possibility that the donors will have a heterozygous mutation of the FMF gene. The goal of this study was to investigate the long-term kidney function of donors who are carriers of the Mediterranean fever (MEFV) gene.

**METHODS:** The medium- to long-term outcomes of 12 asymptomatic donors were compared with MEFV gene carriers and 24 non-FMF recipients' donors.

**RESULTS:** Heterozygous carriers and the control group were similar with respect to age, sex, and follow-up period. The preoperative estimated glomerular filtration rate and 24-hour urine proteinuria levels were similar in the MEFV carrier and control groups. Four years after the donation, both groups had similar estimated glomerular filtration rates, but the change in 24-hour urine protein was statistically higher in the MEFV carrier group, and no significant change was observed in the control group ( $P = .004$ ). At the end of the follow-up period, neither overt proteinuria nor kidney failure was seen in either group.

**CONCLUSIONS:** This study showed that the medium- to long-term results of the kidney donors who are carriers of the MEFV gene seem to be safe. However, there was more of a tendency for an increase in proteinuria in the MEFV gene carriers compared with control subjects, which necessitated further long-term care for these donors.



DOI: 10.1016/j.transproceed.2017.01.012

PMID: 28340799 [Indexed for MEDLINE]

839. JAAD Case Rep. 2017 Mar 10;3(2):103-105. doi: 10.1016/j.jdc.2017.01.004.  
eCollection 2017 Mar.

A case of autoinflammatory skin and bone disease flared by a change in  
osteoporosis management.

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DOI: 10.1016/j.jdc.2017.01.004

PMCID: PMC5347493

PMID: 28337469

840. Arthritis Res Ther. 2017 Mar 24;19(1):69. doi: 10.1186/s13075-017-1222-3.

Treatment of mucocutaneous manifestations in Behçet's disease with anakinra: a  
pilot open-label study.

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**BACKGROUND:** The effect of IL-1 blocking therapy on mucocutaneous manifestations  
of Behçet's disease is incompletely understood.

**METHODS:** Six patients with Behçet's disease and ongoing oral/genital ulcers for

≥1 month were enrolled into an adaptive, two-phase clinical trial and included in the analysis. Study duration was 6 months with extension up to 16 months. All were treated non-blinded with anakinra 100 mg subcutaneous daily with the option to escalate the dose to 200 mg in partial responders after 1 month and 300 mg after 6 months. Patients recorded the number and severity of ulcers in daily diaries. The primary outcome was remission defined as no ulcers on physical exam for two consecutive monthly visits between months 3 and 6. Secondary outcomes included the number and severity of patient-reported ulcers, patient/physician global scores, and standardized disease activity scores.

**RESULTS:** Two of six patients achieved the primary outcome. Five of six patients had improvement in the number and severity of ulcers. Non-statistically significant improvements were seen in secondary outcomes. Over the entire study, patients reported ≥1 oral and ≥1 genital ulcer on 665 (66%) and 139 (14%) days, respectively. On anakinra 200 mg vs 100 mg, patients reported fewer days with oral ulcers (65% vs 74% of days,  $p = 0.01$ ) and genital ulcers (10% vs 22% of days,  $p < 0.001$ ) and milder oral ulcer severity ( $p < 0.001$ ). Increase of anakinra to 300 mg did not result in further improvements. Adverse events were notable for mild infections.

**CONCLUSION:** Anakinra at an optimal dose of 200 mg daily had an acceptable safety profile and was partially effective in the treatment of resistant oral and genital ulcers in Behçet's disease.

**TRIAL REGISTRATION:** Clinicaltrials.gov. NCT01441076 . Registered on 24 September 2011.

DOI: 10.1186/s13075-017-1222-3

PMCID: PMC5364674

PMID: 28335798 [Indexed for MEDLINE]

841. Ophthalmic Epidemiol. 2017 Oct;24(5):346-351. doi: 10.1080/09286586.2017.1294697. Epub 2017 Mar 20.

Retinal and Choroidal Thickness in Adult Patients with Familial Mediterranean Fever.

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**PURPOSE:** We aimed to evaluate changes in retinal, choroidal, ganglion cell complex (GCC) and retinal nerve fiber layer (RNFL) thicknesses in genetically diagnosed adult patients with familial Mediterranean fever (FMF).

**METHODS:** A total of 50 eyes of 50 genetically diagnosed patients with FMF and 50 eyes of controls were analyzed. Patients were recruited from the Genetic Diagnostic Center of Dışkapı Yıldırım Beyazıt Research and Training Hospital, Turkey. Retinal and choroidal thicknesses were obtained using spectral-domain optical coherence tomography from choroid, retina, GCC, and RNFL.

**RESULTS:** Average baseline choroidal thickness was statistically significantly thinner in patients with FMF than controls at Ccenter ( $325.85 \pm 30.8 \mu\text{m}$  and  $338.97 \pm 23.9 \mu\text{m}$ , respectively,  $p = 0.038$ ), Cnasal500 ( $328.77 \pm 31.6 \mu\text{m}$  and  $349.00 \pm 23.3 \mu\text{m}$ , respectively,  $p = 0.002$ ), Cnasal1000 ( $324.97 \pm 33.6 \mu\text{m}$  and  $351.23 \pm 23.8 \mu\text{m}$  respectively,  $p = 0.0001$ ) and Cnasal1500 ( $324.75 \pm 37.1 \mu\text{m}$  and  $344.61 \pm 27.3 \mu\text{m}$ , respectively,  $p = 0.008$ ). However, there was no significant difference in temporal choroidal thickness (Ctemporal500, Ctemporal1000 and Ctemporal1500) in patients with FMF compared to controls ( $p > 0.05$ ). There were no significant differences in retinal, GCC and RNFL thicknesses between the groups ( $p > 0.05$ ).

**CONCLUSION:** We hypothesize that the chronic inflammation seen in FMF could be the reason for the reduction seen in choroidal thickness in adult patients with FMF.

Retinal, GCC and RNFL thicknesses did not differ from controls.

DOI: 10.1080/09286586.2017.1294697

PMID: 28319450 [Indexed for MEDLINE]

842. Dermatol Clin. 2017 Apr;35(2):117-128. doi: 10.1016/j.det.2016.11.002.

Quality of Life, Burden of Disease, Co-morbidities, and Systemic Effects in Vitiligo Patients.

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Vitiligo is a complex, systemic disease associated with many autoimmune and autoinflammatory conditions. Additionally, the cutaneous changes of vitiligo have significant effects on quality of life and self-esteem. Further efforts are needed to increase our understanding of vitiligo comorbidities as well as to increase awareness of the psychological effects of vitiligo.

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DOI: 10.1016/j.det.2016.11.002

PMID: 28317521 [Indexed for MEDLINE]

843. Orphanet J Rare Dis. 2017 Mar 16;12(1):54. doi: 10.1186/s13023-017-0609-1.

A survey of resistance to colchicine treatment for French patients with familial Mediterranean fever.

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**BACKGROUND:** Colchicine is the standard treatment for familial Mediterranean fever (FMF), preventing attacks and inflammatory complications. True resistance is rare and yet not clearly defined. We evaluated physicians' definition of colchicine resistance and report how they manage it.

**PATIENTS AND METHODS:** We recruited patients with a clinical diagnosis of FMF, one exon-10 Mediterranean fever (MEFV) gene mutation and considered resistant to colchicine, via networks of expert physicians. Clinical, biological characteristics and information about colchicine treatment (dose adjustment, compliance) were collected. The severity of FMF was assessed by the Tel Hashomer criteria.

**RESULTS:** We included 51 patients, most females (55%), mean age  $34 \pm 23.1$  years (range 4.7-86.3). Overall, 58% (27/47) patients had homozygous M694 MEFV gene mutations. Seventeen of 42 patients (40%) declared full adherence to colchicine treatment, greater for children (48%) than adults (22%). Physicians considered colchicine resistance with  $> 6$  attacks/year ( $n = 21/51$ , 42%),  $> 4$  attacks in the last 6 months ( $n = 13/51$ , 26%), persistent inflammation ( $n = 23/51$ , 45%), renal amyloidosis in ( $n = 6/28$ , 22%) of adult patients and intolerance to an increase in colchicine dose ( $n = 10/51$ , 19%), and other reasons ( $n = 13/51$ , 23%), including chronic arthralgia ( $n = 6/51$ , 12%). Interleukin 1-targeting drugs represented the only alternative treatments in addition to daily colchicine.

**CONCLUSION:** Resistance to colchicine is rare ( $<10\%$  of patients) and mostly observed in severe MEFV genotypes. The main reasons for physicians assessing resistance were severe clinical symptoms, persistent subclinical inflammation, and secondary amyloidosis. Low adherence to colchicine treatment is a key component of resistance.

DOI: 10.1186/s13023-017-0609-1

PMCID: PMC5356243

PMID: 28302131 [Indexed for MEDLINE]

eCollection 2017.

Recessive coding and regulatory mutations in FBLIM1 underlie the pathogenesis of chronic recurrent multifocal osteomyelitis (CRMO).

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Erratum in

PLoS One. 2017 Jul 7;12 (7):e0181222.

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare, pediatric, autoinflammatory disease characterized by bone pain due to sterile osteomyelitis, and is often accompanied by psoriasis or inflammatory bowel disease. There are two syndromic forms of CRMO, Majeed syndrome and DIRA, for which the genetic cause is known. However, for the majority of cases of CRMO, the genetic basis is unknown. Via whole-exome sequencing, we detected a homozygous mutation in the filamin-binding domain of FBLIM1 in an affected child with consanguineous parents. Microarray analysis of bone marrow macrophages from the CRMO murine model (cmo) determined that the Fblim1 ortholog is the most differentially expressed gene, downregulated over 20-fold in the cmo mouse. We sequenced FBLIM1 in 96 CRMO subjects and found a second proband with a novel frameshift mutation in exon 6 and a rare regulatory variant. In SaOS2 cells, overexpressing the regulatory mutation showed the flanking region acts as an enhancer, and the

mutation ablates enhancer activity. Our data implicate FBLIM1 in the pathogenesis of sterile bone inflammation and our findings suggest CRMO is a disorder of chronic inflammation and imbalanced bone remodeling.

DOI: 10.1371/journal.pone.0169687

PMCID: PMC5354242

PMID: 28301468 [Indexed for MEDLINE]

845. Eur J Rheumatol. 2017 Mar;4(1):66-67. doi: 10.5152/eurjrheum.2017.16075. Epub 2017 Mar 1.

Anakinra use during pregnancy: Report of a case with Familial Mediterranean Fever and infertility.

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Familial Mediterranean fever (FMF), affecting people of Mediterranean origin, is an endemic and sometimes problematic disease because of colchicine resistance/intolerance, with relative lack of treatment alternatives, and disease- or treatment-related issues, such as subfertility. Anakinra, being a rational and effective treatment alternative, has no conclusive human pregnancy data. Here we report a case of FMF with infertility who became pregnant with in vitro fertilization (IVF) under treatment with anakinra, along with the pregnancy outcome.

DOI: 10.5152/eurjrheum.2017.16075

PMCID: PMC5335891

PMID: 28293457

Conflict of interest statement: Conflict of Interest: No conflict of interest was declared by the authors.

846. Balkan J Med Genet. 2017 Mar 5;19(2):23-28. doi: 10.1515/bjmg-2016-0032.  
eCollection 2016 Dec 1.

The MEFV gene pathogenic variants and phenotype-genotype correlation in children with familial Mediterranean fever in the Çanakkale population.

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The aim of the current study was to determine the frequency of the Mediterranean fever (MEFV) gene pathogenic variants in 60 children diagnosed with familial Mediterranean fever (FMF) and to compare the phenotype-genotype correlation. Genomic DNA was isolated by the spin-column method from peripheral blood samples (collected in vacutainers containing EDTA) and buccal smears. The MEFV gene profiles for the current FMF cohort were genotyped by pyrosequencing and direct Sanger sequencing techniques for the target pathogenic variants. The most prominent clinical symptoms were abdominal pain (53.4%), fever (23.4%) and arthritis (23.3%). Eighteen different pathogenic variants were identified and the most frequent were p.Met694Val (20.0%), p.Glu148Gln (13.3%), p.Met680 Ile (11.7%) and p.Arg202Gln (11.7%). Abdominal pain, fever and arthritis were the most common presenting clinical characteristics. Results showed that not only clinical characteristics, but also genotyping of the MEFV gene is needed to establish the correct diagnosis of FMF in children and other family members.

DOI: 10.1515/bjmg-2016-0032

PMCID: PMC5343327

PMID: 28289585



847. Front Immunol. 2017 Feb 27;8:200. doi: 10.3389/fimmu.2017.00200. eCollection 2017.

## Cytokine Signatures in Mucocutaneous and Ocular Behçet's Disease.

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Behçet's disease (BD) is a multi-systemic inflammatory disorder consisting of recurrent oral aphthosis, genital ulcers, and chronic relapsing bilateral uveitis; however, many other organs may be affected. Several pro-inflammatory cytokines, mainly derived from Th1 and Th17 lymphocytes, seem to be involved in different pathogenic pathways leading to development of the clinical manifestations. On this basis, the primary aim of our study was to compare a core set of pro-inflammatory cytokines between patients with BD and healthy control (HC). The secondary goal was to evaluate potential correlations between these putative circulating biomarkers, the status of disease activity, and the specific organ involvement at the time of sample collection. Fifty-four serum samples were collected from 46 BD patients (17 males, 29 females, mean age  $45.5 \pm 11.3$  years), and 19 HC (10 males, 9 females, mean age  $43 \pm 8.3$  years). Twenty-five serum cytokines (APRIL/TNFSF13, BAFF/TNFSF13B, sCD30/TNFRSF8, sCD163, Chitinase3-like1, gp130/sIL-6Rb, IFN $\beta$ , sIL-6Ra, IL-10, IL-11, IL-19, IL-20, IL-26, IL-27 (p28), IL-28A/IFN-lambda2, IL-29/IFN-lambda1, IL-32, IL-34, IL-35, LIGHT/TNFSF-14, Pentraxin-3, sTNF-R1, sTNF-R2, TSLP, and TWEAK/TNFSF-12) were simultaneously quantified using a Bio-Rad cytokine bead arrays. Serum concentration of sTNF-R1 ( $p < 0.01$ ) and sTNF-R2 ( $p < 0.01$ ) resulted higher in both active and inactive BD than HC, while Chitinase3-like1 ( $p < 0.05$ ) and gp130/sIL-6Rb ( $p < 0.01$ ) serum levels were significantly higher in inactive BD, and IL-26 ( $p < 0.01$ ) in active BD than HC. No differences were observed between inactive and active BD group. In addition, we observed that gp130/sIL-6Rb, sIL-6Ra, IL-35, and TSLP serum levels

were significantly enhanced in patients with mucocutaneous manifestations plus ocular involvement (MO-BD) compared to subgroup with only mucocutaneous involvement (M-BD). Our findings may suggest a signature of IL-6, tumor necrosis factor- $\alpha$  as well as of Th17 response in BD patients due to increased levels of gp130/sIL-6Rb, sTNF-R1, sTNF-R2, IL-26, respectively. This evidence could contribute to improve the knowledge regarding the role of these cytokines in the induction of specific BD clinical features.

DOI: 10.3389/fimmu.2017.00200

PMCID: PMC5327443

PMID: 28289419

848. Rheumatol Int. 2017 Jun;37(6):883-889. doi: 10.1007/s00296-017-3688-3. Epub 2017 Mar 7.

Physicians' perspectives on the diagnosis and management of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome.

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To assess the practice patterns of pediatric rheumatology and infectious diseases subspecialists in the diagnosis and treatment of periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome. An online survey assessing diagnostic and treatment approaches was sent to 424 members of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) and 980 members of the Pediatric Infectious Disease Society (PIDS). 277 physicians (123 from CARRA and 154 from PIDS representing 21% of the total membership) completed the survey. To diagnose PFAPA, most respondents agreed that patients must have the following features of the diagnostic criteria: stereotypical fever episodes (95%), asymptomatic intervals between episodes (93%), and normal growth and development (81%). However, 71% of the respondents did not require age of onset <5 years, 33% did not require regular intervals between episodes, and 79% did not require the concomitant signs of aphthous stomatitis, adenitis, or pharyngitis during episodes as long as episodes were regular. Over half (58%) considered episode resolution with steroids to be diagnostic of PFAPA. Corticosteroids, antipyretics, tonsillectomy, and cimetidine were the most commonly prescribed treatments, while steroids and tonsillectomy were most effective. Subspecialists in pediatric rheumatology and infectious diseases showed limited adherence to the complete published criteria for diagnosing PFAPA suggesting heterogeneity in the characteristics of patients diagnosed with the disorder. These findings emphasize the need to develop consensus diagnostic and treatment guidelines in well-characterized patient populations.

DOI: 10.1007/s00296-017-3688-3

PMID: 28271158 [Indexed for MEDLINE]

849. Sci Rep. 2017 Mar 7;7:44127. doi: 10.1038/srep44127.

Double-stranded RNA induces inflammation via the NF- $\kappa$ B pathway and inflammasome activation in the outer root sheath cells of hair follicles.

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Alopecia areata (AA), a chronic, relapsing, hair-loss disorder, is considered to be a T cell-mediated autoimmune disease. It affects approximately 1.7% of the population, but its precise pathogenesis remains to be elucidated. Despite the recent attention focused on the roles of inflammasomes in the pathogenesis of autoinflammatory diseases, little is known about inflammasome activation in AA. Thus, in this study, we investigated the pattern of NLRP3 inflammasome activation in the outer root sheath (ORS) cells of hair follicles. We found that interleukin (IL)-1 $\beta$  and caspase-1 expression was increased in hair follicle remnants and inflammatory cells of AA tissue specimens. After stimulation of ORS cells with the double-stranded (ds)RNA mimic polyinosinic:polycytidylic acid (poly[I:C]), the activation of caspase-1 and secretion of IL-1 $\beta$  were enhanced. Moreover, NLRP3 knockdown decreased this poly(I:C)-induced IL-1 $\beta$  production. Finally, we found that high-mobility group box 1 (HMGB1) translocated from the nucleus to the cytosol and was secreted into the extracellular space by inflammasome activation. Taken together, these findings suggest that ORS cells are important immunocompetent cells that induce NLRP3 inflammasomes. In addition, dsRNA-induced IL-1 $\beta$  and HMGB1 secretion from ORS cells may contribute to clarifying the pathogenesis and therapeutic targets of AA.

DOI: 10.1038/srep44127

PMCID: PMC5339809

PMID: 28266599 [Indexed for MEDLINE]

850. Cell Mol Immunol. 2018 May;15(5):480-492. doi: 10.1038/cmi.2016.69. Epub 2017 Mar 6.

Aberrant Th2 inflammation drives dysfunction of alveolar macrophages and susceptibility to bacterial pneumonia.

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The ubiquitin ligase, Itch, is required to prevent autoinflammatory disease in mice and humans. Itch-deficient mice develop lethal pulmonary inflammation characterized by the production of Th2 cytokines (for example, interleukin-4 (IL-4)); however, the contribution of Itch to immune defense against respiratory pathogens has not been determined. We found that Itch-deficient mice were highly susceptible to intranasal infection with the respiratory pathogen *Klebsiella pneumoniae*. Infected Itch-deficient mice exhibited increased immune cell infiltration, cytokine levels and bacterial burden in the respiratory tract compared with control mice. However, numbers of resident alveolar macrophages were reduced in the lungs from Itch-deficient mice both before and after infection. High levels of Th2 cytokines in the respiratory tract correlated with decreased alveolar macrophages, and genetic ablation of IL-4 restored alveolar macrophages and host defense to *K. pneumoniae* in Itch-deficient mice, suggesting that loss of alveolar macrophages occurred as a consequence of Th2 inflammation. Adoptive transfer of Itch<sup>-/-</sup> CD4<sup>+</sup> T cells into Rag<sup>-/-</sup> mice was sufficient to drive reduction in numbers of Itch-replete alveolar macrophages. Finally, we found that Stat6 signaling downstream of the IL-4 receptor directly reduced fitness of alveolar macrophages when these cells were exposed to the Itch<sup>-/-</sup> inflamed respiratory tract. These data suggest that Th2 inflammation directly impairs alveolar macrophage fitness in Itch<sup>-/-</sup> mice, and elucidate a previously unappreciated link between Th2 cells, alveolar macrophages and susceptibility to bacterial infection.

DOI: 10.1038/cmi.2016.69

PMCID: PMC6068136

PMID: 28260794

851. Exp Clin Transplant. 2017 Feb;15(Suppl 1):261-264.

## Late Diagnosis of E148Q Mutation-Positive Familial Mediterranean Fever in a Kidney Transplant Patient With Fever of Unknown Origin: A Case Report.

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Fever of unknown origin is a rare condition after solid organ transplant and is generally associated with atypical infections (eg, tuberculosis, fungal infections) and/or lymphoproliferative disorders. Here, we present a kidney transplant patient with a late diagnosis of E148Q mutation-positive familial Mediterranean fever as the cause of fever of unknown origin. A 22-year-old female patient with a previous history of 4 years of hemodialysis and unknown primary renal disease received a deceased-donor kidney transplant at our center 5 years previously. She had an uneventful course in the first 3 years following transplant. After this period, she was hospitalized 3 times during a 4-month period with fever, nausea, vomiting, and atypical abdominal pain. At that time, hemogram results were unremarkable, except for mild leukocytosis and slightly elevated acute-phase reactants; blood, urine, and throat cultures were negative, and there were no remarkable findings on imaging tests. Fever was controlled within 48 hours by administering empiric ampicillin-sulbactam therapy and discontinuing immunosuppressive treatment except steroids. Three successive hospital admissions owing to similar complaints suggested periodic fever syndrome, and therapy with 1 g/day colchicine led to an excellent clinical response with no recurrence of fever or other symptoms. An FMF gene mutation analysis revealed heterozygous E148Q mutation positivity. Continuing the current treatment regimen, the patient did well during at approximately 1.5 years of follow-up. In the Mediterranean region population, familial Mediterranean fever should be considered in the diagnosis of fever of unknown origin in patients who have undergone renal transplant. E148Q mutation-positive familial Mediterranean fever has a subclinical course and renal manifestations that differ from AA amyloidosis during childhood and may be responsible for de novo familial Mediterranean fever after renal transplantation.

852. Exp Clin Transplant. 2017 Feb;15(Suppl 1):240-243.

## Infections After Renal Transplant in Recipients With Familial Mediterranean Fever: A Life-Threatening Issue.

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**OBJECTIVES:** We evaluated long-term results and infections requiring hospitalization in kidney transplant patients with Familial Mediterranean Fever (associated amyloidosis-type).

**MATERIALS AND METHODS:** We retrospectively reviewed medical records of patients with familial Mediterranean fever with at least 1-year posttransplant follow-up.

Kidney transplant recipients with primary glomerulonephritis and equivalent demography, immunity status, and follow-up comprised the control group.

**RESULTS:** In 32 patients with familial Mediterranean fever versus 25 control patients (mean follow-up  $82 \pm 57$  vs  $79 \pm 54$  mo;  $P = .82$ ), average serum creatinine values were  $1.7 \pm 0.9$  versus  $1.5 \pm 1.0$  mg/dL ( $P = .41$ ) at discharge,  $1.4 \pm 0.4$  versus  $1.3 \pm 0.5$  mg/dL ( $P = .44$ ) at 1 year,  $1.4 \pm 0.6$  versus  $1.3 \pm 0.5$  mg/dL ( $P = .63$ ) at 3 years, and  $2.0 \pm 1.5$  versus  $2.1 \pm 1.5$  mg/dL ( $P = .92$ ) at last follow-up. Groups were not statistically different regarding average inpatient and number of hospitalizations due to infections at 1 year; however, at last follow-up, 26 patients with familial Mediterranean fever (81%) had 8.6 average admissions and 13 control patients (52%) had 2.8 average admissions ( $P = .02$ ,  $P < .01$ ). Early posttransplant, both groups were taking a triple drug immunosuppression regimen. However, at 1 and 3 years posttransplant, withdrawal and/or minimization occurred in 40.6% and 83.3% of patients with familial Mediterranean fever and 28% and 55.5% of control patients ( $P < .05$ ,  $P < .05$ ). During follow-up, 6 familial Mediterranean fever patients (18.7%) and 2 control patients (8%) died ( $P = .23$ ).

**CONCLUSIONS:** Although renal transplant patients with associated amyloidosis-type familial Mediterranean fever and those with glomerulonephritis have similar

rejection and/or graft loss rates, hospital admissions due to infection and increased mortality are more common in the familial Mediterranean fever group, with immunosuppression drug withdrawal.

DOI: 10.6002/ect.mesot2016.P113

PMID: 28260476 [Indexed for MEDLINE]

853. J Ultrasound Med. 2017 May;36(5):1045-1049. doi: 10.7863/ultra.16.04037. Epub 2017 Mar 4.

Amyloid Goiter: A Diagnosis to Consider in Diffuse Fatty Infiltration of the Thyroid.

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An amyloid goiter is the presence of amyloid protein in the thyroid in sufficient amounts to produce enlargement of the gland, accompanied by fat deposition of varying extents. It can be seen in long-standing inflammatory disorders such as familial Mediterranean fever. Imaging findings depend on the amount of fat and amyloid deposition; however, the main imaging finding is diffuse fatty infiltration of the thyroid. Herein, the multimodality imaging features in 3 cases of amyloid goiters secondary to familial Mediterranean fever are presented.

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DOI: 10.7863/ultra.16.04037

PMID: 28258641 [Indexed for MEDLINE]

854. Z Rheumatol. 2017 May;76(4):292-294. doi: 10.1007/s00393-017-0284-6.

[Genetics of autoinflammatory syndromes].



[Article in German]

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DOI: 10.1007/s00393-017-0284-6

PMID: 28258405

855. Case Rep Gastrointest Med. 2017;2017:6863921. doi: 10.1155/2017/6863921. Epub 2017 Jan 31.

A Case of Eosinophilic Esophagitis Accompanying Familial Mediterranean Fever.

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Background. Eosinophilic esophagitis is an inflammatory condition where there is a dense infiltration of eosinophils typically exceeding fifteen cells per high power field. Familial Mediterranean fever is an autosomal recessive disorder characterized by brief, acute, and self-limited episodes of fever and

polyserositis that recur at irregular intervals. Case Presentation. A three-year-and-nine-month-old Iranian girl was admitted to our center. The patient's parents complained of a history of abdominal pain, poor appetite, and poor weight gain from 1.5 years ago and episodes of food impaction after starting solid foods. Eosinophilic esophagitis was diagnosed based on histology. Because of continuing abdominal pain after treatment of eosinophilic esophagitis, the episodic nature of disease, and the presence of fever with pain, screening for familial Mediterranean fever mutation was performed and the patient was found to be heterozygote for Mediterranean fever. Conclusion. We have reported a case of eosinophilic esophagitis coexisting with familial Mediterranean fever which has not been described previously.

DOI: 10.1155/2017/6863921

PMCID: PMC5306980

PMID: 28255474

Conflict of interest statement: The authors have no conflict of interests with the subject matter of this manuscript.

856. Infection. 2017 Aug;45(4):395-402. doi: 10.1007/s15010-017-0996-1. Epub 2017 Mar 1.

Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome: differential diagnosis of septic arthritis by regular detection of exceedingly high synovial cell counts.

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Pyogenic arthritis, pyoderma gangrenosum and acne syndrome was diagnosed in a 42-year-old patient, after an unusual persistency of high synovial cell counts had been noticed. Clinical peculiarities and problems with diagnosing septic

versus non-septic arthritis are discussed.

DOI: 10.1007/s15010-017-0996-1

PMID: 28251506 [Indexed for MEDLINE]

857. Nihon Jibiinkoka Gakkai Kaiho. 2017 Mar;120(3):209-16.

[Tonsillectomy in Cases with Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis Syndrome].

[Article in Japanese]

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The periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is an autoinflammatory disease, characterized, as its name suggests, by periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis. This syndrome is the most common cause of recurrent fever in children, however the rate of recognition of this syndrome is still low. Tonsillectomy has been suggested as an effective treatment, even though the precise, pathophysiology underlying this syndrome remains unknown. In this study, we investigated the outcomes in patients who underwent tonsillectomy. In particular, we examined the surgical outcomes and clinical features of the patients who underwent tonsillectomy. A total of 19 patients with PFAPA syndrome underwent tonsillectomy at our hospital from July 2013 to May 2016. Before the surgery, while all the patients had received medications, none showed complete resolution of the syndromes. However, of the 19 patients, 15 showed complete resolution of the syndrome immediately after the surgery. Four patients had fever even after the surgery. Three patients showed partial remission, with the frequency and duration of the episodes decreasing after the surgery. However, in one patient, the fever persisted as before the surgery. There were no significant differences in the clinical characteristics, such as the age at onset, fever episodes, associated symptoms, or age at surgery among the three groups. However, we observed a trend towards a higher frequency of a family history in patients with persistent symptoms after surgery. Tonsillectomy was highly effective against PFAPA syndrome, however, some patients failed to respond to the procedure. Therefore, it is important to carefully evaluate the risks and benefits in each case. The indications for tonsillectomy have not yet been clearly established. It

is essential to continue further investigations to establish effective therapeutic strategies for this syndrome.

PMID: 30010303 [Indexed for MEDLINE]

858. Am J Clin Dermatol. 2017 Aug;18(4):555-562. doi: 10.1007/s40257-017-0265-1.

PAPA, PASH and PAPASH Syndromes: Pathophysiology, Presentation and Treatment.

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Pyoderma gangrenosum (PG) is a neutrophilic dermatosis usually manifesting as skin ulcers with undermined erythematous-violaceous borders. It may be isolated, associated with systemic conditions or occurring in the context of autoinflammatory syndromes such as PAPA (pyogenic arthritis, PG and acne), PASH (PG, acne and suppurative hidradenitis) or PAPASH (pyogenic arthritis, acne, PG and suppurative hidradenitis). From a physiopathological point of view, all these conditions share common mechanisms consisting of over-activation of the innate immune system leading to increased production of the interleukin (IL)-1 family and 'sterile' neutrophil-rich cutaneous inflammation. From a genetic point of view, a number of mutations affecting the proteins of the inflammasome complex (the molecular platform responsible for triggering autoinflammation) or the proteins that regulate inflammasome function have been described in these disorders. As these debilitating entities are all associated with the over-expression of IL-1 and tumour necrosis factor (TNF)- $\alpha$ , biological drugs specifically targeting these cytokines are currently the most effective

treatments but, given the emerging role of IL-17 in the pathogenesis of these syndromes, IL-17 antagonists may represent the future management of these conditions.

DOI: 10.1007/s40257-017-0265-1

PMID: 28236224 [Indexed for MEDLINE]

859. Cytokine Growth Factor Rev. 2017 Apr;34:15-26. doi: 10.1016/j.cytogfr.2017.02.001. Epub 2017 Feb 9.

Role of NOD- like Receptors in Glioma Angiogenesis: Insights into future therapeutic interventions.

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Gliomas are the most common solid tumors among central nervous system tumors. Most glioma patients succumb to their disease within two years of the initial diagnosis. The median survival of gliomas is only 14.6 months, even after aggressive therapy with surgery, radiation, and chemotherapy. Gliomas are heavily infiltrated with myeloid- derived cells and endothelial cells. Increasing evidence suggests that these myeloid- derived cells interact with tumor cells promoting their growth and migration. NLRs (nucleotide-binding oligomerization domain (NOD)-containing protein like receptors) are a class of pattern recognition receptors that are critical to sensing pathogen and danger associated molecular patterns. Mutations in some NLRs lead to autoinflammatory diseases in humans. Moreover, dysregulated NLR signaling is central to the pathogenesis of several cancers, autoimmune and neurodegenerative diseases. Our review explores the role of angiogenic factors that contribute to upstream or downstream signaling pathways leading to NLRs. Angiogenesis plays a significant role in the pathogenesis of variety of tumors including gliomas. Though NLRs have been detected in several cancers including gliomas and NLR signaling contributes to

angiogenesis, the exact role and mechanism of involvement of NLRs in glioma angiogenesis remain largely unexplored. We discuss cellular, molecular and genetic studies of NLR signaling and convergence of NLR signaling pathways with angiogenesis signaling in gliomas. This may lead to re-appropriation of existing anti-angiogenic therapies or development of future strategies for targeted therapeutics in gliomas.

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DOI: 10.1016/j.cytogfr.2017.02.001

PMID: 28233643 [Indexed for MEDLINE]

860. J Pediatr Hematol Oncol. 2017 Jul;39(5):e293-e296. doi: 10.1097/MPH.0000000000000805.

Refractory Pure Red Cell Aplasia Manifesting as Deficiency of Adenosine Deaminase 2.

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Primary progress has been made in the last 2 years, particularly in finding novel disease-causing genes for a number of autoinflammatory diseases and primary immunodeficiencies. Whole-exome sequencing has dramatically increased the pace at which causative genes are being discovered. CECR1 (Cat eye syndrome chromosome region, candidate 1) gene encodes adenosine deaminase 2 (ADA2) protein. Patients who carry CECR1 mutation(s) suffer from deficiency of ADA2 (DADA2). Here, we describe a patient with pure red cell aplasia discovered to have DADA2. We also review the literature on DADA2. This report will help raise awareness of physicians for this complex disease.

DOI: 10.1097/MPH.0000000000000805

PMID: 28230570 [Indexed for MEDLINE]

861. Chin Med J (Engl). 2017 Mar 5;130(5):586-593. doi: 10.4103/0366-6999.200537.

A Novel Mutation in the Pyrin Domain of the NOD-like Receptor Family Pyrin Domain Containing Protein 3 in Muckle-Wells Syndrome.

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**BACKGROUND:** Cryopyrin-associated periodic syndrome (CAPS) is a group of rare, heterogeneous autoinflammatory disease characterized by interleukin (IL)-1 $\beta$ -mediated systemic inflammation and clinical symptoms involving skin, joints, central nervous system, and eyes. It encompasses a spectrum of three clinically overlapping autoinflammatory syndromes including familial cold autoinflammatory syndrome, Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease. CAPS is associated with gain-of-function missense mutations in NOD-like receptor family pyrin domain-containing protein 3 (NLRP3), the gene encoding NLRP3. Moreover, most mutations leading to MWS occurred in exon 3 of NLRP3 gene. Here, we reported a novel mutation occurred in exon 1 of NLRP3 gene in an MWS patient and attempted to explore the pathogenic mechanism.

**METHODS:** Genetic sequence analysis of NLRP3 was performed in an MWS patient who presented with periodic fever, arthralgia, and multiform skin lesions. NLRP3 was also analyzed in this patient's parents and 50 healthy individuals. Clinical examinations including X-ray examination, skin biopsy, bone marrow aspiration smear, and blood test of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum levels of IL-1 $\beta$ , immunoglobulin E (IgE), antineutrophil cytoplasmic antibodies, antinuclear antibodies, and extractable nuclear antigen were also analyzed. The protein structure of mutant NLRP3 inflammasome was calculated by SWISS-MODEL software. Proteins of wild type and mutant components of NLRP3 inflammasome were expressed and purified, and the interaction abilities between these proteins were tested by surface plasmon resonance (SPR) assay.

**RESULTS:** X-ray examination showed no abnormality in the patient's knees.

Laboratory tests indicated an elevation of CRP (233.24 mg/L) and ESR (67 mm/h) when the patient had fever. Serum IL-1 $\beta$  increased to 24.37 pg/ml, and serum IgE was higher than 2500.00 IU/ml. Other blood tests were normal. Bone marrow aspiration smear was normal. A novel point mutation c.92A>T in exon 1 of NLRP3 gene was identified, which caused a p.D31V mutation in pyrin domain (PYD) of NLRP3. SPR assay showed that this point mutation may strengthen the interaction between the PYD of NLRP3 and the PYD of the apoptosis-associated speck-like protein. The mutation c.92A>T in exon 1 of the NLRP3 gene was not found in the patient's parents and 50 healthy individuals.

CONCLUSIONS: The mutation c.92A>T in exon 1 of the NLRP3 gene is a novel mutation associated with MWS. The p.D31V mutation might promote the activation of NLRP3 inflammasome and induce MWS in this patient.

DOI: 10.4103/0366-6999.200537

PMCID: PMC5339933

PMID: 28229991 [Indexed for MEDLINE]

862. Clin Exp Rheumatol. 2017 Nov-Dec;35 Suppl 108(6):32-37. Epub 2017 Feb 9.

Normal arterial stiffness in familial Mediterranean fever. Evidence for a possible cardiovascular protective role of colchicine.

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**OBJECTIVES:** Familial Mediterranean fever (FMF) is an autoinflammatory disorder with episodic and persistent inflammation, which is only partially suppressed by continuous colchicine treatment. While chronic inflammation is considered an important cardiovascular risk factor in many inflammatory disorders, its impact in FMF is still disputed. We measured arterial stiffness, a marker of atherosclerotic cardiovascular disease, in a group of FMF patients, in order to evaluate the cardiovascular consequences of inflammation in FMF and the role of colchicine in their development.

**METHODS:** Eighty colchicine treated FMF patients, without known traditional cardiovascular risk factors, were randomly enrolled in the study. Demographic, genetic, clinical and laboratory data were retrieved from patient files and examinations. Arterial stiffness was measured using pulse wave velocity (PWV). The recorded values of PWV were compared with those of an age and blood pressure adjusted normal population, using internationally endorsed values.

**RESULTS:** FMF patients displayed normal PWV values, with an even smaller than expected proportion of patients deviating from the 90th percentile of the reference population (5% vs. 10%,  $p=0.02$ ). The lowest PWV values were recorded in patients receiving the highest dose of colchicine ( $\geq 2$  mg vs. 0-1 mg,  $p=0.038$ ), and in patients of North African Jewish origin, whose disease was typically more severe than that of patients of other ethnicities; both observations supporting an ameliorating colchicine effect ( $p=0.043$ ).

**CONCLUSIONS:** Though subjected to chronic inflammation, colchicine treated FMF patients have normal PWV. Our findings provide direct evidence for a cardiovascular protective role of colchicine in FMF.

PMID: 28229824 [Indexed for MEDLINE]

863. An Bras Dermatol. 2017 Jan-Feb;92(1):72-80. doi: 10.1590/abd1806-4841.20175208.

Skin symptoms as diagnostic clue for autoinflammatory diseases.

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Autoinflammatory disorders are immune-mediated diseases with increased production of inflammatory cytokines and absence of detectable autoantibodies. They course with recurrent episodes of systemic inflammation and fever is the most common symptom. Cutaneous manifestations are prevalent and important to diagnosis and early treatment of the syndromes. The purpose of this review is to emphasize to dermatologists the skin symptoms present in these syndromes in order to provide their early diagnosis.

DOI: 10.1590/abd1806-4841.20175208

PMCID: PMC5312182

PMID: 28225960 [Indexed for MEDLINE]

864. Front Immunol. 2017 Feb 6;8:81. doi: 10.3389/fimmu.2017.00081. eCollection 2017.

Neutrophil Extracellular Traps and Its Implications in Inflammation: An Overview.

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In addition to physical barriers, neutrophils are considered a part of the first

line of immune defense. They can be found in the bloodstream, with a lifespan of 6-8 h, and in tissue, where they can last up to 7 days. The mechanisms that neutrophils utilize for host defense are phagocytosis, degranulation, cytokine production, and, the most recently described, neutrophil extracellular trap (NET) production. NETs are DNA structures released due to chromatin decondensation and spreading, and they thus occupy three to five times the volume of condensed chromatin. Several proteins adhere to NETs, including histones and over 30 components of primary and secondary granules, among them components with bactericidal activity such as elastase, myeloperoxidase, cathepsin G, lactoferrin, pentraxin 3, gelatinase, proteinase 3, LL37, peptidoglycan-binding proteins, and others with bactericidal activity able to destroy virulence factors. Three models for NETosis are known to date. (a) Suicidal NETosis, with a duration of 2-4 h, is the best described model. (b) In vital NETosis with nuclear DNA release, neutrophils release NETs without exhibiting loss of nuclear or plasma membrane within 5-60 min, and it is independent of reactive oxygen species (ROS) and the Raf/MERK/ERK pathway. (c) The final type is vital NETosis with release of mitochondrial DNA that is dependent on ROS and produced after stimuli with GM-CSF and lipopolysaccharide. Recent research has revealed neutrophils as more sophisticated immune cells that are able to precisely regulate their granular enzymes release by ion fluxes and can release immunomodulatory cytokines and chemokines that interact with various components of the immune system. Therefore, they can play a key role in autoimmunity and in autoinflammatory and metabolic diseases. In this review, we intend to show the two roles played by neutrophils: as a first line of defense against microorganisms and as a contributor to the pathogenesis of various illnesses, such as autoimmune, autoinflammatory, and metabolic diseases.

DOI: 10.3389/fimmu.2017.00081

PMCID: PMC5292617

PMID: 28220120

865. Am J Med. 2017 Jun;130(6):662-665. doi: 10.1016/j.amjmed.2017.02.002. Epub 2017 Feb 16.

Labial Pain, Swelling and Fever: An Autoinflammatory Disorder.

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DOI: 10.1016/j.amjmed.2017.02.002

PMCID: PMC5699460

PMID: 28216445 [Indexed for MEDLINE]

866. Trends Immunol. 2017 Apr;38(4):248-260. doi: 10.1016/j.it.2017.01.001. Epub 2017 Feb 15.

NLRP6: A Multifaceted Innate Immune Sensor.

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NLRP6, a member of the nucleotide-binding domain, leucine-rich repeat-containing (NLR) innate immune receptor family, regulates inflammation and host defense against microorganisms. Similar to other NLRs, NLRP6 not only participates in inflammasome formation, but is also involved in nuclear factor- $\kappa$ B (NF- $\kappa$ B) and mitogen-activated protein kinase (MAPK) signaling regulation and facilitation of gastrointestinal antiviral effector functions. Additionally, NLRP6 contributes to the regulation of mucus secretion and antimicrobial peptide production, thereby impacting intestinal microbial colonization and associated microbiome-related infectious, autoinflammatory, metabolic, and neoplastic diseases. However, several of the mechanisms attributed to the functions of NLRP6 remain debatable, leaving open questions as to the relevant molecular mechanisms and interacting partners, and putative human relevance. We herein discuss recent findings related to NLRP6 activity, while highlighting outstanding questions and future perspectives in elucidating its roles in health and disease.

867. Int J Rheum Dis. 2017 Nov;20(11):1770-1775. doi: 10.1111/1756-185X.13042. Epub 2017 Feb 17.

Egyptian tale from India: application of whole-exome sequencing in diagnosis of atypical familial Mediterranean fever.

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Clinical diagnosis of autoinflammatory diseases requires a high degree of clinical suspicion and clinching molecular evidence to substantiate the diagnosis. This is more so in populations with low prevalence of these disorders. In this report, we describe the case of a young man from India with recurrent fever and persistent arthritis. The patient's forefathers were of Egyptian ancestry who practiced consanguinity. Molecular genetic analysis using whole-exome sequencing suggested the presence of variants c.443A>T:p.E148V and c.442G>C:p.E148Q in the MEFV gene, earlier independently shown to be associated with familial Mediterranean fever (FMF) in a compound heterozygous state. The variants were further confirmed by capillary sequencing. This report also highlights the application of whole exome sequencing to delineate the allelic differences in the variants apart from serving as a quick genetic screening approach for autoinflammatory diseases. To the best of our knowledge, this is the

first report of a compound heterozygosity for the two well-characterized variants associated with atypical FMF in a patient.

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DOI: 10.1111/1756-185X.13042

PMID: 28211254 [Indexed for MEDLINE]

868. Mediators Inflamm. 2017;2017:1460491. doi: 10.1155/2017/1460491. Epub 2017 Jan 22.

Update on the Medical Management of Gastrointestinal Behçet's Disease.

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Behçet's disease (BD) is a multisystemic disorder of unknown etiology mainly defined by recurrent oral aphthosis, genital ulcers, and chronic relapsing bilateral uveitis, all of which represent the "stigmata" of disease. However, many other organs including the vascular, neurological, musculoskeletal, and gastrointestinal systems can be affected. The gastrointestinal involvement in

Behçet's disease (GIBD), along with the neurological and vascular ones, represents the most feared clinical manifestation of BD and shares many symptoms with inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis. Consequently, the differential diagnosis is often a daunting task, albeit the presence of typical endoscopic and pathologic findings may be a valuable aid to the exact diagnosis. To date, there are no standardized medical treatments for GIBD; therefore therapy should be tailored to the single patient and based on the severity of the clinical features and their complications. This work provides a digest of all current experience and evidence about pharmacological agents suggested by the medical literature as having a potential role for managing the dreadful features of GIBD.

DOI: 10.1155/2017/1460491

PMCID: PMC5292121

PMID: 28210071 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare that there is no conflict of interests regarding the publication of this paper.

869. *Pediatr Int.* 2017 Jun;59(6):655-660. doi: 10.1111/ped.13265. Epub 2017 Apr 24.

Is colchicine more effective to prevent periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis episodes in Mediterranean fever gene variants?

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**BACKGROUND:** Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome is the most frequent repetitive fever syndrome in childhood. It is characterized by fever episodes lasting for approximately 3-6 days, once every 3-8 weeks.

**METHODS:** Clinical and laboratory data for PFAPA syndrome patients between January 2010 and December 2014 followed up at a tertiary pediatric care hospital were reviewed.

**RESULTS:** Four hundred children (256 male, 144 female; mean age at diagnosis, 4.2

± 2.2 years), were enrolled in the study. During the episodes, mean leukocyte number was high (12 725/mm<sup>3</sup>) with predominant neutrophils. The mean number of monocytes was 1256/mm<sup>3</sup>, and 90.2% had monocytosis. Serum amyloid A and C-reactive protein were high in 84.6% and in 77.8% of the patients, respectively. Mediterranean fever (MEFV) gene heterozygous mutation was identified in 57 of the 231 patients (24.7%) in whom genetic analysis had been performed. The most frequent mutation was heterozygous M694V (10%, n = 23). Extension of between-episode interval following prophylaxis was noted in 85% of those on regular colchicine treatment (n = 303). In the colchicine group, between-episode interval was prolonged from 18.8 ± 7.9 days (before colchicine treatment) to 49.5 ± 17.6 days on prophylactic colchicine therapy; also, prophylactic treatment was more effective in reducing episode frequency in patients with MEFV gene variant (n = 54, 96%) than in those without (n = 122, 80%; P = 0.003).

**CONCLUSIONS:** This study has involved the largest number of PFAPA syndrome patients in the literature. It is particularly important to assess and to demonstrate the high rate of response to colchicine prophylaxis in PFAPA syndrome patients, especially those with MEFV variant. On blood screening, neutrophilia associated with monocytosis and low procalcitonin could contribute to diagnosis.

© 2017 Japan Pediatric Society.

DOI: 10.1111/ped.13265

PMID: 28207965 [Indexed for MEDLINE]

870. Z Rheumatol. 2017 May;76(4):313-321. doi: 10.1007/s00393-017-0271-y.

[Genetics of cryopyrin-associated periodic syndrome].

[Article in German]

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Familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and chronic infantile neurological, cutaneous and articular syndrome/neonatal onset multisystem inflammatory disease (CINCA/NOMID) were originally described as three distinct diseases. After the identification of their common genetic origin in 2001 and 2002, they are now perceived as a continuum of one disease entity and labelled cryopyrin-associated periodic syndromes (CAPS). Mutations in the NLRP3 gene on chromosome 1q44 can be detected in many affected patients. These lead to the synthesis of an altered gene product named cryopyrin. This is part of the NLRP3 inflammasome and causes the activation of caspase 1 and an excess production of IL-1 $\beta$ , which is the driving force behind the inflammatory reactions observed in CAPS patients. In symptomatic patients, confirmation of a mutation using traditional methods of genetic analysis may not always be successful (up to 40% in the case of CINCA/NOMID phenotypes); however, in many cases somatic mutations can be found using modern methods, such as next generation sequencing (NGS) technologies. In contrast, low-penetrance NLRP3 variants may also be identified in healthy family members and are present in low frequencies in the general population. Some of the mutation carriers nevertheless present with typical signs of autoinflammation; however, their phenotype is different compared to the classical CAPS presentation. These patients display unspecific systemic inflammatory signs more frequently but show an organ involvement less often. While the detection of NLRP3 gene mutations may be viewed as confirmatory, CAPS is still predominantly a clinical diagnosis; therefore, recently published diagnostic criteria do not require the demonstration of a mutation.

DOI: 10.1007/s00393-017-0271-y

PMID: 28197772 [Indexed for MEDLINE]

871. Case Rep Hematol. 2017;2017:5375793. doi: 10.1155/2017/5375793. Epub 2017 Jan 18.

Allogeneic Transplant in ELANE and MEFV Mutation Positive Severe Cyclic Neutropenia: Review of Prognostic Factors for Secondary Severe Events.

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**Objective and Importance.** Cyclic neutropenia (CyN) is a rare autosomal dominant inherited disorder due to the mutation ELANE primarily affecting bone marrow stem cells and is characterized by recurrent neutropenia every 2 to 4 weeks. Symptoms vary from benign to severe, including death. Postulations on the cause of wide spectrum in symptom presentation include the possibility of other genetic mutations, such as MEFV. Recommended treatment for CyN is G-CSF to keep ANC higher to minimize risk of infection. **Case.** A 25-year-old male diagnosed with CyN, on G-CSF but worsening quality of life. Pretransplant investigations revealed ELANE mutation positive severe CyN along with familial Mediterranean fever (MEFV) mutation. **Intervention.** Bone marrow transplantation as treatment for dual mutation (ELANE and MEFV mutation) positive severe CyN. **Conclusion.** BMT may be considered as an alternative treatment for severe CyN in patients who are refractory to G-CSF. It is postulated that in our patient the combined mutations (CyN and MEFV) may have contributed to the severity of this individual's symptoms. We suggest CyN patients who present with severe symptoms have evaluation with ELANE mutation testing, Periodic Fever Syndromes Panel, and routine marrow assessment with FISH, conventional cytogenetics, and morphological evaluation for MDS/AML.

DOI: 10.1155/2017/5375793

PMCID: PMC5286543

PMID: 28197346

**Conflict of interest statement:** All authors declare no conflict of interests.

872. Clin Transl Immunology. 2017 Jan 6;6(1):e124. doi: 10.1038/cti.2016.83. eCollection 2017 Jan.

Caspase-8: not so silently deadly.

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Apoptosis is a caspase-dependent programmed form of cell death, which is commonly believed to be an immunologically silent process, required for mammalian development and maintenance of cellular homeostasis. In contrast, lytic forms of cell death, such as RIPK3- and MLKL-driven necroptosis, and caspase-1/11-dependent pyroptosis, are postulated to be inflammatory via the release of damage associated molecular patterns (DAMPs). Recently, the function of apoptotic caspase-8 has been extended to the negative regulation of necroptosis, the cleavage of inflammatory interleukin-1 $\beta$  (IL-1 $\beta$ ) to its mature bioactive form, either directly or via the NLRP3 inflammasome, and the regulation of cytokine transcriptional responses. In view of these recent advances, human autoinflammatory diseases that are caused by mutations in cell death regulatory machinery are now associated with inappropriate inflammasome activation. In this review, we discuss the emerging crosstalk between cell death and innate immune cell inflammatory signalling, particularly focusing on novel non-apoptotic functions of caspase-8. We also highlight the growing number of autoinflammatory diseases that are associated with enhanced inflammasome function.

DOI: 10.1038/cti.2016.83

PMCID: PMC5292560

PMID: 28197335

873. J Autoimmun. 2017 Jun;80:28-38. doi: 10.1016/j.jaut.2017.01.007. Epub 2017 Feb 11.

Toll-like receptor 4 antagonist TAK-242 inhibits autoinflammatory symptoms in DITRA.

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**BACKGROUND:** IL36RN encodes the IL-36 receptor antagonist (IL-36Ra), and loss-of-function mutations in IL36RN define a recessively inherited autoinflammatory disease named "deficiency of IL-36Ra" (DITRA). DITRA causes systemic autoinflammatory diseases, including generalized pustular psoriasis (GPP), an occasionally life-threatening disease that is characterized by widespread sterile pustules on the skin, fever and other systemic symptoms. GPP can present at any age, and provocative factors include various infections, medicines and pregnancy.

**OBJECTIVE:** We aimed to elucidate the role of toll-like receptor 4 (TLR4) signaling in DITRA and to innovate an efficient treatment for DITRA.

**METHODS:** We generated *Il36rn*<sup>-/-</sup> mice and treated them with TLR4 agonist to establish DITRA model mice. Furthermore, we administrated TLR4 antagonist TAK-242 to the model mice to inhibit the DITRA symptoms.

**RESULT:** *Il36rn*<sup>-/-</sup> mice treated by TLR4 agonist showed autoinflammatory symptoms in skin, articulation and liver. Thus, we established model mice for DITRA or GPP that show cutaneous, articular, and hepatic autoinflammatory symptoms typical of DITRA or GPP: sterile pustules on the skin, liver abscesses and enthesitis of the hind paws. Additionally, these symptoms were canceled by TAK-242 administration. We demonstrated the inhibitory effects of the TLR4 antagonist TAK-242 on the autoinflammatory symptoms exhibited by the DITRA models.

**CONCLUSION:** We suggested that blockage of TLR4 signaling is a promising treatment for DITRA and GPP.

DOI: 10.1016/j.jaut.2017.01.007

PMID: 28196704 [Indexed for MEDLINE]

874. Orphanet J Rare Dis. 2017 Feb 14;12(1):33. doi: 10.1186/s13023-017-0589-1.

Neurological outcome of patients with cryopyrin-associated periodic syndrome (CAPS).

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**BACKGROUND:** To assess the neurological involvement and outcome, including school and professional performances, of adults and children with cryopyrin-associated periodic syndrome (CAPS).

**METHODS:** In this observational study, patients with genetically proven CAPS and followed in the national referral centre for autoinflammatory diseases at Bicêtre hospital were assessed. Neurological manifestations, CSF data and MRI results at diagnosis and during follow-up were analyzed.

**RESULTS:** Twenty-four patients (15 adults and 9 children at diagnosis) with CAPS were included. The median age at disease onset was 0 year (birth) [range 0-14], the median age at diagnosis was 20 years [range 0-53] and the mean duration of

follow-up was  $10.4 \pm 2$  years. Neurological involvement at diagnosis, mostly headaches and hearing loss, was noted in 17 patients (71%). Two patients of the same family had abnormal brain MRI. A439V mutation is frequently associated with a non-neurological phenotype while R260W mutation tends to be associated with neurological involvement. Eleven adult patients (61%) and 3 children (50%) underwent school difficulties.

**CONCLUSION:** Neurological involvement is frequent in patients with CAPS and the majority of patients presented difficulties in school performances with consequences in the professional outcome during adulthood. Further studies in larger cohorts of children with CAPS focusing in intellectual efficiency and school performances are necessary.

DOI: 10.1186/s13023-017-0589-1

PMCID: PMC5309976

PMID: 28196516 [Indexed for MEDLINE]

875. Int J Dermatol. 2017 Jun;56(6):660-663. doi: 10.1111/ijd.13503. Epub 2017 Feb 14.

Familial Mediterranean fever patients with hidradenitis suppurativa.

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**BACKGROUND:** Hidradenitis suppurativa (HS) has recently been described as a component of two autoinflammatory syndromes: PASH (pyoderma gangrenosum, acne, and HS) and PAPASH (pyoderma gangrenosum, acne, pyogenic arthritis, and HS). These associations together with others such as inflammatory bowel diseases suggest that defects in autoinflammatory pathways may play a role in the pathogenesis of HS.

**OBJECTIVES:** To describe clinical and genetic characteristics of two unrelated patients with HS and familial Mediterranean fever (FMF).

**METHODS:** Case study.

**RESULTS:** Besides FMF and HS, the first patient had acne conglobata, and the second patient had pyoderma gangrenosum and ankylosing spondyloarthritis. Both

patients had M694V/V726A MEFV gene mutations.

CONCLUSION: PASH and PAPASH have recently been associated with genetic alterations of gene encoding proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1), which interacts with the product of MEFV gene in the autoinflammatory pathway. This intriguing molecular interaction may explain shared phenotypic characteristics seen in genetic defects. Association of one more autoinflammatory disorders with HS adds another brick to the wall.

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DOI: 10.1111/ijd.13503

PMID: 28194777 [Indexed for MEDLINE]

876. Intern Emerg Med. 2017 Aug;12(5):605-611. doi: 10.1007/s11739-017-1622-z. Epub 2017 Feb 13.

The diagnostic evaluation of patients with a suspected hereditary periodic fever syndrome: experience from a referral center in Italy.

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The study aims are to describe the activity of our Unit on the diagnostics of

monogenic autoinflammatory diseases (AIDs), and to apply the clinical classification criteria for periodic fevers from the Eurofever Registry to our cohort of patients, thus evaluating their usefulness in the real life. We retrospectively analyzed data from patients referring to our Center for recurrent fever attacks, and undergoing genetic analysis between April 2014 and July 2016, and we applied the classification criteria to both genetically positive and -negative patients. We visited 195 patients (101 females, 94 males); 126 (64.6%) were adults and 192 (98.5%) Caucasians; 12.3% carried mutations and 12.7% of adults were genetically positive. No statistically significant differences were identified in the frequency of genetic diagnosis between adults and children ( $p = 0.82$ ) as well as in the frequency of genetic diagnosis, based on the number of genes evaluated ( $p = 0.57$ ). When we applied the Eurofever criteria, 126/195 (64.6%) patients were classified for at least one among the four main monogenic AIDs; 22 (11.3%) patients fulfilled criteria for 2 diseases and 4 (2.1%) for 3 diseases. Among patients carrying mutations, 12/24 (50%) correctly fulfilled the score, 3/24 (12.5%) fulfilled criteria differently from their genetic diagnosis; 9/22 (40.9%) received no classification. An expanded genetic testing does not seem useful, while a correct interpretation of patients' clinical picture may allow performing specific genetic testing. The classification criteria from the Eurofever Registry have shown to be a beneficial tool in the evaluation of patients with a suspected monogenic AID.

DOI: 10.1007/s11739-017-1622-z

PMID: 28194697 [Indexed for MEDLINE]

877. Front Immunol. 2017 Jan 27;8:43. doi: 10.3389/fimmu.2017.00043. eCollection 2017.

The NLRP3 and Pyrin Inflammasomes: Implications in the Pathophysiology of Autoinflammatory Diseases.

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Inflammasomes are multiprotein complexes that critically control different aspects of innate and adaptive immunity. Among them we could highlight the release of pro-inflammatory cytokines that induce and maintain the inflammatory response. Usually, inflammasomes result from oligomerization of a nucleotide-binding domain-like receptor (NLR) after sensing different pathogenic or endogenous sterile dangerous signals; however, other proteins such as absent in melanoma 2, retinoic acid-inducible gene I, or pyrin could also form inflammasome platforms. Inflammasome oligomerization leads to caspase-1 activation and the processing and release of the pro-inflammatory cytokines, such as interleukin (IL)-1 $\beta$  and IL-18. Mutations in different inflammasomes are causative for multiple periodic hereditary syndromes or autoinflammatory diseases, characterized by acute systemic inflammatory flares not associated with infections, tumors, or autoimmunity. This review focuses on germline mutations that have been described in cryopyrin-associated periodic syndrome (CAPS) for NLRP3 or in familial Mediterranean fever (FMF) and pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND) for MEFV. Besides the implication of inflammasomes in autoinflammatory syndromes, these molecular platforms are involved in the pathophysiology of different illnesses, including chronic inflammatory diseases, degenerative processes, fibrosis, or metabolic diseases. Therefore, drug development targeting inflammasome activation is a promising field in expansion.

DOI: 10.3389/fimmu.2017.00043

PMCID: PMC5271383

PMID: 28191008

878. J Interferon Cytokine Res. 2017 Mar;37(3):119-128. doi: 10.1089/jir.2016.0036.  
Epub 2017 Feb 10.

Eosinophils Regulate Interferon Alpha Production in Plasmacytoid Dendritic Cells  
Stimulated with Components of Neutrophil Extracellular Traps.

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Eosinophils constitute an important component of helminth immunity and are not only associated with various allergies but are also linked to autoinflammatory disorders, including the skin disease psoriasis. Here we demonstrate the functional relationship between eosinophils and plasmacytoid dendritic cells (pDCs) as related to skin diseases. We previously showed that pDCs colocalize with neutrophil extracellular traps (NETs) in psoriatic skin. Here we demonstrate that eosinophils are found in psoriatic skin near neutrophils and NETs, suggesting that pDC responses can be regulated by eosinophils. Eosinophils inhibited pDC function in vitro through a mechanism that did not involve cell contact but depended on soluble factors. In pDCs stimulated by specific NET components, eosinophil-conditioned media attenuated the production of interferon  $\alpha$  (IFN $\alpha$ ) but did not affect the maturation of pDCs as evidenced by the unaltered expression of the costimulatory molecules CD80 and CD86. As pDCs and IFN $\alpha$  play a key role in autoimmune skin inflammation, these data suggest that eosinophils may influence autoinflammatory responses through their impact on the production of IFN $\alpha$  by pDCs.

DOI: 10.1089/jir.2016.0036

PMID: 28186428 [Indexed for MEDLINE]

879. Dig Endosc. 2017 May;29(3):394-395. doi: 10.1111/den.12843. Epub 2017 Apr 10.

Rare cause of duodenojejunal pseudopolyposis: Report of a case of adult-onset familial Mediterranean fever.

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DOI: 10.1111/den.12843

PMID: 28181703 [Indexed for MEDLINE]

880. Rambam Maimonides Med J. 2017 Jan 30;8(1). doi: 10.5041/RMMJ.10277.

An Up-to-date Approach to a Patient with a Suspected Autoinflammatory Disease.

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Autoinflammatory diseases (AID) are characterized by seemingly unprovoked self-limited attacks of fever and systemic inflammation potentially leading to amyloidosis. Familial Mediterranean fever (FMF) is the most common AID and therefore the most studied. Besides FMF, the other main hereditary AID are tumor necrosis factor-associated periodic fever syndrome (TRAPS), mevalonate kinase deficiency (MKD), and cryopyrin-associated periodic fever syndrome (CAPS). These hereditary diseases result from a mutant gene that is involved in the regulation of inflammation, resulting in a characteristic clinical phenotype. The differential diagnosis of AID can be challenging due to a wide overlap in clinical manifestations. Moreover, a considerable proportion of patients present with autoinflammatory symptoms but without a pathogenetic variant on genetic analysis. Furthermore, non-hereditary AID, such as the periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) syndrome, which is the most common AID in children worldwide, must be excluded in certain circumstances. Herein we shall review the main AID and describe a practical approach to diagnosis in a patient with a clinical suspicion of AID.

DOI: 10.5041/RMMJ.10277

PMCID: PMC5298363

PMID: 28178435

Conflict of interest statement: No potential conflict of interest relevant to this article was reported.

881. Clin Exp Immunol. 2017 May;188(2):311-322. doi: 10.1111/cei.12939. Epub 2017 Mar 13.

Circulating NK cells and their subsets in Behçet's disease.

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Behçet's disease (BD) is an autoinflammatory, chronic relapsing/remitting disease of unknown aetiology with both innate and acquired immune cells implicated in disease pathogenesis. Peripheral blood natural killer (NK) cells and their CD56Dim /CD56Bright subsets were surface phenotyped using CD27 and CD16 surface markers in 60 BD patients compared to 60 healthy controls (HCs). Functional potential was assessed by production of interferon (IFN)- $\gamma$ , granzyme B, perforin and the expression of degranulation marker CD107a. The effects of disease activity (BDActive versus BDQuiet ) and BD medication on NK cells were also investigated. Peripheral blood NK cells ( $P < 0.0001$ ) and their constituent CD56Dim ( $P < 0.0001$ ) and CD56Bright ( $P = 0.0015$ ) subsets were depleted significantly in BD patients compared to HCs, and especially in those with active disease (BDActive ) ( $P < 0.0001$ ). BD patients taking azathioprine also had significantly depleted NK cells compared to HCs ( $P < 0.0001$ ). A stepwise multivariate linear regression model confirmed BD activity and azathioprine therapy as significant independent predictor variables of peripheral blood NK percentage ( $P < 0.001$ ). In general, CD56Dim cells produced more perforin ( $P < 0.0001$ ) and granzyme B ( $P < 0.01$ ) expressed higher CD16 levels ( $P < 0.0001$ ) compared to CD56Bright cells, confirming their increased cytotoxic potential with overall higher NK cell CD107a expression in BD compared to HCs ( $P < 0.01$ ). Interestingly, IFN- $\gamma$  production and CD27 expression were not significantly different between CD56Dim /CD56Bright subsets. In conclusion, both BD activity

and azathioprine therapy have significant independent depletive effects on the peripheral blood NK cell compartment.

© 2017 The Authors. Clinical & Experimental Immunology published by John Wiley & Sons Ltd on behalf of British Society for Immunology.

DOI: 10.1111/cei.12939

PMCID: PMC5383445

PMID: 28170096 [Indexed for MEDLINE]

882. Mod Rheumatol. 2017 Nov;27(6):1047-1050. doi: 10.1080/14397595.2017.1285846.  
Epub  
2017 Mar 23.

Survey of attitudes of non-pediatric rheumatologists among councilors of the Japan College of Rheumatology regarding transitional care.

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**OBJECTIVES:** The transition from pediatric to adult healthcare systems has recently received worldwide attention. Surveys of the attitudes of Japanese non-pediatric rheumatologists regarding transitional care were conducted.

**METHODS:** Non-pediatric rheumatologists among councilors of the Japan College of Rheumatology were enrolled in the surveys. Experiences of adult patients with childhood-onset rheumatic diseases, ideal medical care for these patients, and factors that made the transition to adult care difficult were examined via e-mail.

**RESULTS:** Overall, 201 non-pediatric rheumatologists (21.2%) responded to the surveys. Ninety-one percent had previous experience with patients with childhood-onset rheumatic disorders. Transition to non-pediatric institutes was supported by about 90% of respondents. However, only 32% of non-pediatric

rheumatologists had no hesitation about caring for adults with childhood-onset rheumatology disorders. Two main factors prevented smooth transitions to non-pediatric care: inadequacy of non-pediatric care (57%) and lack of independence from parents/family (53%). The majority of non-pediatric rheumatologists hesitated about medical care for patients with autoinflammatory syndromes, whereas they became familiar with articular juvenile idiopathic arthritis without hesitation (86.6%); 93% of respondents requested more opportunities to learn about pediatric rheumatology disorders.

CONCLUSIONS: Sharing additional knowledge about pediatric rheumatology within the non-pediatric rheumatology field is required.

DOI: 10.1080/14397595.2017.1285846

PMID: 28165841 [Indexed for MEDLINE]

883. Mod Rheumatol. 2017 Nov;27(6):1040-1046. doi: 10.1080/14397595.2017.1285845.

Epub

2017 Feb 16.

Microarray analysis of circulating microRNAs in familial Mediterranean fever.

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OBJECTIVES: Familial Mediterranean fever (FMF) is an autoinflammatory disease caused by mutations in MEFV. Mutations in exon 10 are associated with typical FMF phenotypes, whereas the pathogenic role of variants in exons 2 and 3 remains uncertain. Recent evidence suggests that circulating microRNAs (miRNAs) are potentially useful biomarkers in several diseases. Therefore, their expression was assessed in FMF.

METHODS: The subjects were 24 patients with FMF who were between attacks: eight with exon 10 mutations (group A), eight with exon 3 mutations (group B), and

eight without exon 3 or 10 mutations (group C). We also investigated eight cases of PFAPA as disease controls. Exosome-rich fractionated RNA was subjected to miRNA profiling by microarray.

**RESULTS:** Using the expression patterns of 26 miRNAs, we classified FMF (groups A, B, and C) and PFAPA with 78.1% accuracy. In FMF patients, groups A and B, A and C, and B and C were distinguished with 93.8, 87.5, and 100% accuracy using 24, 30, and 25 miRNA expression patterns, respectively.

**CONCLUSIONS:** These findings suggest that expression patterns of circulating miRNAs differ among FMF subgroups based on MEFV mutations between FMF episodes. These patterns may serve as a useful biomarker for detecting subgroups of FMF.

DOI: 10.1080/14397595.2017.1285845

PMID: 28165838 [Indexed for MEDLINE]

884. Z Rheumatol. 2017 May;76(4):303-312. doi: 10.1007/s00393-017-0265-9.

[Role of genetics in familial Mediterranean fever].

[Article in German]

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Familial Mediterranean fever (FMF) is caused by mutations within the Mediterranean fever (MEFV) gene. These gain of function mutations lead to an increased activation of the inflammasome pyrin with a subsequent disproportional

proinflammatory reaction. Classically, in FMF patients two pathogenic mutations affecting both alleles are found in the molecular genetic analysis; however, it is well known that the phenotype can also be caused either by mutations with lower penetrance or unknown significance. Furthermore, in a significant number of patients only one or even no MEFV mutations can be detected. Heterozygous mutation carriers who do not suffer from classical FMF, can also present with other signs of inflammation, e. g. subclinical increased inflammation markers, associated inflammatory diseases or unclassified symptoms. Thus, FMF does not follow a classical autosomal recessive inheritance and a variable gene dose effect has to be considered, which is furthermore modulated by other mostly unknown genetic variants and environmental factors. This article summarizes the broad spectrum of clinical presentations associated with MEFV mutations and analyzes the effect of the gene dose on the phenotypical expression. Furthermore, the impact of the molecular genetic analysis on the diagnostics of a patient and on the individualized management of the disease is discussed.

DOI: 10.1007/s00393-017-0265-9

PMID: 28154935 [Indexed for MEDLINE]

885. Mod Rheumatol. 2017 Nov;27(6):1036-1039. doi: 10.1080/14397595.2016.1270497.  
Epub  
2017 Feb 21.

The frequency of the celiac disease among children with familial Mediterranean fever.

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We aimed to assess the frequency of celiac disease (CD) in patients with Familial Mediterranean Fever (FMF). This prospective study was carried out from October 2015 to March 2016 and included 303 patients with FMF. We used 98 sex- and



age-matched healthy subjects as a control group. Levels of total IgA and tissue transglutaminase (tTG) IgA antibody were measured in all groups. Those with increased level of tTG IgA were tested for anti-endomysium IgA antibodies (EMA). Patients with positive EMA underwent gastro-duodenoscopy and intestinal biopsy for a definite diagnosis of CD. Only 9 of 303 patients (2.9%) were positive for tTG IgA. Patients positive for tTG IgA were then tested for EMA and only one of them (0.3%) had a positive result. This patient underwent gastro-duodenoscopy. The pathological report was compatible with Marsh 0 classification score for the diagnosis of CD. Two subjects from the control group were positive for tTG IgA but none of them had positive EMA antibodies. We did not find CD in the large cohort of childhood FMF patients. The prevalence of CD did not show association with presence of childhood FMF in this study and CD would not be a considerable complication of childhood FMF.

DOI: 10.1080/14397595.2016.1270497

PMID: 28151032 [Indexed for MEDLINE]

886. Eur J Rheumatol. 2016 Dec;3(4):146-152. doi: 10.5152/eurjrheum.2016.15099. Epub 2016 Dec 1.

Immune and inflammatory gene expressions are different in Behçet's disease compared to those in Familial Mediterranean Fever.

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**OBJECTIVE:** The immune classification of Behçet's disease (BD) is still controversial. In this study, we aimed to compare the immune/inflammatory gene expressions in BD with those in familial Mediterranean fever (FMF), an autoinflammatory disorder with innate immune activation.

**MATERIAL AND METHODS:** CD4<sup>+</sup> T cells and CD14<sup>+</sup> monocytes were isolated from the peripheral blood mononuclear cells of Behçet's disease patients (n=10), FMF (n=6) patients, and healthy controls (n=4) with microbeads, and then, the mRNA was isolated. The expressions of 440 genes associated with immune and inflammatory responses were studied with a focused DNA microarray using a chemiluminescent tagging system. Changes above 1.5-fold and below 0.8-fold were accepted to be significant.

**RESULTS:** In BD patients, in the CD4<sup>+</sup> T-lymphocyte subset, interleukin 18 receptor accessory protein (1.7-fold), IL-7 receptor (1.9-fold), and prokineticin 2 (2.5-fold) were all increased compared to those in FMF patients, whereas chemokine (C-X3-C motif ) receptor-1 (CX3CR1) (0.7-fold) and endothelial cell growth factor-1 (0.6-fold) were decreased. In the CD14<sup>+</sup> monocyte population, the V-fos FBJ murine osteosarcoma viral oncogene homolog (1.5-fold), Interleukin-8 (IL-8) (2.1-fold), and Tumor Necrosis Factor alpha (TNF- $\alpha$ ) (1.8-fold) were all increased, whereas the chemokine (C-C motif ) ligand 5 (CCL5) (0.6-fold), C-C chemokine receptor type 7 (0.6-fold), and CX3CR1 (0.7-fold) were decreased, again when compared to those in FMF. Compared to healthy controls in the CD4<sup>+</sup> T-lymphocyte population, in both BD and FMF patients, pro-platelet basic protein and CD27 had elevated expression. In BD and FMF patients, 24 and 19 genes, respectively, were downregulated, with 15 overlapping genes between both disorders. In the CD14<sup>+</sup> monocytes population, chemokine (C-C motif ) receptor-1 (CCR1) was upregulated both in BD and FMF patients compared to that in the controls, whereas CCL5 was downregulated.

**CONCLUSION:** Immune and inflammatory gene expressions seem to be variable in both the innate (CD14<sup>+</sup>) and adaptive (CD4<sup>+</sup>) immune responses in BD and FMF patients compared to those in controls, suggesting differences in immune regulation between the two disorders.

DOI: 10.5152/eurjrheum.2016.15099

PMCID: PMC5283560

PMID: 28149656

**Conflict of interest statement:** No conflict of interest was declared by the authors.

887. Cell Rep. 2017 Jan 31;18(5):1285-1297. doi: 10.1016/j.celrep.2017.01.015.

The Atypical Ubiquitin E2 Conjugase UBE2L3 Is an Indirect Caspase-1 Target and Controls IL-1 $\beta$  Secretion by Inflammasomes.

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Caspase-1 activation by inflammasome signaling scaffolds initiates inflammation and antimicrobial responses. Caspase-1 proteolytically converts newly induced pro-interleukin 1 beta (IL-1 $\beta$ ) into its mature form and directs its secretion, triggering pyroptosis and release of non-substrate alarmins such as interleukin 1 alpha (IL-1 $\alpha$ ) and HMGB1. While some caspase-1 substrates involved in these events are known, the identities and roles of non-proteolytic targets remain unknown. Here, we use unbiased proteomics to show that the UBE2L3 ubiquitin conjugase is an indirect target of caspase-1. Caspase-1, but not caspase-4, controls pyroptosis- and ubiquitin-independent proteasomal degradation of UBE2L3 upon canonical and non-canonical inflammasome activation by sterile danger signals and bacterial infection. Mechanistically, UBE2L3 acts post-translationally to promote K48-ubiquitylation and turnover of pro-IL-1 $\beta$  and dampen mature-IL-1 $\beta$  production. UBE2L3 depletion increases pro-IL-1 $\beta$  levels and mature-IL-1 $\beta$  secretion by inflammasomes. These findings regarding UBE2L3 as a molecular rheostat have implications for IL-1-driven pathology in hereditary fever syndromes and in autoinflammatory conditions associated with UBE2L3 polymorphisms.

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DOI: 10.1016/j.celrep.2017.01.015

PMCID: PMC5300903

PMID: 28147281 [Indexed for MEDLINE]

888. Lett Appl Microbiol. 2017 Apr;64(4):254-260. doi: 10.1111/lam.12722. Epub 2017 Feb 27.

*Lactobacillus acidophilus* INMIA 9602 Er-2 strain 317/402 probiotic regulates growth of commensal *Escherichia coli* in gut microbiota of familial Mediterranean fever disease subjects.

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Previously, we reported a positive effect the probiotic formulation, *Lactobacillus acidophilus* INMIA 9602 Er-2 strain 317/402 (Narine strain), had on the blood characteristics of patients with familial Mediterranean fever disease (FMF). The aim of this investigation was to evaluate the effect of the Narine probiotic on growth characteristics in the predominant commensal *Escherichia coli* isolates from the gut microbiota in FMF-positive study participants. Bacterial growth of 192 prevalent commensal *E. coli* isolates found in the volunteer participants' guts was evaluated using Verhulst's logistic function. This study showed that the duration of the preparatory growth phase for the *E. coli* isolates collected from FMF-positive volunteers was significantly shorter, whereas the duration of the logarithmic growth phase was significantly longer ( $P < 0.03$ ) than that of the isolates collected from healthy participants. The Narine probiotic formulation caused a significant extension ( $P < 0.001$ ) of the preparatory growth phase in the commensal *E. coli* isolated from FMF subjects a month after the Narine probiotic administration was terminated. The data suggest that the mathematical model characterizes the growth of commensal *E. coli* isolates from

FMF-positive participants and it can be useful in a decision-making process on the practical use of probiotics during FMF. SIGNIFICANCE AND IMPACT OF THE STUDY: This is the first study to demonstrate the effects of Narine, containing the probiotic *Lactobacillus acidophilus*, on the growth of gut commensal *Escherichia coli* from study participants with familial Mediterranean fever disease (FMF). Verhulst's logistic function was demonstrated to act as a possible tool for the evaluation and quantification of effects produced by the probiotic formulation in FMF participants.

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DOI: 10.1111/lam.12722

PMID: 28140472 [Indexed for MEDLINE]

889. Rev Med Interne. 2018 Apr;39(4):211-213. doi: 10.1016/j.revmed.2016.12.021. Epub 2017 Jan 27.

[Autoinflammatory diseases].

[Article in French]

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DOI: 10.1016/j.revmed.2016.12.021

PMID: 28139336 [Indexed for MEDLINE]

890. J Immunol. 2017 Mar 1;198(5):2063-2069. doi: 10.4049/jimmunol.1600760. Epub 2017 Jan 30.

Periodic Fever with Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis

## Syndrome Is Associated with a CARD8 Variant Unable To Bind the NLRP3 Inflammasome.

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Periodic fever with aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) is a relatively common autoinflammatory condition that primarily affects children. Although tendencies were reported for this syndrome, genetic variations influencing risk and disease progression are poorly understood. In this study, we performed next-generation sequencing for 82 unrelated PFAPA patients and identified a frameshift variant in the CARD8 gene (CARD8-FS). Subsequently, we compared the frequency of CARD8-FS carriers in our PFAPA cohort (13.9%) with a healthy local population group (3.2%) and found a significant association between the CARD8-FS polymorphism and risk for PFAPA syndrome ( $p = 0.012$ ; odds ratio: 4.96 [95% confidence interval, 1.33-18.47]). Moreover, CARD8-FS carriers display a distinct PFAPA phenotype that is characterized by a higher prevalence of symptoms out of flares and oral aphthosis (both  $p = 0.02$  compared with PFAPA patients without the frameshift variant). CARD8 encodes a protein component of the NLRP3 inflammasome, which plays an important role in inflammation and contributes to the pathology of various autoinflammatory diseases. We found that the CARD8-FS variant led to a truncated CARD8 protein lacking the FIIND and CARD domains. As a result, the mutant CARD8 protein lost the ability to interact with the NOD domain of NLRP3. In summary, these results identify a new CARD8 variant

associated with PFAPA and further suggest that disruption of the interaction between CARD8 and NLRP3 can regulate autoinflammation in patients.

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DOI: 10.4049/jimmunol.1600760

PMID: 28137891 [Indexed for MEDLINE]

891. Clin Exp Rheumatol. 2017 Nov-Dec;35 Suppl 108(6):128-129. Epub 2017 Jan 26.

Digenic MEFV/TNFRSF1A autoinflammatory syndrome with relapsing aseptic neutrophilic meningitis and chronic myelitis.

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PMID: 28134085 [Indexed for MEDLINE]

892. Iran J Allergy Asthma Immunol. 2016 Dec;15(6):430-444.

Monogenic Auto-inflammatory Syndromes: A Review of the Literature.

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Auto-inflammatory syndromes are a new group of distinct hereditary disorders characterized by episodes of seemingly unprovoked inflammation (most commonly in skin, joints, gut, and eye), the absence of a high titer of auto-antibodies or auto-reactive T cells, and an inborn error of innate immunity. A narrative literature review was carried out of studies related to auto-inflammatory syndromes to discuss the pathogenesis and clinical manifestation of these syndromes. This review showed that the main monogenic auto-inflammatory syndromes are familial Mediterranean fever (FMF), mevalonate kinase deficiency (MKD), Blau syndrome, TNF receptor-associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndrome (CAPS), and pyogenic arthritis with pyoderma gangrenosum and acne (PAPA). The data suggest that correct diagnosis and treatment of monogenic auto-inflammatory diseases relies on the physicians' awareness. Therefore, understanding of the underlying pathogenic mechanisms of auto-inflammatory syndromes, and especially the fact that these disorders are mediated by IL-1 secretion stimulated by monocytes and macrophages, facilitated significant progress in patient management.

PMID: 28129677 [Indexed for MEDLINE]



[Clinical aspects and genetics of proteasome-associated autoinflammatory syndromes (PRAAS)].

[Article in German]

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Functional disorders of the proteasome can have a severe impact on the innate immune system. Characterized by an autosomal recessive mode of inheritance, this novel type of interferonopathy is considered to be a spectrum of diseases of proteasome-associated autoinflammatory syndromes (PRAAS). Accumulation of ubiquitinated proteins and the induction of type I interferon (IFN) genes seem to play a role in the pathogenesis. The typical clinical manifestations are lipodystrophy, skin, joint and muscle involvement accompanied by a remarkable variability of other associated symptoms. This article provides an overview on currently known molecular alterations as well as clinical similarities and differences of PRAAS. Furthermore, the reported effects of the immunosuppressive therapy approaches used so far are summarized.

DOI: 10.1007/s00393-017-0264-x

PMID: 28124745 [Indexed for MEDLINE]

894. Arthritis Rheumatol. 2017 Jun;69(6):1325-1336. doi: 10.1002/art.40055. Epub 2017 May 10.

Cerebrospinal Fluid Cytokines Correlate With Aseptic Meningitis and Blood-Brain Barrier Function in Neonatal-Onset Multisystem Inflammatory Disease: Central Nervous System Biomarkers in Neonatal-Onset Multisystem Inflammatory Disease

Correlate With Central Nervous System Inflammation.

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**OBJECTIVE:** To evaluate proinflammatory cytokines and leukocyte subpopulations in the cerebrospinal fluid (CSF) and blood of patients with neonatal-onset multisystem inflammatory disease (NOMID) after treatment, and to compare inflammatory cytokines in the CSF and blood in 6 patients treated with 2 interleukin-1 (IL-1) blockers-anakinra and canakinumab.

**METHODS:** During routine follow-up visits between December 2011 and October 2013, we immunophenotyped the CSF of 17 pediatric NOMID patients who were treated with anakinra, and analyzed CSF cytokine levels in samples obtained at baseline and at 3-5-year follow-up visits and compared them to samples from healthy controls.

**RESULTS:** CSF levels of IL-6, interferon- $\gamma$ -inducible 10-kd protein (IP-10/CXCL10), and IL-18 and monocyte and granulocyte counts significantly decreased with anakinra treatment but did not normalize to levels in the controls, even in patients fulfilling criteria for clinical remission. CSF IL-6 and IL-18 levels significantly correlated with measures of blood-brain barrier function, specifically CSF protein ( $r = 0.75$  and  $r = 0.81$ , respectively) and albumin quotient ( $r = 0.79$  and  $r = 0.68$ , respectively). When patients were treated with canakinumab versus anakinra, median CSF white blood cell counts and IL-6 levels were significantly higher with canakinumab treatment (10.2 cells/mm<sup>3</sup> versus 3.7 cells/mm<sup>3</sup> and 150.7 pg/ml versus 28.5 pg/ml, respectively) despite similar serum cytokine levels.

**CONCLUSION:** CSF leukocyte subpopulations and cytokine levels significantly

improve with optimized IL-1 blocking treatment, but do not normalize. The correlation of CSF IL-6, IP-10/CXCL10, and IL-18 levels with clinical laboratory measures of inflammation and blood-brain barrier function suggests that they may have a role as biomarkers in central nervous system (CNS) inflammation. The difference in inhibition of CSF biomarkers between 2 IL-1 blocking agents, anakinra and canakinumab, suggests differences in efficacy in the intrathecal compartment, with anakinra being more effective. Our data indicate that intrathecal immune responses shape CNS inflammation and should be assessed in addition to blood markers.

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DOI: 10.1002/art.40055

PMCID: PMC5449229

PMID: 28118536 [Indexed for MEDLINE]

895. Med Clin (Barc). 2017 Mar 22;148(6):283-285. doi: 10.1016/j.medcli.2016.12.013. Epub 2017 Jan 21.

Risk-benefit balance assessment of colchicine use during pregnancy.

[Article in English, Spanish]

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Comment on

Med Clin (Barc). 2016 Oct 21;147(8):352-360.

DOI: 10.1016/j.medcli.2016.12.013

PMID: 28117087 [Indexed for MEDLINE]

896. J Allergy Clin Immunol. 2017 Sep;140(3):782-796. doi: 10.1016/j.jaci.2016.10.054.

Damaging heterozygous mutations in NFKB1 lead to diverse immunologic phenotypes.

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**BACKGROUND:** The nuclear factor  $\kappa$  light-chain enhancer of activated B cells (NF- $\kappa$ B) signaling pathway is a key regulator of immune responses. Accordingly, mutations in several NF- $\kappa$ B pathway genes cause immunodeficiency.

**OBJECTIVE:** We sought to identify the cause of disease in 3 unrelated Finnish kindreds with variable symptoms of immunodeficiency and autoinflammation.

**METHODS:** We applied genetic linkage analysis and next-generation sequencing and functional analyses of NFKB1 and its mutated alleles.

**RESULTS:** In all affected subjects we detected novel heterozygous variants in NFKB1, encoding for p50/p105. Symptoms in variant carriers differed depending on the mutation. Patients harboring a p.I553M variant presented with antibody deficiency, infection susceptibility, and multiorgan autoimmunity. Patients with a p.H67R substitution had antibody deficiency and experienced autoinflammatory episodes, including aphthae, gastrointestinal disease, febrile attacks, and

small-vessel vasculitis characteristic of Behçet disease. Patients with a p.R157X stop-gain experienced hyperinflammatory responses to surgery and showed enhanced inflammasome activation. In functional analyses the p.R157X variant caused proteasome-dependent degradation of both the truncated and wild-type proteins, leading to a dramatic loss of p50/p105. The p.H67R variant reduced nuclear entry of p50 and showed decreased transcriptional activity in luciferase reporter assays. The p.I553M mutation in turn showed no change in p50 function but exhibited reduced p105 phosphorylation and stability. Affinity purification mass spectrometry also demonstrated that both missense variants led to altered protein-protein interactions.

**CONCLUSION:** Our findings broaden the scope of phenotypes caused by mutations in NFKB1 and suggest that a subset of autoinflammatory diseases, such as Behçet disease, can be caused by rare monogenic variants in genes of the NF-κB pathway.

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DOI: 10.1016/j.jaci.2016.10.054

PMID: 28115215 [Indexed for MEDLINE]

897. Trends Mol Med. 2017 Feb;23(2):165-180. doi: 10.1016/j.molmed.2016.12.007. Epub 2017 Jan 18.

Inflammasome Priming in Sterile Inflammatory Disease.

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The inflammasome is a cytoplasmic protein complex that processes interleukins (IL)-1 $\beta$  and IL-18, and drives a form of cell death known as pyroptosis.

Oligomerization of this complex is actually the second step of activation, and a priming step must occur first. This involves transcriptional upregulation of pro-IL-1 $\beta$ , inflammasome sensor NLRP3, or the non-canonical inflammasome sensor caspase-11. An additional aspect of priming is the post-translational modification of particular inflammasome constituents. Priming is typically accomplished in vitro using a microbial Toll-like receptor (TLR) ligand. However, it is now clear that inflammasomes are activated during the progression of sterile inflammatory diseases such as atherosclerosis, metabolic disease, and neuroinflammatory disorders. Therefore, it is time to consider the endogenous factors and mechanisms that may prime the inflammasome in these conditions.

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DOI: 10.1016/j.molmed.2016.12.007

PMID: 28109721 [Indexed for MEDLINE]

898. Int Ophthalmol. 2018 Feb;38(1):183-190. doi: 10.1007/s10792-017-0446-1. Epub 2017 Jan 21.

Peripapillary retinal nerve fiber layer and ganglion cell-inner plexiform layer thickness in adult-onset familial Mediterranean fever.

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**OBJECTIVE:** The purpose of the present study was to evaluate the thickness of the peripapillary retinal nerve fiber layer (RNFL) and retinal ganglion cell-inner plexiform layer (GCIPL) in adult-onset familial Mediterranean fever (FMF).

**METHODS:** Forty two adult-onset FMF patients and forty two healthy controls were included in the present study. Detailed ocular examination was performed, and then the thickness of the peripapillary RNFL and GCIPL was measured by Spectral domain optical coherence tomography. The patients were divided into two groups according to their disease severity score, M694V gene mutation, colchicine dosage used per day, colchicine usage time period and number of FMF attacks per year.

**RESULTS:** There were no statistically significant differences in peripapillary RNFL and retinal GCIPL thickness in patients with adult-onset FMF and controls.

**CONCLUSION:** According to our study, it looks like that neither adult-onset FMF nor colchicine has any effect on the RNFL and GCIPL thicknesses. Further studies with a large sample size are needed.

DOI: 10.1007/s10792-017-0446-1

PMID: 28108907 [Indexed for MEDLINE]

899. Br J Dermatol. 2017 Jan;176(1):18-19. doi: 10.1111/bjd.15011.

Expanding the skin and histopathology manifestations of autoinflammatory diseases.

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DOI: 10.1111/bjd.15011

PMID: 28098378 [Indexed for MEDLINE]

900. Scand J Rheumatol. 2017 Sep;46(5):407-409. doi: 10.1080/03009742.2016.1245780. Epub 2017 Jan 18.

Treatment of familial Mediterranean fever with anakinra in patients unresponsive to colchicine.

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DOI: 10.1080/03009742.2016.1245780

PMID: 28097903 [Indexed for MEDLINE]

901. Semin Diagn Pathol. 2017 May;34(3):273-284. doi: 10.1053/j.semdp.2016.12.002. Epub 2016 Dec 14.

Disorders characterized by predominant or exclusive dermal inflammation.

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Some cutaneous inflammatory disorders are typified by a predominant or exclusive localization in the dermis. They can be further subdivided by the principal cell types into lymphocytic, neutrophilic, and eosinophilic infiltrates, and mixtures of them are also seen in a proportion of cases. This review considers such conditions. Included among the lymphoid lesions are viral exanthems, pigmented purpuras, gyrate erythemas, polymorphous light eruption, lupus tumidus, and cutaneous lymphoid hyperplasia. Neutrophilic infiltrates are represented by infections, Sweet syndrome, pyoderma gangrenosum, and hidradenitis suppurativa, as well as a group of so-called "autoinflammatory" dermatitides comprising polymorphonuclear leukocytes. Eosinophil-dominated lesions include arthropod bite reactions, cutaneous parasitic infestations, the urticarial phase of bullous pemphigoid, Wells syndrome (eosinophilic cellulitis), hypereosinophilic syndrome, and Churg-Strauss disease. In other conditions, eosinophils are admixed with neutrophils in the corium, with or without small-vessel vasculitis. Exemplary disorders with those patterns include drug eruptions, chronic idiopathic urticaria, urticarial vasculitis, granuloma faciale, and Schnitzler syndrome (chronic urticarial with a monoclonal gammopathy).

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DOI: 10.1053/j.semdp.2016.12.002

PMID: 28094164 [Indexed for MEDLINE]

902. Clin Transl Immunology. 2016 Dec 16;5(12):e118. doi: 10.1038/cti.2016.75. eCollection 2016 Dec.

Immunopathogenesis of granulomas in chronic autoinflammatory diseases.

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Granulomas are clusters of immune cells. These structures can be formed in reaction to infection and display signs of necrosis, such as in tuberculosis. Alternatively, in several immune disorders, such as sarcoidosis, Crohn's disease and common variable immunodeficiency, non-caseating granulomas are formed without an obvious infectious trigger. Despite advances in our understanding of the human immune system, the pathogenesis underlying these non-caseating granulomas in chronic inflammatory diseases is still poorly understood. Here, we review the current knowledge about the immunopathogenesis of granulomas, and we discuss how the involved immune cells can be targeted with novel therapeutics.

DOI: 10.1038/cti.2016.75

PMCID: PMC5192066

PMID: 28090320

903. Clin Rheumatol. 2017 Sep;36(9):2071-2077. doi: 10.1007/s10067-016-3532-2. Epub 2017 Jan 10.

Evaluation of endothelial dysfunction in patients with familial Mediterranean fever: the relationship between the levels of asymmetric dimethylarginine and endocan with carotid intima-media thickness and endothelium-dependent vasodilation.

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It has been suggested that there is an ongoing subclinical inflammation in familial Mediterranean fever (FMF) patients also in attack-free periods as well. Due to this ongoing inflammation, endothelial dysfunction (ED) may develop. Previously, ED has been suggested to increase the risk of the atherosclerosis and cardiovascular disease (CVD). Endocan is recognized as a specific molecule of the endothelium and has been shown to increase in some cases associated with inflammation. However, there is not sufficient data whether those with FMF could develop ED in the early period of life. In this study, we aimed to investigate ED and its relation with endocan in young FMF patients. A total of 57 male patients diagnosed with FMF according to the Tel Hashomer criteria and a total of 33 healthy males with similar characteristics to the patient group were included in this research. Complete blood count, erythrocyte sedimentation rate (ESR), fibrinogen, serum glucose, serum LDL cholesterol (LDL-C) and triglyceride (TG), asymmetric dimethylarginine (ADMA), and endocan levels were tested from fasting blood samples. Moreover, carotid intima-media thickness (CIMT) and flow-mediated dilatation (FMD) were measured. The endocan levels of the FMF patients during an attack-free period were significantly higher than those of the control group ( $p < 0.001$ ). On the other hand, FMD measurements were significantly lower among FMF patients ( $p < 0.001$ ). ADMA levels were higher in the patient group; however, this difference was similar ( $p > 0.05$ ). CIMT values were similar among FMF patients and healthy controls ( $p > 0.05$ ). These results have suggested that ED may develop in the patients with FMF who have no additional CVD risk, even during young adulthood, and endocan may be a favorable biomarker at demonstration of ED than ADMA among FMF patients.

DOI: 10.1007/s10067-016-3532-2

PMID: 28074304 [Indexed for MEDLINE]

904. Int J Rheumatol. 2016;2016:7354018. doi: 10.1155/2016/7354018. Epub 2016 Dec 13.

Serum Amyloid A Level in Egyptian Children with Familial Mediterranean Fever.

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**Background and Objectives.** SAA is an acute-phase reactant detected during an FMF attack or other inflammatory conditions. High SAA levels may increase the risk of amyloidosis. The aim of the study is to measure the serum amyloid A (SAA) level in a group of Egyptian children with familial Mediterranean fever (FMF) and study its various correlates, if any. **Methods.** The study enrolled seventy-one children with FMF. **Results.** SAA level was high in 78.9% of the studied patients with a mean of  $81.62 \pm 31.6$  mg/L, and CRP was positive in 31% of patients. There was no significant relation between SAA level and any demographic or clinical manifestation. High SAA was more frequent in V726A allele (16.9%) followed by M694V allele (12.3%). Elevated SAA levels were more frequent in patients on low colchicine doses. Forty-five percent (45%) of patients have low adherence to colchicine therapy. **Interpretation and Conclusion.** High SAA levels were detected two weeks after last FMF attack in a large percentage of Egyptian FMF children. This indicates that subclinical inflammation continues during attack-free periods, and SAA could be used as a marker of it.

DOI: 10.1155/2016/7354018

PMCID: PMC5187476

PMID: 28070191

**Conflict of interest statement:** The authors declare that there is no conflict of interests regarding the publication of this paper.

905. Expert Rev Clin Immunol. 2017 Jun;13(6):571-597. doi: 10.1080/1744666X.2017.1280396. Epub 2017 Feb 1.

A systematic approach to autoinflammatory syndromes: a spelling booklet for the beginner.

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**INTRODUCTION:** Hallmark of autoinflammatory syndromes (AIS) is the periodic recurrence of 'sterile' inflammatory attacks characterized by fever and organ- or tissue-specific inflammation. Basic research projects over the last two decades have boosted our understanding of pathological pathways, mainly involving interleukin (IL)-1 biosynthesis, and also revealed that their dysregulation results from genetically-heterogeneous inborn errors of innate immunity and leads to multiple inflammatory phenotypes. Starting from the evidence of poor response to IL-1 inhibitors of some patients with multi-organ inflammation, further research studies have disclosed a crucial role for nuclear factor (NF)- $\kappa$ B and type I interferon (IFN) in specific AIS. Presently, new genetically-defined AIS have been identified, following the in-depth analysis of molecular pathways which involve either constitutive NF- $\kappa$ B activation or IFN signaling. Areas covered: This review is intended as a spelling booklet to help clinicians approaching patients with AIS in a simple way, using the component of the innate immunity they mainly affect. AIS have been split into 4 groups: IL-1-mediated disorders, NF- $\kappa$ B-mediated disorders, IFN-mediated disorders, and syndromes with still unraveled pathogenetic mechanisms or without any dominating cytokine involved. This classification has mere scholastic purposes and does not reflect the intimate complexity of each disorder discussed herein. Expert commentary: The understanding of dysregulated molecular pathways driving specific phenotypes in most AIS has prompted numerous projects to discover therapies targeting directly cytokine-mediated manifestations in such problematic patients, hopefully aimed to decrease or cancel inflammation and lead to a drastic change in patients' lives. The future has only begun.

DOI: 10.1080/1744666X.2017.1280396

PMID: 28064547 [Indexed for MEDLINE]

906. North Clin Istanbul. 2016 May 25;3(1):39-45. doi: 10.14744/nci.2016.52824. eCollection 2016.

Is triglyceride/HDL ratio a reliable screening test for assessment of

atherosclerotic risk in patients with chronic inflammatory disease?

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**OBJECTIVE:** The term chronic inflammatory disease (CID) refers to a category of inflammatory diseases that includes Ankylosing spondylitis (AS) and familial Mediterranean fever (FMF). The incidence of adverse cardiovascular events is greater among patients with CID, though they may not have conventional atherosclerotic risk factors. Endothelial dysfunction is one of the underlying fundamental mechanisms that trigger development of atherosclerotic alterations in arteries, and flow-mediated dilatation (FMD) is a noninvasive method to determine endothelial dysfunction. Recent studies have shown a relationship between high triglyceride high-density lipoprotein cholesterol (TG/HDL-C) ratio and coronary atherosclerosis. Many studies have demonstrated that patients with CID have lower FMD values compared to healthy population, indicating endothelial dysfunction. However TG/HDL ratio and its relationship to FMD in patients with CID has not been investigated. The present study investigated whether TG/HDL ratio in CID patients differs from that of healthy population, and its relationship to FMD in patients with CID.

**METHODS:** A total of 58 patients with CID and a group of 58 healthy volunteer individuals were enrolled in the study. FMD measurements were taken with high resolution ultrasound (US), and TG/HDL ratios were calculated.

**RESULTS:** Patients with CID had significantly higher TG/HDL-C ratio (2.5 [2.2-2.8] vs 2.3 [2.1-2.5];  $p=0.03$ ) and lower FMD values (5.2 [4.2-6.3] vs 6.7 [6.3-9.7];  $p<0.001$ ), compared to healthy group, and a negative correlation was found between FMD levels and TG/HDL ratio of the study population.

**CONCLUSION:** Higher TG/HDL ratio and lower FMD values found in CID patients may reflect increased atherosclerotic risk.

DOI: 10.14744/nci.2016.52824

PMCID: PMC5175076

PMID: 28058384

Conflict of interest statement: Conflicts of Interest: None declared.

907. Case Rep Ophthalmol Med. 2016;2016:2916027. doi: 10.1155/2016/2916027. Epub 2016 Dec 4.

Frosted Branch Angiitis Secondary to Familial Mediterranean Fever Resembling Central Retinal Vein Occlusion.

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**Purpose.** To report a case of unilateral frosted branch angiitis (FBA) resembling central retinal vein occlusion associated with Familial Mediterranean Fever (FMF). **Case Report.** A 32-year-old woman presented with progressive, painless vision loss in her left eye lasting for 2 days. She was clinically diagnosed with FMF 2 months ago. The best-corrected visual acuity (BCVA) was 20/20 in her right eye and there was light perception in the left. Ophthalmologic examination revealed severe retinal vasculitis showing clinical features of FBA in the left eye. 64 mg/day oral methylprednisolone was started. A significant improvement in retinal vasculitis was observed in two weeks. However, BCVA did not increase significantly due to subhyaloid premacular hemorrhage. Argon laser posterior hyaloidotomy was performed. One week after hyaloidotomy, visual acuity improved to 20/20 and intravitreal hemorrhage disappeared. Four months after the first attack, FBA recurred. Oral methylprednisolone dosage was increased to 64 mg/day and combined with azathioprine 150 mg. At the end of 12-month follow-up, the BCVA was 20/25 and development of epiretinal membrane was observed in the left eye. **Conclusions.** Frosted branch angiitis may occur with gene abnormalities as an underlying condition. Our case showed that FMF might be a causative disease.

DOI: 10.1155/2016/2916027

PMCID: PMC5164904

PMID: 28044118

Conflict of interest statement: The authors declare that there are no competing



interests regarding the publication of this paper.

908. Case Rep Med. 2016;2016:5869250. doi: 10.1155/2016/5869250. Epub 2016 Dec 4.

Enthesitis in a 16-Year-Old Boy with M694V Mutation.

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**Introduction.** FMF (Familial Mediterranean Fever) is characterized by recurrent attacks of fever and articular pain. Enthesitis is the hallmark of pain in spondyloarthropathy. Literature suggests association of M694V mutation and enthesitis. We report a case of a 16-year-old boy with enthesitis and FMF. **Case Presentation.** A 16-year-old boy of Turkish origin with a history of FMF presented with localized tenderness of the heel and severe disability. MRI showed an enthesitis of the plantar fascia. Standard treatment of FMF and enthesitis was not successful. After referral to a university hospital and expert opinion of a professor in rheumatology, this enthesitis should be treated as an enthesitis related arthritis. With this treatment, our patient fully recovered 8 months after the onset of the disease symptoms. **Conclusion.** M694V mutation related enthesitis should be considered in FMF patients with enthesitis. We would suggest treatment for enthesitis related arthritis in similar cases. This is of clinical importance because the treatment is different from treatment of enthesitis or articular pain caused by FMF.

DOI: 10.1155/2016/5869250

PMCID: PMC5164889

PMID: 28044082

**Conflict of interest statement:** The authors declare that there is no conflict of interests regarding the publication of this paper.

909. Ann Rheum Dis. 2017 Aug;76(8):e26. doi: 10.1136/annrheumdis-2016-210918. Epub 2017 Jan 2.

Response to: 'Autoinflammatory disease damage index (ADDI): a possible newborn also in hidradenitis suppurativa daily practice' by Damiani et al.

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DOI: 10.1136/annrheumdis-2016-210918

PMID: 28043999

Conflict of interest statement: Competing interests: None declared.

910. Cell Mol Immunol. 2017 Jan 2. doi: 10.1038/cmi.2016.59. [Epub ahead of print]

Mesenchymal stem cells ameliorate B-cell-mediated immune responses and increase IL-10-expressing regulatory B cells in an EBI3-dependent manner.

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Effector B cells are central contributors to the development of autoimmune disease by activating autoreactive T cells, producing pro-inflammatory cytokines and organizing ectopic lymphoid tissue. Conversely, IL-10-producing regulatory B (Breg) cells have pivotal roles in maintaining immunological tolerance and restraining excessive inflammation in autoinflammatory disease. Thus, regulating the equilibrium between antibody-producing effector B cells and Breg cells is critical for the treatment of autoimmune disease. In this study, we investigated

the effect of human palatine tonsil-derived mesenchymal stem cells (T-MSCs) on estradiol (E2)-induced B-cell responses in vivo and in vitro. Transplantation of T-MSC into E2-treated mice alleviated B-cell-mediated immune responses and increased the population of IL-10-producing Breg cells. T-MSCs regulated the B-cell populations by producing Epstein-Barr virus (EBV)-induced 3 (EBI3), one of the two subunits of IL-35 that is the well-known inducer of Breg cells. We demonstrate a critical role of EBI3 (IL-35) in vitro by depleting EBI3 in T-MSCs and by adding exogenous IL-35 to the culture system. Taken together, our data suggest that IL-35-secreting MSCs may become an attractive therapeutic to treat B-cell-mediated autoimmune diseases via expanding Breg cells. *Cellular & Molecular Immunology* advance online publication, 2 January 2017; doi:10.1038/cmi.2016.59.

DOI: 10.1038/cmi.2016.59

PMCID: PMC5675953

PMID: 28042143

911. *J Rheumatol.* 2017 Jan;44(1):102-109. doi: 10.3899/jrheum.160518. Epub 2016 Nov 15.

Longterm Beneficial Effect of Canakinumab in Colchicine-resistant Familial Mediterranean Fever.

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**OBJECTIVE:** To assess the efficacy and safety of the interleukin-1 $\beta$  (IL-1 $\beta$ ) inhibitor canakinumab in all adolescent and adult patients with familial Mediterranean fever (FMF) identified from the Greek National Registry for off-label drug use between 2010 and 2015.

**METHODS:** In this retrospective longitudinal outcome study, clinical and laboratory data were collected from 14 patients (7 men) aged median 38.5 years (range 13-70), with median disease duration of 14 years, and active FMF despite colchicine (n = 9) or both colchicine and anakinra (n = 5).

**RESULTS:** All patients continued to receive canakinumab at last visit (median of 18 mos, range 13-53), which was initially given as monotherapy (n = 8) or in combination with colchicine and/or corticosteroids, every 4 (n = 7), 6 (n = 2), or 8 weeks (n = 5). Eleven patients (79%), including 6 receiving monotherapy, achieved complete clinical remission within 2 months (median), while normalization of all laboratory variables denoting inflammation occurred in 92% at 3 months (median). The remaining 3 patients achieved partial responses. Responses were sustained in all but 4 patients, who relapsed. Reducing the canakinumab administration interval from 8 or 6 weeks to 4 weeks led to suppression of disease activity in the relapsing patients. On the other hand, drug administration interval could be safely increased in 2 patients in remission. Corticosteroid doses were significantly reduced during followup. Canakinumab was well tolerated; 1 patient experienced a urinary tract infection and another one a viral gastroenteritis.

**CONCLUSION:** Treatment with canakinumab in an individualized dosing scheme results in rapid and sustained remission in colchicine-resistant FMF.

DOI: 10.3899/jrheum.160518

PMID: 28042127 [Indexed for MEDLINE]

912. QJM. 2017 May 1;110(5):287-290. doi: 10.1093/qjmed/hcw230.

Familial Mediterranean fever-associated diseases in children.

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**Background:** MEditerranean FeVer (MEFV) gene encodes for the pyrin protein and a mutated pyrin is associated with a prolonged or augmented inflammation. Hence, various diseases were reported to be associated with familial Mediterranean fever (FMF) or carriers of MEFV mutations. However, systematic evaluation of all associated diseases in children with FMF has not been done previously.

**Aim:** The aim of this study was to investigate the frequency and type of FMF-associated diseases in children.

**Design and Methods:** Files of FMF patients who had been seen in two reference hospitals in Ankara, in the last two years, were retrospectively evaluated.

Patients with FMF and concomitant diseases were included to the study.

**Results:** Among 600 FMF patients, 77 were found to have a concomitant disease (12.8%). Thirty patients (5%) had vasculitis; 21 (3.5%) had juvenile idiopathic arthritis (JIA); 7 (1.16%) had inflammatory bowel disease (IBD) and 19 had other diseases including 5 patients with isolated sacroiliitis. Overall, 13 (2.17%) patients had sacroiliitis in our cohort. The most frequent mutation was M694V/M694V (44%) and 81% of the patients had at least one M694V mutation. Majority of the patients (74%) developed associated diseases while they were not receiving colchicine therapy.

**Conclusions:** Certain inflammatory diseases including vasculitis, chronic arthritis and IBD were more frequently detected in patients with FMF during childhood. M694V mutation is a susceptibility factor for associated diseases. In countries where FMF is prevalent, clinicians dealing with FMF and other inflammatory diseases should be aware of these associations.

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DOI: 10.1093/qjmed/hcw230

PMID: 28040706 [Indexed for MEDLINE]

913. Turk J Pediatr. 2017;59(4):467-470. doi: 10.24953/turkjpmed.2017.04.015.

Two cases of periodic fever syndrome with coexistent mevalonate kinase and Mediterranean fever gene mutations.

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Çakan M, Aktay-Ayaz N, Keskindemirci G, Karadağ ŞG. Two cases of periodic fever syndrome with coexistent mevalonate kinase and Mediterranean fever gene mutations. Turk J Pediatr 2017; 59: 467-470. The periodic fever syndromes are autoinflammatory diseases that present with recurrent fever, serositis and rash. Familial Mediterranean fever is the most common periodic fever syndrome and characterized by recurrent attacks of fever, arthritis, peritonitis, pleuritis that typically last 1-3 days. Hyperimmunoglobulinemia D syndrome is another example of periodic fever syndromes and patients have recurrent fever attacks for 3-7 days accompanied by abdominal pain, rash, vomiting, diarrhea, arthralgia, arthritis, aphthous ulcers, and cervical lymphadenopathy. In some cases the clinical picture of the patient does not fit to one autoinflammatory syndrome because of the digenic inheritance. This may cause to overlap or atypical clinical features or an unexpected response to treatment. Herein we report two cases of hyperimmunoglobulinemia D syndrome that also had MEFV gene mutations and familial Mediterranean fever phenotype.

DOI: 10.24953/turkjpmed.2017.04.015

PMID: 29624229 [Indexed for MEDLINE]

914. Turk J Pediatr. 2017;59(4):357-368. doi: 10.24953/turkjpmed.2017.04.001.

Current information about vaccination practice in pediatric rheumatic diseases

and recommendations for future applications.

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Açarı C, Ünsal E. Current information about vaccination practice in pediatric rheumatic diseases and recommendations for future applications. Turk J Pediatr 2017; 59: 357-368. Pediatric patients with autoinflammatory or rheumatic diseases are at increased risk of infections; therefore, safe and effective immunizations are crucial in the management of these group of patients. Current aggressive treatments involving the early use of immunosuppressive drugs and biological agents have further increased the susceptibility to infections in this group of patients. Therefore, effective and safe vaccination with adequate serological responses is important. In patients with rheumatic diseases, immunogenicity of a vaccine can differ from the healthy population, because of the disease itself or the immunosuppressive treatment received. Moreover, possible effects of vaccination on the underlying disease should be considered. In general, live attenuated vaccines should not be administered when high-dose immunosuppressive drugs are used for immunosuppressed patients. Inactivated vaccine agents have proven to be generally safe in patients with RD. The immune-modulating of biologic agents effects can last for weeks to months after discontinuation, depending on their half lifes. Also, live virus vaccines are contraindicated during therapy and for weeks to months following discontinuation of the biologics. The aim of this review is to cover the current information about vaccination practice in pediatric rheumatologic diseases and to give recommendations for future applications.

DOI: 10.24953/turkjpmed.2017.04.001

PMID: 29624215 [Indexed for MEDLINE]

915. Clin Rheumatol. 2017 Oct;36(10):2307-2318. doi: 10.1007/s10067-016-3527-z. Epub 2016 Dec 28.

The emerging role of interleukin (IL)-1 in the pathogenesis and treatment of inflammatory and degenerative eye diseases.



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Interleukin (IL)-1 plays a key role in the pathogenesis and thereafter in the search for specific treatments of different inflammatory and degenerative eye diseases. Indeed, an overactivity of IL-1 might be an initiating factor for many immunopathologic sceneries in the eye, as proven by the efficacy of the specific IL-1 blockade in different ocular diseases. For instance, the uveitis in monogenic autoinflammatory disorders, such as Blau syndrome and cryopyrin-associated periodic syndrome, or in complex polygenic autoinflammatory disorders, such as Behçet's disease, has been successfully treated with IL-1 blockers. Similarly, therapy with the IL-1 receptor antagonist anakinra has proven successful also in scleritis and episcleritis in the context of different rheumatic conditions. Moreover, interesting findings deriving from animal models of ocular disease have set a rational basis from a therapeutic viewpoint to manage patients also with dry eye disease and a broadening number of ocular inflammatory and degenerative conditions, which start from an imbalance between IL-1 and its receptor antagonist.

DOI: 10.1007/s10067-016-3527-z

PMID: 28032234 [Indexed for MEDLINE]

# Genetic risk analysis of a patient with fulminant autoimmune type 1 diabetes mellitus secondary to combination ipilimumab and nivolumab immunotherapy.

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**BACKGROUND:** Checkpoint inhibitor immunotherapy is becoming an effective treatment modality for an increasing number of malignancies. As a result, autoinflammatory side-effects are also being observed more commonly in the clinic. We are currently unable to predict which patients will develop more severe toxicities associated with these treatment regimens.

**CASE PRESENTATION:** We present a patient with stage IV melanoma that developed rapid onset autoimmune type 1 diabetes (T1D) in response to combination ipilimumab and nivolumab immunotherapy. At the time of the patient's presentation with diabetes ketoacidosis, a confirmed anti-GAD antibody seroconversion was noted. Longer-term follow-up of this patient has demonstrated a durable complete response based on PET CT imaging along with a persistently undetectable C-peptide level. Single nucleotide polymorphism gene sequencing and HLA risk allele analysis has revealed the patient to lack any established genetic predisposition to the development of autoimmune T1D.

**CONCLUSIONS:** While larger studies are necessary to better understand the role of genetic risk factors for the development of autoimmune toxicities in those patients undergoing checkpoint inhibitor immunotherapy, these results suggest that pre-screening patients for known T1D risk alleles may not be indicated. Additional investigation is needed to determine whether an approach such as T cell receptor clonotypic analysis to identify the presence of autoreactive T cell clones may be an effective approach for predicting which patients are at risk for the development of autoinflammatory toxicities while undergoing checkpoint inhibitor immunotherapy.

DOI: 10.1186/s40425-016-0196-z

PMCID: PMC5170902

PMID: 28031819

917. Anticancer Drugs. 2017 Mar;28(3):250-262. doi: 10.1097/CAD.0000000000000464.

Potential anticancer role of colchicine-based derivatives: an overview.

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Colchicine, the main alkaloid of the poisonous plant meadow saffron (*Colchicum autumnale* L.), is a classical drug used for the treatment of gout and familial Mediterranean fever. Although colchicine is not clinically used to treat cancer because of toxicity, it exerts antiproliferative effects through the inhibition of microtubule formation by blocking the cell cycle at the G2/M phase and triggering apoptosis. Colchicine can still be used as a lead compound for the generation of potential anticancer drugs. Thus, numerous analogues of colchicine have been synthesized in the hope of developing novel, useful drugs with more favourable pharmacological profiles. Several colchicine semisynthetics are less toxic than colchicine and research is being carried out on effective, less toxic colchicine semisynthetic formulations with potential drug-delivery strategies directly targeting multiple solid cancers. This review focuses on the anticancer role of some of colchicine-based derivatives and their therapeutic importance.

DOI: 10.1097/CAD.0000000000000464

PMID: 28030380 [Indexed for MEDLINE]

918. Allergol Immunopathol (Madr). 2017 Mar - Apr;45(2):134-144. doi: 10.1016/j.aller.2016.06.007. Epub 2016 Oct 28.

Management of chronic spontaneous urticaria in routine clinical practice: A

Delphi-method questionnaire among specialists to test agreement with current European guidelines statements.

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**BACKGROUND:** Chronic spontaneous urticaria (CSU) is a frequent clinical entity that often presents a diagnostic and therapeutic challenge.

**OBJECTIVE:** To explore the degree of agreement that exists among the experts caring for patients with CSU diagnosis, evaluation, and management.

**METHODS:** An online survey was conducted to explore the opinions of experts in CSU, address controversial issues, and provide recommendations regarding its definition, natural history, diagnosis, and treatment. A modified Delphi method was used for the consensus.

**RESULTS:** The questionnaire was answered by 68 experts (dermatologists, allergologists, and primary care physicians). A consensus was reached on 54 of

the 65 items posed (96.4%). The experts concluded that CSU is a difficult-to-control disease of unpredictable evolution. Diagnostic tests should be limited and based on clinical history and should not be indiscriminate. Autoinflammatory syndromes and urticarial vasculitis must be ruled out in the differential diagnosis. A cutaneous biopsy is only recommended when wheals last more than 24h, to rule out urticarial vasculitis. The use of specific scales to assess the severity of the disease and the quality of life is recommended. In patients with severe and resistant CSU, second-generation H1-antihistamines could be used at doses up to four times the standard dose before giving second-line treatments. Omalizumab is a safe and effective treatment for CSU that is refractory to H1-antihistamines treatment. In general, diagnosis and treatment recommendations given for adults could be extrapolated to children.

CONCLUSIONS: This work offers consensus recommendations that may be useful in the management of CSU.

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DOI: 10.1016/j.aller.2016.06.007

PMID: 28029407 [Indexed for MEDLINE]

919. Clin Rheumatol. 2017 Apr;36(4):965-969. doi: 10.1007/s10067-016-3523-3. Epub 2016 Dec 27.

Muckle-Wells syndrome in Chinese patients: a single center case series.

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Muckle-Wells syndrome (MWS) is a rare autoinflammatory disease. This study aimed to report the clinical features and gene variations of the first case series of MWS patients in Chinese population. Four Han Chinese patients were diagnosed with MWS and followed up at our adult clinic for autoinflammatory diseases. All relevant phenotypes and genotypes were collected. All patients were adult male.

The median age of disease onset was 4.5 years, and one patient had adult-onset disease. No positive family history was observed. All patients had a remittent disease course. The duration of fever attacks ranged from 0.5 to 7 days. Skin rashes were present in all patients. The other manifestations included polyarthralgia/arthritis (n = 3), oral ulcers (n = 2), conjunctivitis (n = 2), myalgia (n = 2), headache (n = 2), pharyngitis (n = 1), abdominal pain (n = 1), severe sensorineural hearing loss (n = 1), and chronic meningitis with communicating hydrocephalus (n = 1). None of the patients showed evidence of renal amyloidosis. Each patient carried a heterozygous mutation in an NLRP3 gene, including D29V, V70M, T348M, and Q703K, respectively. D29V and V70M variants were novel mutations in exon 1 of NLRP3. All patients had good response to corticosteroids. Our study suggests that MWS could be identified in Chinese population. Our finding of novel mutations in NLRP3 may expand the diversity of MWS.

DOI: 10.1007/s10067-016-3523-3

PMID: 28028683 [Indexed for MEDLINE]

920. Korean J Pediatr. 2016 Nov;59(Suppl 1):S53-S56. doi: 10.3345/kjp.2016.59.11.S53. Epub 2016 Nov 30.

Familial Mediterranean fever presenting as fever of unknown origin in Korea.

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Familial Mediterranean fever (FMF) is the most common Mendelian autoinflammatory disease, characterized by uncontrolled activation of the innate immune system that manifests as recurrent brief fever and polyserositis (e.g., peritonitis, pleuritic, and arthritis). FMF is caused by autosomal recessive mutations of the Mediterranean fever gene, MEFV which encodes the pyrin protein. Although FMF predominantly affects people from Mediterranean and Middle Eastern ethnic origins, 3 cases of FMF have been reported in Korea since 2012. We report another case of FMF in Korea in which the patient presented with a month-long fever

without serositis. After treatment with colchicine was initiated, the patient's symptoms quickly subsided. The response to colchicine was helpful for diagnosis. We compare the FMF genotypes in Korea with in other countries. Studying FMF cases in Korea will help establish the best MEFV exons to use for screening and diagnosis of Korean FMF.

DOI: 10.3345/kjp.2016.59.11.S53

PMCID: PMC5177713

PMID: 28018446

Conflict of interest statement: No potential conflict of interest relevant to this article was reported.

921. Ann Rheum Dis. 2017 Aug;76(8):e25. doi: 10.1136/annrheumdis-2016-210901. Epub 2016 Dec 23.

Autoinflammatory Disease Damage Index (ADDI): a possible newborn also in hidradenitis suppurativa daily practice.

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DOI: 10.1136/annrheumdis-2016-210901

PMID: 28011453

Conflict of interest statement: Competing interests: None declared.

922. J Innate Immun. 2017;9(2):111-125. doi: 10.1159/000453397. Epub 2016 Dec 23.

Cellular Innate Immunity: An Old Game with New Players.

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Innate immunity is a rapidly evolving field with novel cell types and molecular pathways being discovered and paradigms changing continuously. Innate and adaptive immune responses are traditionally viewed as separate from each other, but emerging evidence suggests that they overlap and mutually interact. Recently discovered cell types, particularly innate lymphoid cells and myeloid-derived suppressor cells, are gaining increasing attention. Here, we summarize and highlight current concepts in the field, focusing on innate immune cells as well as the inflammasome and DNA sensing which appear to be critical for the activation and orchestration of innate immunity, and may provide novel therapeutic opportunities for treating autoimmune, autoinflammatory, and infectious diseases.

© 2016 S. Karger AG, Basel.

DOI: 10.1159/000453397

PMID: 28006777 [Indexed for MEDLINE]

923. Kidney Blood Press Res. 2016;41(6):1016-1024. doi: 10.1159/000452605. Epub 2016 Dec 23.

The Prevalence of Fabry Disease in Patients with Chronic Kidney Disease in Turkey: The TURKFAB Study.

Turkmen K(1), Guclu A, Sahin G, Kocyigit I, Demirtas L, Erdur FM, Sengül E, Ozkan O, Emre H, Turgut F, Unal H, Karaman M, Acikel C, Esen H, Balli E, Bitirgen G, Tonbul HZ, Yilmaz MI, Ortiz A.

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BACKGROUND/AIMS: Fabry disease is a treatable cause of chronic kidney disease (CKD) characterized by a genetic deficiency of  $\alpha$ -galactosidase A. European Renal



Best Practice (ERBP) recommends screening for Fabry disease in CKD patients. However, this is based on expert opinion and there are no reports of the prevalence of Fabry disease in stage 1-5 CKD. Hence, we investigated the prevalence of Fabry disease in CKD patients not receiving renal replacement therapy.

**METHODS:** This prospective study assessed  $\alpha$ -galactosidase activity in dried blood spots in 313 stage 1-5 CKD patients, 167 males, between ages of 18-70 years whose etiology of CKD was unknown and were not receiving renal replacement therapy. The diagnosis was confirmed by GLA gene mutation analysis.

**RESULTS:** Three (all males) of 313 CKD patients (0.95%) were diagnosed of Fabry disease, for a prevalence in males of 1.80%. Family screening identified 8 additional Fabry patients with CKD. Of a total of 11 Fabry patients, 7 were male and started enzyme replacement therapy and 4 were female. The most frequent manifestations in male patients were fatigue (100%), tinnitus, vertigo, acroparesthesia, hypohidrosis, cornea verticillata and angiokeratoma (all 85%), heat intolerance (71%), and abdominal pain (57%). The most frequent manifestations in female patients were fatigue and cornea verticillata (50%), and tinnitus, vertigo and angiokeratoma (25%). Three patients had severe episodic abdominal pain attacks and proteinuria, and were misdiagnosed as familial Mediterranean fever.

**CONCLUSIONS:** The prevalence of Fabry disease in selected CKD patients is in the range found among renal replacement therapy patients, but the disease is diagnosed at an earlier, treatable stage. These data support the ERBP recommendation to screen for Fabry disease in patients with CKD of unknown origin.

© 2016 The Author(s) Published by S. Karger AG, Basel.

DOI: 10.1159/000452605

PMID: 28006774 [Indexed for MEDLINE]

924. Mod Rheumatol. 2017 Mar;27(2):356-359. doi: 10.1080/14397595.2017.1267173.

Familial Mediterranean fever with P369S/R408Q exon3 variant in pyrin presenting as symptoms of PFAPA.

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Familial Mediterranean fever (FMF) can be classified into typical and incomplete/atypical types. Periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome-like symptoms have been found in atypical type carrying P369S-R408Q mutations in the responsible gene MEFV. A 28-year-old female with recurrent fever and her young sisters and mother, all of whom had tonsillectomy for tonsillitis, carried heterozygous alterations involving E148Q/P369S/R408Q. A diagnosis of atypical FMF, MEFV exon3 variants with PFAPA syndrome-like symptoms, was made.

DOI: 10.1080/14397595.2017.1267173

PMID: 28001092 [Indexed for MEDLINE]

925. Am J Pathol. 2017 Feb;187(2):236-244. doi: 10.1016/j.ajpath.2016.10.015. Epub 2016 Dec 18.

IL-1 $\beta$  and Caspase-1 Drive Autoinflammatory Disease Independently of IL-1 $\alpha$  or Caspase-8 in a Mouse Model of Familial Mediterranean Fever.

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Mutations in the gene encoding pyrin are associated with autoinflammatory

disorder Familial Mediterranean Fever (FMF). A FMF-knock-in mouse strain that expresses chimeric pyrin protein with a V726A mutation (MefvV726A/V726A) was generated to model human FMF. This mouse strain shows an autoinflammatory disorder that is prevented by genetic deletion of IL-1 (IL-1) receptor or apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (ASC). ASC-mediated cell death leads to the release of IL-1 $\alpha$  and IL-1 $\beta$ , both of which signal through IL-1 receptor. Furthermore, caspase-1 and caspase-8 can interact with ASC to mediate secretion of IL-1 cytokines. The specific IL-1 cytokine instigating development of FMF and the enzymatic caspase involved in its secretion currently are unknown. In this study, we show that the autoinflammation observed in MefvV726A/V726A mice is mediated specifically by IL-1 $\beta$  and not IL-1 $\alpha$ . Furthermore, the disorder is dependent on the caspase-1-ASC axis, whereas caspase-8 is dispensable. Concurrently, aberrant IL-1 $\beta$  release by MefvV726A/V726A monocytes in response to stimulation with lipopolysaccharide also is dependent on the caspase-1-ASC axis. In conclusion, our studies have uncovered a specific role for caspase-1-mediated IL-1 $\beta$  release in the manifestation of FMF.

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DOI: 10.1016/j.ajpath.2016.10.015

PMCID: PMC5389372

PMID: 27998728 [Indexed for MEDLINE]

926. J Genet. 2016 Dec;95(4):761-766.

Evidence of digenic inheritance in autoinflammation-associated genes.

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Familial Mediterranean fever (FMF) has traditionally been considered as a monogenic autosomal recessive disorder caused by mutations in the MEFV gene with highest incidence among Mediterranean populations. In a considerable number of

patients with typical FMF, only one MEFV mutation was identified and the possibility that more than one autoinflammatory gene may be responsible for their disease was investigated. In the present study, an extensive search for possible mutations in three hereditary recurrent fever (HRF) genes was performed in 128 MEFV heterozygous Greek-Cypriots clinically diagnosed based on their phenotype with FMF-like disease from a previous study. Sequence analysis was performed for MVK, TNFRSF1A and NLRP3 genes which is also known to cause HRFs. In total, three patients were identified with heterozygous mutations and a second mutation in an autoinflammatory gene. Two patients carried a MEFV mutation and a NLRP3 mutation, and an additional third carried a MEFV mutation and a TNFRSF1A mutation. Patient 1 carried MEFV p.[Val726Ala] (NM\_000243.2:c.2177T>C) and NLRP3 p.[Val198Met] (NM\_001243133.1:c.592G>A) variants and patient 2 carried MEFV p.[Glu148Gln] (NM\_000243.2:c.442G>C) variant which is of uncertain significance and NLRP3 p.[Arg176Trp] (NM\_001243133.1:c.526C>T). Lastly, patient 3 was identified to carry MEFV p.[Met694Val] (NM\_000243.2:c.2080A>G) and TNFRSF1A p.[Arg121Gln] (NM\_001065.3:c.362G>A) variants. The results from this study indicate that screening of genes known to cause HRFs in patients already identified with a single MEFV mutation, can reveal quite rare but potentially causative mutational combinations at different loci. Such interaction provide further evidence for possible locus-locus interactions and phenotypes resulting from digenic inheritance.

PMID: 27994174 [Indexed for MEDLINE]

927. Rheumatology (Oxford). 2017 Mar 1;56(3):390-398. doi: 10.1093/rheumatology/kew446.

Paediatric rheumatology clinic population in Southeast Asia: are we different?

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**Objectives:** To examine the descriptive epidemiology of the patient population referred to paediatric rheumatology centres (PRCs) in Southeast Asia (SEA) and to compare the frequency of conditions encountered with other PRC populations.

**Methods:** A web-based Registry for Childhood Onset Paediatric Rheumatic Diseases was established in 2009 and seven PRCs in four SEA countries, where paediatric rheumatologists are available, participated in a prospective 24 month data collection (43 months for Singapore).

**Results:** The number of patients analysed was 4038 (788 from Malaysia, 711 from the Philippines, 1943 from Singapore and 596 from Thailand). Over 70% of patients evaluated in PRCs in Malaysia, the Philippines and Thailand had rheumatic diseases (RDs), as compared with one-half of the proportion seen in Singaporean PRCs, which was similar to the Western PRC experience. Among RDs diagnosed (n = 2602), JIA was the most common disease encountered in Malaysia (41%) and Thailand (61%) as compared with systemic vasculitides in the Philippines (37%) and Singapore (35%) among which Henoch-Schönlein purpura was the most prevalent. SLE and related diseases were more common, but idiopathic pain syndrome and abnormal immunological laboratory tests were rarer than those seen in the West. JIA subtype distributions were different among countries. Among non-RDs (n = 1436), orthopaedic and related conditions predominated (21.7-59.4%).

**Conclusion:** The frequencies of RDs seen by SEA PRCs were different from those in the West. Systemic vasculitides and SLE were common in addition to JIA.

Paediatric rheumatologist availability and healthcare accessibility partially explain these observed discrepancies.

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DOI: 10.1093/rheumatology/kew446

PMID: 27994096 [Indexed for MEDLINE]

928. J Exp Med. 2017 Jan;214(1):59-71. doi: 10.1084/jem.20161228. Epub 2016 Dec 19.

Autoinflammatory periodic fever, immunodeficiency, and thrombocytopenia (PFIT) caused by mutation in actin-regulatory gene WDR1.

Standing AS(1)(2), Malinova D(3), Hong Y(3), Record J(3), Moulding D(3), Blundell MP(3), Nowak K(3), Jones H(3), Omoyinmi E(3), Gilmour KC(4), Medlar A(5), Stanescu H(5), Kleta R(3)(5)(4), Anderson G(4), Nanthapisal S(3), Gomes SM(3), Klein N(3), Eleftheriou D(3), Thrasher AJ(3), Brogan PA(3).

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The importance of actin dynamics in the activation of the inflammasome is becoming increasingly apparent. IL-1 $\beta$ , which is activated by the inflammasome, is known to be central to the pathogenesis of many monogenic autoinflammatory diseases. However, evidence from an autoinflammatory murine model indicates that IL-18, the other cytokine triggered by inflammasome activity, is important in its own right. In this model, autoinflammation was caused by mutation in the actin regulatory gene WDR1. We report a homozygous missense mutation in WDR1 in two siblings causing periodic fevers with immunodeficiency and thrombocytopenia. We found impaired actin dynamics in patient immune cells. Patients had high serum levels of IL-18, without a corresponding increase in IL-18-binding protein or

IL-1 $\beta$ , and their cells also secreted more IL-18 but not IL-1 $\beta$  in culture. We found increased caspase-1 cleavage within patient monocytes indicative of increased inflammasome activity. We transfected HEK293T cells with pyrin and wild-type and mutated WDR1. Mutant protein formed aggregates that appeared to accumulate pyrin; this could potentially precipitate inflammasome assembly. We have extended the findings from the mouse model to highlight the importance of WDR1 and actin regulation in the activation of the inflammasome, and in human autoinflammation.

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DOI: 10.1084/jem.20161228

PMCID: PMC5206503

PMID: 27994071 [Indexed for MEDLINE]

929. Int J Rheum Dis. 2017 Apr;20(4):510-514. doi: 10.1111/1756-185X.13029. Epub 2016 Dec 19.

Efficacy of anakinra in an adult patient with recurrent pericarditis and cardiac tamponade as initial manifestations of tumor necrosis factor receptor-associated periodic syndrome due to the R92Q TNFRSF1A variant.

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Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is a dominantly inherited autoinflammatory disease caused by TNFRSF1A mutations. Patients with TRAPS suffer from recurrent, long episodes with fever, arthralgia/arthritis, migratory myalgias, abdominal pain, serositis, conjunctivitis and migratory erythematous skin rash. More than 70 different TNFRSF1A mutations have been reported to date, and as consequence of its genetic heterogeneity, TRAPS shows a variable phenotypic expression. Among TNFRSF1A

variants, the low-penetrance p.Arg92Gln variant represents the most commonly detected, and is typically associated with mild and short episodes, with a higher tendency to spontaneous resolution, and less familial association than the structural TNFRSF1A mutations. Pericardial involvement is rare but a well-known clinical feature of TRAPS, with a significant increased rate in those adult patients in whom the onset of the disease occurred during adulthood. Moreover, idiopathic recurrent acute pericarditis has also been occasionally described as a clinical presentation of TRAPS. However, cardiac tamponade is an unusual initial manifestation of the disease. Herein, we present a brief review based on the description of the exceptional case of a 35-year-old female patient who presented with recurrent pericardial effusions and cardiac tamponade. TNFRSF1A analyses showed a heterozygous genotype for the low-penetrance p.Arg92Gln variant. Due to disease severity, the patient was treated with the anti-interleukin-1 drug anakinra, showing a prompt resolution of her clinical manifestations.

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DOI: 10.1111/1756-185X.13029

PMID: 27990755 [Indexed for MEDLINE]

930. Immunol Lett. 2016 Dec;180:77-78. doi: 10.1016/j.imlet.2016.10.007. Epub 2016 Oct 29.

A position for tumor necrosis factor inhibitors in the management of colchicine-resistant familial Mediterranean fever?

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DOI: 10.1016/j.imlet.2016.10.007



931. Am J Med. 2017 Mar;130(3):365.e13-365.e18. doi: 10.1016/j.amjmed.2016.09.028. Epub 2016 Oct 28.

## A Systematic Analysis of Treatment and Outcomes of NOD2-Associated Autoinflammatory Disease.

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**OBJECTIVES:** Yao syndrome, formerly named NOD2-associated autoinflammatory disease, is a periodic disease characterized by fever, dermatitis, polyarthritides/leg swelling, and gastrointestinal and sicca-like symptoms associated with specific NOD2 sequence variants. Our aim was to evaluate the treatment and outcomes of the disease.

**METHODS:** A total of 52 adult patients with autoinflammatory disease phenotype were diagnosed with Yao syndrome and enrolled at the Cleveland Clinic between November 2009 and May 2015. All patients were genotyped for the NOD2 variants, and systematically studied for treatment outcomes.

**RESULTS:** Among the 52 Yao syndrome patients, all were white, and 72% were women. The mean age at diagnosis was  $38.0 \pm 12.0$  years, and the disease duration was  $8.8 \pm 5.8$  years. In the multi-organ disease, more common and typical manifestations were recurrent dermatitis and inflammatory arthritis with or without distal leg swelling besides recurrent fever. It was genotypically associated with the NOD2 IVS8+158 or R702W. Therapeutically, glucocorticoids markedly decreased the disease severity and duration of flares in 19 patients (36.6%), sulfasalazine treatment achieved a significant symptomatic improvement in 22 (42%) patients, and 3 patients received canakinumab or tocilizumab with benefits. Prognostically, 13% of the 52 patients had somewhat physical impairment, and there was no mortality during the follow-up. Associated comorbidities were fibromyalgia, asthma, renal stones, and ventricular hypertrophy.

**CONCLUSIONS:** As a systemic disease, Yao syndrome uncommonly affects the solid

internal organs, but it can be complicated with chronic pain syndrome and even disability. Glucocorticoids or sulfasalazine may be considered as the first-line treatment option, and interleukin (IL)-1/IL-6 inhibitors may be tried for refractory cases. The potential associations between certain comorbidities and Yao syndrome deserve further study.

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DOI: 10.1016/j.amjmed.2016.09.028

PMID: 27984003 [Indexed for MEDLINE]

932. Int J Mol Sci. 2016 Dec 15;17(12). pii: E2111.

Lung Involvement in Children with Hereditary Autoinflammatory Disorders.

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Short-lived systemic inflammatory reactions arising from disrupted rules in the innate immune system are the operating platforms of hereditary autoinflammatory disorders (HAIDs). Multiple organs may be involved and aseptic inflammation leading to disease-specific phenotypes defines most HAIDs. Lungs are infrequently involved in children with HAIDs: the most common pulmonary manifestation is pleuritis in familial Mediterranean fever (FMF) and tumor necrosis factor receptor-associated periodic syndrome (TRAPS), respectively caused by mutations in the MEFV and TNFRSF1A genes, while interstitial lung disease can be observed in STING-associated vasculopathy with onset in infancy (SAVI), caused by mutations in the TMEM173 gene. The specific pleuropulmonary diseases may range from sub-clinical abnormalities during inflammatory flares of FMF and TRAPS to a severe life-threatening disorder in children with SAVI.

DOI: 10.3390/ijms17122111

PMCID: PMC5187911

PMID: 27983684 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare no conflict of interest.

933. Clin Rheumatol. 2017 Jan;36(1):191-197. doi: 10.1007/s10067-016-3506-4. Epub 2016 Dec 16.

Interleukin (IL)-1 inhibition with anakinra and canakinumab in Behçet's disease-related uveitis: a multicenter retrospective observational study.

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This study aimed to evaluate the role of interleukin (IL)-1 inhibitors anakinra (ANA) and canakinumab (CAN) in the treatment of Behçet's disease (BD)-related uveitis. Multicenter retrospective observational study includes 19 consecutive BD patients (31 affected eyes) received treatment with anti-IL-1 agents. Data were analyzed at baseline and at 3 and 12 months. The primary endpoint is the reduction of ocular inflammatory flares (OIF). The secondary endpoints are improvement of best corrected visual acuity (BCVA); reduction of macular thickness defined by optical coherence tomography (OCT) and of vasculitis identified with fluorescein angiography (FA); evaluation of statistically significant differences between patients treated with IL-1 inhibitors as monotherapy, subjects also administered with disease modifying anti-rheumatic drugs (DMARDs) and/or corticosteroids as well as between patients administered with IL-1 inhibitors as first line biologic treatment and those previously treated with TNF- $\alpha$  inhibitors. At 12 months, OIF significantly decreased from 200 episodes/100 patients/year to 48.87 episodes/100 patients/year ( $p < 0.0001$ ). The frequency of retinal vasculitis identified by FA significantly decreased between baseline and 3- and 12-month follow-up visits ( $p < 0.0001$  and  $p = 0.001$ , respectively). OIF rate was significantly higher in patients co-administered with DMARDs (81.8 episodes/100 patients/year) than in patients undergoing IL-1 inhibitors as monotherapy (0.0 episodes/100 patients/year) ( $p = 0.03$ ). No differences were identified on the basis of corticosteroid use and between patients administered with IL-1 inhibitors as first line biologic approach or second line. Steroid dosage was significantly decreased at 12-month visit compared to baseline ( $p = 0.02$ ). Treatment with IL-1 inhibitors is effective in the management of BD-related uveitis and provides a long-term control of ocular inflammation in refractory and long-lasting cases.

DOI: 10.1007/s10067-016-3506-4

PMID: 27981463 [Indexed for MEDLINE]

## Unusual Presentations of Childhood Systemic Lupus Erythematosus to the Emergency Department.

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**INTRODUCTION:** Systemic lupus erythematosus (SLE) is a multisystemic autoinflammatory disease that can involve any organ system; therefore, diagnosis can be challenging. Hereby, we present 4 cases that presented to pediatric emergency department with unusual clinical pictures of SLE.

**CASES:** Case 1 presented with inability to walk or talk for the last 1 week as well as intermittent pain and swelling in her joints. Case 2 presented with generalized edema and severe dyspnea. Case 3 and 4 presented to pediatric emergency department with rashes on the legs.

**DISCUSSION:** Systemic lupus erythematosus may mimic many clinical entities, and differential diagnosis may be difficult, especially if presentation is atypical. In every emergency physician, right diagnosis and prompt treatment are very important especially in life-threatening conditions such as cardiac involvement in SLE.

DOI: 10.1097/PEC.0000000000000829

PMID: 27977505 [Indexed for MEDLINE]

935. Turk J Pediatr. 2016;58(2):125-131.

Serum vitamin D levels during activation and remission periods of patients with juvenile idiopathic arthritis and familial Mediterranean fever.

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The aim of this study was to determine the frequency of vitamin D deficiency and/or insufficiency in children with juvenile idiopathic arthritis (JIA) and familial Mediterranean fever (FMF) and to assess the relationship between vitamin D and disease activity. Sixty four patients with JIA, thirty six patients with FMF and one hundred healthy children were enrolled in this study. Vitamin D levels were measured during activation and remission periods in the patients with JIA and during attack and attack free periods in the patients with FMF. The mean vitamin D levels were found to be  $18.9 \pm 11$  ng/ml and  $18.6 \pm 9.2$  ng/ml during activation and remission periods of disease, respectively, in the patients with JIA,  $16 \pm 8.5$  ng/ml and  $13.1 \pm 6.4$  ng/ml during attack and attack-free periods, respectively, in the patients with FMF and  $26.7 \pm 10.5$  ng/ml in the healthy children. There was no significant difference between vitamin D levels during activation and remission periods in the patients with JIA, whereas vitamin D levels during attack free periods were lower compared to attack periods in the patients with FMF. No significant relationship was found between disease activity and serum vitamin D levels. The vitamin D levels of the children with JIA and FMF were significantly lower compared to the healthy children. The frequency of vitamin D deficiency and insufficiency was considerably high among the patients with JIA and FMF.

PMID: 27976551 [Indexed for MEDLINE]

936. J Biol Chem. 2017 Jan 27;292(4):1218-1230. doi: 10.1074/jbc.M116.763979. Epub 2016 Dec 14.

A Disease-associated Mutant of NLRC4 Shows Enhanced Interaction with SUG1 Leading to Constitutive FADD-dependent Caspase-8 Activation and Cell Death.

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Nod-like receptor family card containing 4 (NLRC4)/Ipaf is involved in recognition of pathogen-associated molecular patterns leading to caspase-1 activation and cytokine release, which mediate protective innate immune response. Point mutations in NLRC4 cause autoinflammatory syndromes. Although all the mutations result in constitutive caspase-1 activation, their phenotypic presentations are different, implying that these mutations cause different alterations in properties of NLRC4. NLRC4 interacts with SUG1 and induces caspase-8-mediated cell death. Here, we show that one of the autoinflammatory syndrome-causing mutants of NLRC4, H443P, but not T337A and V341A, constitutively activates caspase-8 and induces apoptotic cell death in human lung epithelial cells. Compared with wild type NLRC4, the H443P mutant shows stronger interaction with SUG1 and with ubiquitinated cellular proteins. Phosphorylation of NLRC4 at Ser533 plays a crucial role in caspase-8 activation and cell death. However, H443P mutant does not require Ser533 phosphorylation for caspase-8 activation and cell death. Caspase-8 activation by NLRC4 and its H443P mutant are dependent on the adaptor protein FADD. A phosphomimicking mutant of NLRC4, S533D does not require SUG1 activity for inducing cell death. Ubiquitin-tagged NLRC4 could induce cell death and activate caspase-8 independent of Ser533 phosphorylation. Our work suggests that SUG1-mediated signaling results in enhanced ubiquitination and regulates FADD-dependent caspase-8 activation by NLRC4. We show that the autoinflammation-associated H443P mutant is altered in interaction with SUG1 and ubiquitinated proteins, triggering constitutive caspase-8-mediated cell death dependent on FADD but independent of Ser533 phosphorylation.

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DOI: 10.1074/jbc.M116.763979

PMCID: PMC5270468

PMID: 27974463 [Indexed for MEDLINE]

## An NLRP3 Mutation Causes Arthropathy and Osteoporosis in Humanized Mice.

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The NLRP3 inflammasome plays a critical role in host defense by facilitating caspase 1 activation and maturation of IL-1 $\beta$  and IL-18, whereas dysregulation of inflammasome activity results in autoinflammatory disease. Factors regulating human NLRP3 activity that contribute to the phenotypic heterogeneity of NLRP3-related diseases have largely been inferred from the study of Nlrp3 mutant mice. By generating a mouse line in which the NLRP3 locus is humanized by syntenic replacement, we show the functioning of the human NLRP3 proteins in vivo, demonstrating the ability of the human inflammasome to orchestrate immune reactions in response to innate stimuli. Humanized mice expressing disease-associated mutations develop normally but display acute sensitivity to endotoxin and develop progressive and debilitating arthritis characterized by granulocytic infiltrates, elevated cytokines, erosion of bones, and osteoporosis. This NLRP3-dependent arthritis model provides a platform for testing therapeutic reagents targeting the human inflammasome.

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DOI: 10.1016/j.celrep.2016.11.052

PMID: 27974218 [Indexed for MEDLINE]



A new autoinflammatory and autoimmune syndrome associated with NLRP1 mutations: NAIAD (NLRP1-associated autoinflammation with arthritis and dyskeratosis).

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**OBJECTIVES:** Inflammasomes are multiprotein complexes that sense pathogens and trigger biological mechanisms to control infection. Nucleotide-binding oligomerisation domain-like receptor (NLR) containing a PYRIN domain 1 (NLRP1),

NLRP3 and NLRC4 plays a key role in this innate immune system by directly assembling in inflammasomes and regulating inflammation. Mutations in NLRP3 and NLRC4 are linked to hereditary autoinflammatory diseases, whereas polymorphisms in NLRP1 are associated with autoimmune disorders such as vitiligo and rheumatoid arthritis. Whether human NLRP1 mutation is associated with autoinflammation remains to be determined.

**METHODS:** To search for novel genes involved in systemic juvenile idiopathic arthritis, we performed homozygosity mapping and exome sequencing to identify causative genes. Immunoassays were performed with blood samples from patients.

**RESULTS:** We identified a novel disease in three patients from two unrelated families presenting diffuse skin dyskeratosis, autoinflammation, autoimmunity, arthritis and high transitional B-cell level. Molecular screening revealed a non-synonymous homozygous mutation in NLRP1 (c.2176C>T; p.Arg726Trp) in two cousins born of related parents originating from Algeria and a de novo heterozygous mutation (c.3641C>G, p.Pro1214Arg) in a girl of Dutch origin. The three patients showed elevated systemic levels of caspase-1 and interleukin 18, which suggested involvement of NLRP1 inflammasome.

**CONCLUSIONS:** We demonstrate the responsibility of human NLRP1 in a novel autoinflammatory disorder that we propose to call NAIAD for NLRP1-associated autoinflammation with arthritis and dyskeratosis. This disease could be a novel autoimmuno-inflammatory disease combining autoinflammatory and autoimmune features. Our data, combined with that in the literature, highlight the pleomorphic role of NLRP1 in inflammation and immunity.

**TRIAL REGISTRATION NUMBER:** NCT02067962; Results.

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DOI: 10.1136/annrheumdis-2016-210021

PMID: 27965258 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: None.

939. Genome Med. 2016 Dec 13;8(1):129.

XGR software for enhanced interpretation of genomic summary data, illustrated by application to immunological traits.

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**BACKGROUND:** Biological interpretation of genomic summary data such as those resulting from genome-wide association studies (GWAS) and expression quantitative trait loci (eQTL) studies is one of the major bottlenecks in medical genomics research, calling for efficient and integrative tools to resolve this problem.

**RESULTS:** We introduce eXploring Genomic Relations (XGR), an open source tool designed for enhanced interpretation of genomic summary data enabling downstream knowledge discovery. Targeting users of varying computational skills, XGR utilises prior biological knowledge and relationships in a highly integrated but easily accessible way to make user-input genomic summary datasets more interpretable. We show how by incorporating ontology, annotation, and systems biology network-driven approaches, XGR generates more informative results than conventional analyses. We apply XGR to GWAS and eQTL summary data to explore the genomic landscape of the activated innate immune response and common immunological diseases. We provide genomic evidence for a disease taxonomy supporting the concept of a disease spectrum from autoimmune to autoinflammatory disorders. We also show how XGR can define SNP-modulated gene networks and pathways that are shared and distinct between diseases, how it achieves functional, phenotypic and epigenomic annotations of genes and variants, and how it enables exploring annotation-based relationships between genetic variants.

**CONCLUSIONS:** XGR provides a single integrated solution to enhance interpretation of genomic summary data for downstream biological discovery. XGR is released as both an R package and a web-app, freely available at <http://galahad.well.ox.ac.uk/XGR>.

DOI: 10.1186/s13073-016-0384-y

PMCID: PMC5154134

PMID: 27964755 [Indexed for MEDLINE]

Shohat M(1)(2).

In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018.

2000 Aug 8.

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**CLINICAL CHARACTERISTICS:** Familial Mediterranean fever (FMF) is divided into two phenotypes: type 1 and type 2. FMF type 1 is characterized by recurrent short episodes of inflammation and serositis including fever, peritonitis, synovitis, pleuritis, and, rarely, pericarditis and meningitis. The symptoms and severity vary among affected individuals, sometimes even among members of the same family. Amyloidosis, which can lead to renal failure, is the most severe complication, if untreated. FMF type 2 is characterized by amyloidosis as the first clinical manifestation of FMF in an otherwise asymptomatic individual.

**DIAGNOSIS/TESTING:** The diagnosis of FMF is established in a proband with Tel Hashomer clinical criteria of major and minor features. Major features include fever, abdominal pain, chest pain, joint pain, and skin eruption. Minor features include increased erythrocyte sedimentation rate (ESR), leukocytosis, and elevated serum fibrinogen. Identification of biallelic MEFV pathogenic variants on molecular genetic testing confirms the diagnosis. Up to 25% of individuals with FMF have only one MEFV pathogenic variant identified. A six-month trial of colchicine therapy can establish the diagnosis if molecular testing is inconclusive.

**MANAGEMENT:** Treatment of manifestations: Treatment of an acute episode is mainly supportive, including administration of intravenous saline for hydration and use of nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol, or dipyrrone for pain relief; treatment of febrile and inflammatory episodes with NSAIDs; routine treatment of end-stage renal disease, including renal transplantation. Prevention of primary manifestations: Homozygotes for the p.Met694Val pathogenic variant or compound heterozygotes for p.Met694Val and another disease-causing allele require lifelong treatment with colchicine (1-2 mg/day orally in adults and 0.5-1 mg/day in children according to age and weight). Colchicine prevents the inflammatory

attacks and the deposition of amyloid. Individuals who do not have the p.Met694Val pathogenic variant and who are only mildly affected (those with infrequent inflammatory attacks) should either be treated with colchicine or monitored every six months for the presence of proteinuria. Individuals who are homozygous or compound heterozygous for p.Glu148Gln should only be treated with colchicine if they develop severe inflammatory episodes and/or proteinuria as a result of amyloidosis. Symptomatic individuals with a heterozygous MEFV pathogenic variant may benefit from a trial of colchicine. Individuals who are unresponsive to colchicine may respond to intravenous colchicine or one of several other medications. Surveillance: Annual physical examination, urine spot test for protein, and evaluation for hematuria for all affected individuals including those treated with colchicine; consider monitoring of acute-phase reactants (ESR and fibrinogen levels) at regular intervals during attack-free periods, particularly in those with the p.Met694Val pathogenic variant. Agents/circumstances to avoid: Possible worsening of symptoms with cisplatin; possible adverse effect on renal transplant graft survival with cyclosporin A. Evaluation of relatives at risk: Offer molecular genetic testing to all first-degree relatives and other family members (regardless of symptoms) especially when the p.Met694Val allele is present because renal amyloidosis can be prevented with colchicine treatment.

GENETIC COUNSELING: FMF is usually inherited in an autosomal recessive manner, although recent studies have suggested that some heterozygotes manifest a spectrum of findings from classic FMF to mild FMF. For autosomal recessive FMF: In general, both parents of an affected individual with biallelic MEFV pathogenic variants are unaffected heterozygotes. However, in populations with a high carrier rate and/or a high rate of consanguineous marriages, it is possible that one or both parents have biallelic pathogenic variants and are affected. Symptomatic heterozygotes have also been reported. Thus, it is appropriate to consider molecular genetic testing of the parents of the proband to establish their genetic status. If both parents are heterozygotes, the risk to sibs of inheriting two pathogenic variants and being affected is 25%. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if the MEFV pathogenic variants in the family are known.

PMID: 20301405

## The M694I/M694I genotype: A genetic risk factor of AA-amyloidosis in a group of Algerian patients with familial Mediterranean fever.

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Familial Mediterranean fever (FMF, OMIM 249100) is the most common hereditary fever, resulting from mutations in MEFV. FMF is characterized by episodic febrile attacks and polyserositis. Renal AA-amyloidosis is a major complication, which often leads to end-stage renal disease in untreated patients. The data about the renal AA-amyloidosis secondary to FMF are scarce in North African countries and non-existent in Algeria. We aimed to investigate the MEFV mutations associated with this complication in an Algerian patient cohort. Molecular analysis included 28 unrelated Algerian FMF patients with ascertained amyloidosis, 23 of them were symptomatic and 5 were asymptomatic. For this study, a group of 20 FMF patients without renal amyloidosis were selected as controls according to their age, disease onset and disease duration. The mutations were detected by sequencing exon 10 of MEFV. A total of 87.5% (49/56) mutant alleles were identified in 27/28

analyzed patients; p.M694I was predominant and appeared with an allele frequency of 62.5%, followed by p.M694V (17.85%), p.M680I (5.35%) and p.I692Del (1.78%). Remarkably, only p.M694I mutation was observed among the asymptomatic patients. The M694I/M694I genotype, identified in 14/27 (52%) patients, was significantly associated with the development of amyloidosis compared to group of controls ( $p = 0.022$ ). This study did not link the M694V/M694V genotype to the renal complication despite the fact that it has been observed only in the patients with amyloidosis (3/27; 11%) ( $p = 0.349$ ). The association of other identified genotypes to this complication was statistically insignificant. The progression of amyloidosis led to end-stage renal disease in 14 patients with 6 deaths. This study shows that p.M694I homozygosity is a potential genetic risk factor for the development of renal AA-amyloidosis in Algerian FMF patients.

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DOI: 10.1016/j.ejmg.2016.12.003

PMID: 27956278 [Indexed for MEDLINE]

942. Blood Purif. 2017;43(1-3):125-135. doi: 10.1159/000454669. Epub 2016 Dec 13.

Colchicine in Renal Medicine: New Virtues of an Ancient Friend.

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Colchicine is a plant-derived alkaloid that disrupts the cell microtubule system and accumulates in neutrophils, inhibiting neutrophil adhesion and recruitment. Colchicine has been used extensively in the prevention and treatment of gouty arthritis attacks, familial Mediterranean fever attacks and resultant AA amyloidosis, and recurrent pericarditis. Colchicine also disrupts the intracellular traffic of additional inflammatory and fibrosis mediators. Renal fibrosis is the final common pathway of chronic renal disease. Colchicine had anti-fibrotic effects in experimental diabetic nephropathy, renal mass reduction, and cyclosporine nephrotoxicity among others and is undergoing clinical trials for non-diabetic metabolic syndrome and diabetic nephropathy. In this review, we

summarize the anti-inflammatory and anti-fibrotic properties of colchicine in experimental and clinical studies in renal diseases or other fibrotic disease processes with renal consequences. We also discuss the potential future uses of colchicine in renal medicine and challenges faced with its use in patients with impaired kidney function.

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DOI: 10.1159/000454669

PMID: 27951538 [Indexed for MEDLINE]

943. Br J Dermatol. 2017 Jun;176(6):1588-1598. doi: 10.1111/bjd.15226. Epub 2017 Apr 16.

Autoinflammation in pyoderma gangrenosum and its syndromic form (pyoderma gangrenosum, acne and suppurative hidradenitis).

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**BACKGROUND:** Pyoderma gangrenosum (PG) is a rare skin disease characterized clinically by ulcers with undermined borders, and histologically by neutrophil-rich infiltrates. PG may occur alone, in syndromic forms or associated with systemic diseases, such as inflammatory bowel disease and haematological or rheumatological disorders.

**OBJECTIVES:** To determine a specific genetic background related to autoinflammation for PG.

**METHODS:** We assessed autoinflammation by evaluating the cytokine profile and genes involved in classic autoinflammatory diseases in 13 patients with PG and in seven patients with the syndromic form, known as PASH (pyoderma gangrenosum, acne and suppurative hidradenitis).

**RESULTS:** In skin samples, the expression of interleukin (IL)-1 $\beta$  and its



receptors, IL-17 and its receptor, and tumour necrosis factor- $\alpha$  and its receptors were significantly higher in both PG ( $P = 0.001$ ) and in PASH ( $P < 0.001$ ) than in controls. The chemokines IL-8; chemokine (C-X-C motif) ligand 1/2/3; chemokine (C-X-C motif) ligand 16; and RANTES (regulated on activation, normal T-cell-expressed and secreted) were also overexpressed. Cases of PG and PASH showed mutations in the autoinflammatory genes MEFV, NLRP3, NLRP12, NOD2, LPIN2 and PSTPIP1.

**CONCLUSIONS:** Overexpression of cytokines/chemokines, along with genetic changes, supports the hypothesis that PG and its syndromic form, PASH, are a spectrum of polygenic autoinflammatory conditions.

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DOI: 10.1111/bjd.15226

PMID: 27943240 [Indexed for MEDLINE]

944. J Clin Immunol. 2017 Feb;37(2):123-132. doi: 10.1007/s10875-016-0359-1. Epub 2016 Dec 9.

Assessment of Type I Interferon Signaling in Pediatric Inflammatory Disease.

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**PURPOSE:** Increased type I interferon is considered relevant to the pathology of a number of monogenic and complex disorders spanning pediatric rheumatology, neurology, and dermatology. However, no test exists in routine clinical practice to identify enhanced interferon signaling, thus limiting the ability to diagnose and monitor treatment of these diseases. Here, we set out to investigate the use of an assay measuring the expression of a panel of interferon-stimulated genes (ISGs) in children affected by a range of inflammatory diseases.

**DESIGN, SETTING, AND PARTICIPANTS:** A cohort study was conducted between 2011 and 2016 at the University of Manchester, UK, and the Institut Imagine, Paris, France. RNA PAXgene blood samples and clinical data were collected from controls and symptomatic patients with a genetically confirmed or clinically well-defined inflammatory phenotype. The expression of six ISGs was measured by quantitative polymerase chain reaction, and the median fold change was used to calculate an interferon score (IS) for each subject compared to a previously derived panel of 29 controls (where +2 SD of the control data, an IS of >2.466, is considered as abnormal). Results were correlated with genetic and clinical data.

**RESULTS:** Nine hundred ninety-two samples were analyzed from 630 individuals comprising symptomatic patients across 24 inflammatory genotypes/phenotypes, unaffected heterozygous carriers, and controls. A consistent upregulation of ISG expression was seen in 13 monogenic conditions (455 samples, 265 patients; median IS 10.73, interquartile range (IQR) 5.90-18.41), juvenile systemic lupus erythematosus (78 samples, 55 patients; median IS 10.60, IQR 3.99-17.27), and juvenile dermatomyositis (101 samples, 59 patients; median IS 9.02, IQR 2.51-21.73) compared to controls (78 samples, 65 subjects; median IS 0.688, IQR 0.427-1.196), heterozygous mutation carriers (89 samples, 76 subjects; median IS 0.862, IQR 0.493-1.942), and individuals with non-molecularly defined autoinflammation (89 samples, 69 patients; median IS 1.07, IQR 0.491-3.74).

**CONCLUSIONS AND RELEVANCE:** An assessment of six ISGs can be used to define a spectrum of inflammatory diseases related to enhanced type I interferon signaling. If future studies demonstrate that the IS is a reactive biomarker, this measure may prove useful both in the diagnosis and the assessment of treatment efficacy.

DOI: 10.1007/s10875-016-0359-1

PMCID: PMC5325846

PMID: 27943079 [Indexed for MEDLINE]

945. *Pediatr Rheumatol Online J.* 2016 Dec 9;14(1):66.

Macrophage activation syndrome triggered by coeliac disease: a unique case report.

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**BACKGROUND:** Macrophage activation syndrome is described as a "clinical syndrome of hyperinflammation resulting in an uncontrolled and ineffective immune response" in the context of an autoinflammatory or rheumatic disease. Current

associations of macrophage activation syndrome with autoimmune disease most notably include a host of rheumatological conditions and inflammatory bowel disease. Epidemiological studies have shown that macrophage activation syndrome is precipitated by autoimmune disease more commonly than previously thought. Diagnosing the precipitating factor is essential for effective treatment and prognosis.

**CASE PRESENTATION:** We report a case of a six year old girl with coeliac disease diagnosed after two episodes of secondary haemophagocytic lymphohistiocytosis. Her condition only responded to treatment once the patient was placed on a gluten free diet. Further immunological testing confirmed anti-transglutaminase and anti-endomysial antibodies, however histological biopsy was deemed inappropriate due to the severity of her condition. She has remained stable with no further episodes of macrophage activation syndrome since commencing a gluten free diet.

**CONCLUSION:** This case report is the first literature that links macrophage activation syndrome to coeliac disease and highlights the challenge of diagnosing coeliac disease with unusual features such as associated prolonged fever. Clinicians should have a low threshold for screening children with other autoimmune diseases for coeliac disease.

DOI: 10.1186/s12969-016-0128-y

PMCID: PMC5148910

PMID: 27938384 [Indexed for MEDLINE]

946. Cold Spring Harb Protoc. 2016 Dec 1;2016(12). doi: 10.1101/pdb.top070508.

In the Midst of Life-Cell Death: What Is It, What Is It Good for, and How to Study It.

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Cell death, one of the most fundamental biological processes, has not made it into the public consciousness in the same way that genetic inheritance, cell division, or DNA replication has. Everyone knows they get their genes from their parents, but few would be aware that even before they were born a lot of essential cell death has shaped their development. The greater population, for the most part, is blissfully unaware that every day millions of their own cells die in a programmed way and that this is essential for normal human physiology-their well-being, in fact. Nowhere is the burial liturgy, "In the midst of life we are in death," more apt. Despite this public underappreciation, cell death research is a major industry. A search in PubMed for "apoptosis," a special form of cell death that is caused by caspases, returns approximately 280,000 hits. The intense research interest arises from the realization that abnormal cell death responses play an important role in two of the biggest killers in the western world: cancer and cardio/cerebrovascular disease. Furthermore, the manner in which cells die can also influence the development of autoimmune and autoinflammatory diseases. It is therefore of paramount importance to ensure that experiments accurately quantitate and correctly identify cell death in all its guises. That is the goal of this protocol collection.

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DOI: 10.1101/pdb.top070508

PMID: 27934692 [Indexed for MEDLINE]

947. Medicine (Baltimore). 2016 Dec;95(49):e5516.

Cytotoxic Th1 and Th17 cells infiltrate the intestinal mucosa of Behcet patients and exhibit high levels of TNF- $\alpha$  in early phases of the disease.

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Internal Medicine, Center for Autoimmune Systemic Diseases -Behçet Center and Lupus Clinic - AOU Careggi eRheumatology and Clinical Immunology, Humanitas Research Hospital fBIOMETRA Department, University of Milan, Milan, Italy.

**BACKGROUND:** Gastrointestinal involvement is one of the most serious in Behçet disease, potentially leading to severe complications. Aim of this study was to investigate at mucosal level the T-cell responses in Behçet patients with early intestinal involvement.

**METHODS:** We isolated T cells from intestinal mucosa of 8 patients with intestinal symptoms started within 6 months. T lymphocytes were cloned and analyzed for surface phenotype and cytokines production.

**RESULTS:** We obtained 382 T-cell clones: 324 were CD4+ and 58 were CD8+. Within the 324 CD4+ clones, 195 were able to secrete IFN- $\gamma$  and TNF- $\alpha$ , but not IL-4, nor IL-17 thus showing a polarized Th1 profile, whereas CD4 clones producing both IFN- $\gamma$  and IL-17 (Th1/Th17 profile) were 79. Likewise, the number of CD8 clones producing type 1 cytokines was higher than those of CD8 clones producing both type 1 and 2 cytokines. Almost all intestinal-derived T-cell clones expressed perforin-mediated cytotoxicity and Fas-Fas Ligand-mediated pro-apoptotic activity.

**CONCLUSIONS:** Our results indicate that in the early stages of the disease, both Th1 and Th17 cells drive inflammation leading to mucosal damage via abnormal and long-lasting cytokines production as well as via both perforin- and Fas-Fas ligand-mediated cytotoxicity. Finally, all the T cells at mucosal level were able to produce large amount of TNF- $\alpha$ , suggesting that its production is a property of intestinal T cells of patients with early active intestinal disease. These results support the therapy with anti-TNF- $\alpha$  agents and suggest the use of anti-IL-17 monoclonal antibodies in Behçet patients with early intestinal involvement.

DOI: 10.1097/MD.00000000000005516

PMCID: PMC5266013

PMID: 27930541 [Indexed for MEDLINE]

**Conflict of interest statement:** The authors have no funding and conflicts of interest to disclose.

948. Nat Rev Rheumatol. 2017 Jan;13(1):7-8. doi: 10.1038/nrrheum.2016.201. Epub 2016 Dec 8.

Autoinflammatory diseases: New diagnostic criteria for CAPS - turning horses into zebras?

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DOI: 10.1038/nrrheum.2016.201

PMID: 27928157

949. Ann Rheum Dis. 2017 May;76(5):906-913. doi: 10.1136/annrheumdis-2016-210324. Epub 2016 Dec 7.

Genetic architecture distinguishes systemic juvenile idiopathic arthritis from other forms of juvenile idiopathic arthritis: clinical and therapeutic implications.

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**OBJECTIVES:** Juvenile idiopathic arthritis (JIA) is a heterogeneous group of  
conditions unified by the presence of chronic childhood arthritis without an  
identifiable cause. Systemic JIA (sJIA) is a rare form of JIA characterised by

systemic inflammation. sJIA is distinguished from other forms of JIA by unique clinical features and treatment responses that are similar to autoinflammatory diseases. However, approximately half of children with sJIA develop destructive, long-standing arthritis that appears similar to other forms of JIA. Using genomic approaches, we sought to gain novel insights into the pathophysiology of sJIA and its relationship with other forms of JIA.

**METHODS:** We performed a genome-wide association study of 770 children with sJIA collected in nine countries by the International Childhood Arthritis Genetics Consortium. Single nucleotide polymorphisms were tested for association with sJIA. Weighted genetic risk scores were used to compare the genetic architecture of sJIA with other JIA subtypes.

**RESULTS:** The major histocompatibility complex locus and a locus on chromosome 1 each showed association with sJIA exceeding the threshold for genome-wide significance, while 23 other novel loci were suggestive of association with sJIA.

Using a combination of genetic and statistical approaches, we found no evidence of shared genetic architecture between sJIA and other common JIA subtypes.

**CONCLUSIONS:** The lack of shared genetic risk factors between sJIA and other JIA subtypes supports the hypothesis that sJIA is a unique disease process and argues for a different classification framework. Research to improve sJIA therapy should target its unique genetics and specific pathophysiological pathways.

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DOI: 10.1136/annrheumdis-2016-210324

PMCID: PMC5530341

PMID: 27927641 [Indexed for MEDLINE]

950. Orphanet J Rare Dis. 2016 Dec 7;11(1):167.

Chronic Infantile Neurological Cutaneous and Articular (CINCA) syndrome: a review.

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**INTRODUCTION:** The Chronic Infantile Neurological Cutaneous and Articular (CINCA, or Neonatal-onset multisystem inflammatory disease NOMID) is a rare autoinflammatory disease identified in 1987 by Prieur et al., typically characterized by the triad of skin rash, arthropathy and central nervous system manifestations. It represents the most severe phenotype of the cryopyrin-associated periodic syndrome (CAPS).

**CLINICAL DESCRIPTION AND ETIOLOGY:** The syndrome is due to autosomal dominant gain of function mutations in NLRP3, which encodes a key component of the innate immunity that regulates the activation and secretion of interleukin (IL)-1 $\beta$ . From the first days of life, patients display an urticarial rash in association with chronic inflammation with a typical facies featured by frontal bossing and saddle back nose. The CNS manifestations include chronic aseptic meningitis leading to brain atrophy, mental delay and sensorineural hearing loss. Chronic polyarthritides and alteration of the growth cartilage also may be present. CINCA/NOMID diagnosis is made clinically, based on the presence of characteristic features. The detection of NLRP3 mutations is diagnostic in 65-70% of cases. Indeed, up to 40% of affected patients are negative for germline NLRP3 mutations and several subjects are carriers of somatic mosaicism. Due to the pivotal role of Cryopyrin in the control of Caspase-1 activation and the massive secretion of active IL-1 $\beta$  observed in cryopyrin-mutated individuals, anti-IL1 treatment represents the standard therapy.

**CONCLUSION:** Prognosis of CINCA/NOMID syndrome has been changed by the availability of anti-IL1 drugs. Nowadays, the use of anti-IL-1 drugs has sensibly reduced the risk of developing main complications such as severe intellectual disability, hearing-loss and amyloidosis, if treatment is started early on.

DOI: 10.1186/s13023-016-0542-8

PMCID: PMC5142346

PMID: 27927236 [Indexed for MEDLINE]

951. Laryngoscope Investig Otolaryngol. 2016 Oct;1(5):110-115. Epub 2016 Sep 21.

AAO: Autoimmune and Autoinflammatory (Disease) in Otology: What is New in Immune-Mediated Hearing Loss.

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**OBJECTIVES:** Autoinflammatory diseases are a family of immune-mediated, rare diseases, some of which, exhibit sensorineural hearing loss (SNHL), suggesting potentially similar mechanisms of molecular pathogenesis between autoinflammatory-mediated hearing loss and autoimmune inner ear disease (AIED) may exist. The purpose of this review is to compare the clinical features of autoimmune and autoinflammatory diseases that affect hearing, discuss the limitations of our knowledge, and highlight potential new disease mechanisms and therapeutics.

**DATA SOURCES:** Pubmed Literature Review; Google Scholar Literature review.

**REVIEW METHODS:** A focused comparison of AIED with a number of autoinflammatory diseases that manifest with sensorineural hearing loss was performed. The pathogenesis of these diseases is reviewed in the context of the innate and adaptive immune system, cytokine expression and genetic polymorphisms.

**RESULTS:** AIED, since first described by Cogan and Lehnhardt and first clinically characterized by McCabe, has remained an enigmatic disease, with limited advances in both new diagnostics and new therapeutics. Since the discovery of autoinflammatory diseases, a number of systemic autoimmune diseases have either been re-classed as autoinflammatory diseases or identified to have features of autoinflammatory disease.

**CONCLUSION:** AIED has clinical features of both autoimmune and autoinflammatory disease. It is critical that autoinflammatory diseases be correctly identified, as failure to do so may result in systemic amyloidosis and kidney damage.

DOI: 10.1002/liv.2.28

PMCID: PMC5113311

PMID: 27917401

952. Afr Health Sci. 2016 Sep;16(3):877-879.

Abdominal epilepsy as an unusual cause of abdominal pain: a case report.

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**INTRODUCTION:** Abdominal pain, in etiology sometimes difficult to be defined, is a frequent complaint in childhood. Abdominal epilepsy is a rare cause of abdominal pain.

**OBJECTIVES:** In this article, we report on 5 year old girl patient with abdominal epilepsy.

**METHODS:** Some investigations (stool investigation, routine blood tests, ultrasonography (USG), electrocardiogram (ECHO) and electrocardiography (ECG), holter for 24hr.) were done to understand the origin of these complaints; but no abnormalities were found. Finally an EEG was done during an episode of abdominal pain and it was shown that there were generalized spikes especially precipitated by hyperventilation. The patient did well on valproic acid therapy and EEG was normal 1 month after beginning of the treatment.

**DISCUSSION:** The cause of chronic recurrent paroxymal abdominal pain is difficult for the clinicians to diagnose in childhood. A lot of disease may lead to paroxysmal gastrointestinal symptoms like familial mediterranean fever and porfira. Abdominal epilepsy is one of the rare but easily treatable cause of abdominal pain.

**CONCLUSION:** In conclusion, abdominal epilepsy should be suspected in children with recurrent abdominal pain.

DOI: 10.4314/ahs.v16i3.32

PMCID: PMC5111992

PMID: 27917225 [Indexed for MEDLINE]

953. Cytokine Growth Factor Rev. 2017 Feb;33:19-34. doi: 10.1016/j.cytogfr.2016.11.001. Epub 2016 Nov 22.

## Cytokine signatures in hereditary fever syndromes (HFS).

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Hereditary fever syndromes (HFS) include a group of disorders characterized by recurrent self-limited episodes of fever accompanied by inflammatory manifestations occurring in the absence of infection or autoimmune reaction. Advances in the genetics of HFS have led to the identification of new gene families and pathways involved in the regulation of inflammation and innate immunity. The key role of several cytokine networks in the pathogenesis of HFS has been underlined by several groups, and supported by the rapid response of patients to targeted cytokine blocking therapies. This can be due to the direct effect of cytokine overproduction or to an absence of receptor antagonist resulting in dysbalance of downstream pro- and anti-inflammatory cytokine networks. The aim of this study was to present an overview and to discuss the major concepts regarding the cellular and molecular immunology of HFS, with a particular focus on their specific cytokine signatures and physiopathological implications. Based on their molecular and cellular mechanisms, HFS have been classified into intrinsic and extrinsic IL-1 $\beta$  activation disorders or inflammasomopathies, and protein misfolding disorders. This review integrates all recent data in an updated classification of HFS.

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DOI: 10.1016/j.cytogfr.2016.11.001

954. Proc Natl Acad Sci U S A. 2016 Dec 13;113(50):14384-14389. Epub 2016 Nov 22.

Familial Mediterranean fever mutations lift the obligatory requirement for microtubules in Pyrin inflammasome activation.

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Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease worldwide. It is caused by mutations in the inflammasome adaptor Pyrin, but how FMF mutations alter signaling in FMF patients is unknown. Herein, we

establish *Clostridium difficile* and its enterotoxin A (TcdA) as Pyrin-activating agents and show that wild-type and FMF Pyrin are differentially controlled by microtubules. Diverse microtubule assembly inhibitors prevented Pyrin-mediated caspase-1 activation and secretion of IL-1 $\beta$  and IL-18 from mouse macrophages and human peripheral blood mononuclear cells (PBMCs). Remarkably, Pyrin inflammasome activation persisted upon microtubule disassembly in PBMCs of FMF patients but not in cells of patients afflicted with other autoinflammatory diseases. We further demonstrate that microtubules control Pyrin activation downstream of Pyrin dephosphorylation and that FMF mutations enable microtubule-independent assembly of apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) micrometer-sized perinuclear structures (specks). The discovery that Pyrin mutations remove the obligatory requirement for microtubules in inflammasome activation provides a conceptual framework for understanding FMF and enables immunological screening of FMF mutations.

DOI: 10.1073/pnas.1613156113

PMCID: PMC5167202

PMID: 27911804 [Indexed for MEDLINE]

Conflict of interest statement: H.V.G., P.H.V.S., and M.L. are listed as inventor on a patent application on immunological FMF diagnosis.

955. *Abdom Radiol* (NY). 2017 May;42(5):1393-1399. doi: 10.1007/s00261-016-1005-3.

Evaluation of upper abdominal organs with DWI in patients with familial Mediterranean fever.

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**PURPOSE:** To investigate the diagnostic efficiency of diffusion-weighted magnetic resonance imaging (DWI) for the evaluation of functional changes that can occur in upper abdominal organs in patients with familial Mediterranean fever (FMF).



**METHODS:** The study included 50 controls, 45 patients with FMF, and 14 patients with FMF who had accompanying proteinuria. Measurement of apparent diffusion coefficient (ADC) was performed using DWI sections obtained from liver, spleen, kidney, and pancreas parenchyma with 1.5T MRI using  $b = 500$  and  $b = 1000$  s/mm<sup>2</sup> values both in patients and control groups. Mean ADC values were compared between patient and control groups.

**RESULTS:** Renal ADC values were lower in the patient groups compared to the control group. Additionally, renal ADC values showed further decrease in the patient group in the presence of accompanying proteinuria, when compared to the FMF group without proteinuria ( $p < 0.001$ ). Based on the ROC analysis, calculated cutoff values for the determination of FMF and FMF accompanied by proteinuria were  $2.26 \times 10^{-3}$  and  $2.04 \times 10^{-3}$  mm<sup>2</sup>/s, respectively. Liver, spleen, and pancreas ADC values did not show remarkable change between patient and control groups.

**CONCLUSION:** Present findings indicate that the presence of FMF and its clinical progression expressed by proteinuria can be differentially determined with renal DWI.

DOI: 10.1007/s00261-016-1005-3

PMID: 27909774 [Indexed for MEDLINE]

956. Clin Exp Rheumatol. 2017 May-Jun;35 Suppl 104(2):8. Epub 2016 Nov 10.

Vitamin D levels in children with familial Mediterranean fever.

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Comment on

Semin Cell Dev Biol. 2016 Jan;49:37-43.

PMID: 27908310 [Indexed for MEDLINE]

957. Clin Exp Rheumatol. 2017 Jan-Feb;35(1):170-171. Epub 2016 Oct 27.

Long-term tocilizumab efficacy in a patient with psoriatic arthritis and AA amyloidosis.

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Comment in

Clin Exp Rheumatol. 2017 Jan-Feb;35(1):171.

PMID: 27908297 [Indexed for MEDLINE]

958. Curr Opin Rheumatol. 2017 Mar;29(2):187-194. doi: 10.1097/BOR.0000000000000362.

Lessons from characterization and treatment of the autoinflammatory syndromes.

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PURPOSE OF REVIEW: The list of genes associated with systemic inflammatory

diseases has been steadily growing because of the explosion of new genomic technologies. Significant advances in the past year have deepened our understanding of the molecular mechanisms linked to inflammation and elucidated insights on the efficacy of specific therapies for these and related conditions. We review the molecular pathogenesis of four recently characterized monogenic autoinflammatory diseases: haploinsufficiency of A20, otulipenia, a severe form of pyrin-associated disease, and a monogenic form of systemic juvenile idiopathic arthritis.

RECENT FINDINGS: The scope of autoinflammation has been broadened to include defects in deubiquitination and cellular redox homeostasis. At the clinical level, we discuss the biological rationale for treatment with cytokine inhibitors and colchicine in respective conditions and the use of interleukin-1 antagonism for diagnostic and therapeutic purposes in the management of undifferentiated autoinflammatory disorders.

SUMMARY: Gene discoveries coupled with studies of molecular function provide knowledge into the biology of inflammatory responses and form the basis for genomically informed therapies. Diseases of dysregulated ubiquitination constitute a novel category of human inflammatory disorders.

DOI: 10.1097/BOR.0000000000000362

PMCID: PMC5823535

PMID: 27906774 [Indexed for MEDLINE]

959. Eur Rev Med Pharmacol Sci. 2016 Nov;20(22):4623-4625.

Letter to the Editor - Arrhythmic risk evaluation in familial mediterranean fever: the role of electrocardiographic and echocardiographic parameters.

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Comment on

Eur Rev Med Pharmacol Sci. 2016 Aug;20(16):3427-33.

PMID: 27906444 [Indexed for MEDLINE]

960. Br J Dermatol. 2018 Mar;178(3):603-613. doi: 10.1111/bjd.15105. Epub 2016 Nov 30.

Are neutrophilic dermatoses autoinflammatory disorders?

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Neutrophils constitute essential players in inflammatory responses and are the first line of defence against harmful stimuli. However, dysregulation of neutrophil homeostasis can result in excessive inflammation and subsequent tissue damage. Neutrophilic dermatoses are a spectrum of inflammatory disorders characterized by skin lesions resulting from a neutrophil-rich inflammatory infiltrate in the absence of infection. The exact molecular pathophysiology of neutrophilic dermatoses has long been poorly understood. Interestingly, neutrophil-rich cutaneous inflammation is also a cardinal feature of several autoinflammatory diseases with skin involvement, the latter being caused by aberrant innate immune responses. Overactivation of the innate immune system leading to increased production of interleukin-1 family members and 'sterile' neutrophil-rich cutaneous inflammation are features of both inherited autoinflammatory syndromes with skin involvement and an increasing number of neutrophilic dermatoses. Therefore, we propose that autoinflammation may be a cause of neutrophilic dermatoses.

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DOI: 10.1111/bjd.15105

PMID: 27905098

961. BMJ Case Rep. 2016 Nov 29;2016. pii: bcr2016217616. doi: 10.1136/bcr-2016-217616.

Hyper-IgD and periodic fever syndrome (HIDS) due to compound heterozygosity for G336S and V377I in a 44-year-old patient with a 27-year history of fever.

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Hereditary autoinflammatory syndromes are a rare, but notable cause of fever of unknown origin. During the last few years, the knowledge of the genetic background has significantly increased. Here, we report a novel pathogenic mutation in the MVK gene as the cause of fever in a 44-year-old male patient with a history of fever over a period of 27 years.

2016 BMJ Publishing Group Ltd.

DOI: 10.1136/bcr-2016-217616

PMCID: PMC5174846

PMID: 27899390 [Indexed for MEDLINE]

Conflict of interest statement: Conflicts of Interest: None declared.

962. Ann Dermatol Venereol. 2016 Dec;143 Suppl 3:S23-S28. doi:

10.1016/S0151-9638(18)30046-2.

[What's new in internal medicine?]

[Article in French]

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Answering the question « what's new in internal medicine in 2016? » is very

challenging. We used 3 methods of article selection to reduce the selection bias: 3 authors, a systematic review of the articles discussed in the weekly bibliographic meeting of our unit (Dermatology department, Saint-Louis Hospital, Paris, France) and a selection of the best articles by several internal medicine practitioners in Paris. Eleven « hot topics » were analyzed: i/ lowering cholesterol level but not blood pressure has a significant impact on cardiovascular morbidity-mortality in cardiovascular intermediate risk patients; ii/ the « treat to target » is efficient in psoriatic arthritis; iii/ a genotype/ phenotype correlation favors the separation of ileal Crohn's disease, colonic Crohn's disease and ulcerative colitis; iv/ tocilizumab treatment (anti-IL-6 monoclonal antibody) is very efficient in giant cell arteritis and slightly efficient in systemic sclerosis; v/ combination therapy using methotrexate plus steroids compared with steroids alone becomes the « gold standard » treatment for juvenile dermatomyositis; vi/ dupilumab treatment (antibody blocking IL-4 and IL-13 receptors) is not only efficient in atopic dermatitis but also in asthma; vii/ think of eosinophilic oesophagitis in a patient with atopic dermatitis and dysphagia or food impaction; viii/ genetic A2 protein dysfunction induces NF- $\kappa$ B hyperactivation and an autoinflammatory disorder with features similar to Behcet's disease; ix/ no new biotherapies have shown high efficacy in systemic lupus erythematosus; x/ nanoparticles loaded with autoantigens induce Tregs and Bregs and may be a promising therapeutic option to treat auto-immune disease in the future; xi/ ipilimumab treatment (anti-CTLA4 antibody, immune checkpoint inhibitor) may induce complete remission in acute myeloid leukemia patients relapsing after haematological stem cell transplantation. Year 2016 is full of great discoveries in internal medicine keeping the dermatologist brain fully open minded.

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DOI: 10.1016/S0151-9638(18)30046-2

PMID: 29429506 [Indexed for MEDLINE]

963. J Leukoc Biol. 2017 Apr;101(4):927-947. doi: 10.1189/jlb.4VMA0716-316R. Epub 2016 Nov 28.

Rats with a missense mutation in Atm display neuroinflammation and neurodegeneration subsequent to accumulation of cytosolic DNA following unrepaired DNA damage.

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Mutations in the ataxia-telangiectasia (A-T)-mutated (ATM) gene give rise to the human genetic disorder A-T, characterized by immunodeficiency, cancer predisposition, and neurodegeneration. Whereas a series of animal models recapitulate much of the A-T phenotype, they fail to present with ataxia or neurodegeneration. We describe here the generation of an Atm missense mutant [amino acid change of leucine (L) to proline (P) at position 2262 (L2262P)] rat by intracytoplasmic injection (ICSI) of mutant sperm into oocytes. Atm-mutant rats (AtmL2262P/L2262P) expressed low levels of ATM protein, suggesting a destabilizing effect of the mutation, and had a significantly reduced lifespan compared with Atm+/+. Whereas these rats did not show cerebellar atrophy, they succumbed to hind-limb paralysis (45%), and the remainder developed tumors. Closer examination revealed the presence of both dsDNA and ssDNA in the cytoplasm of cells in the hippocampus, cerebellum, and spinal cord of AtmL2262P/L2262P rats. Significantly increased levels of IFN- $\beta$  and IL-1 $\beta$  in all 3 tissues were

indicative of DNA damage induction of the type 1 IFN response. This was further supported by NF- $\kappa$ B activation, as evidenced by p65 phosphorylation (P65) and translocation to the nucleus in the spinal cord and parahippocampus. Other evidence of neuroinflammation in the brain and spinal cord was the loss of motor neurons and the presence of increased activation of microglia. These data provide support for a proinflammatory phenotype that is manifested in the Atm mutant rat as hind-limb paralysis. This mutant represents a useful model to investigate the importance of neuroinflammation in A-T.

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DOI: 10.1189/jlb.4VMA0716-316R

PMID: 27895165 [Indexed for MEDLINE]

964. *Pediatr Clin North Am*. 2017 Feb;64(1):39-56. doi: 10.1016/j.pcl.2016.08.004.

Eczema and Urticaria as Manifestations of Undiagnosed and Rare Diseases.

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Eczema and urticaria are common disorders encountered in pediatric patients, but they may occasionally be the presenting complaint in a child with an underlying rare disease. Immunodeficiency syndromes should be suspected when eczema is associated with neonatal onset, recurrent infections, chronic lymphadenopathy, or failure to thrive. Nutritional deficiencies and mycosis fungoides are in the differential diagnosis for a child with a recalcitrant eczematous eruption.

Autoinflammatory syndromes should be suspected in a child with chronic urticaria, fever, and other systemic signs of inflammation. Although these disorders are rare, early recognition allows for appropriate treatment and decreased morbidity for the child.



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DOI: 10.1016/j.pcl.2016.08.004

PMID: 27894451 [Indexed for MEDLINE]

965. *Pediatr Clin North Am.* 2017 Feb;64(1):111-125. doi: 10.1016/j.pcl.2016.08.008.

When to Suspect Autoinflammatory/Recurrent Fever Syndromes.

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Autoinflammatory disorders are disorders characterized by rash, arthritis, fever, and systemic inflammation. These disorders are caused by mutations in genes important in innate immune system sensors. This review highlights the workup of an individual with recurrent episodes of inflammation, features of these disorders, the genetic defects that cause these disorders, and the specific treatments available.

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DOI: 10.1016/j.pcl.2016.08.008

PMID: 27894439 [Indexed for MEDLINE]

966. *Dermatol Clin.* 2017 Jan;35(1):21-38. doi: 10.1016/j.det.2016.07.005.

Dermatologic Manifestations of Monogenic Autoinflammatory Diseases.

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Autoinflammatory disorders are sterile inflammatory conditions characterized by episodes of early-onset fever, rash, and disease-specific patterns of organ inflammation. Gain-of-function mutations in innate danger-sensing pathways, including the inflammasomes and the nucleic acid sensing pathways, play critical roles in the pathogenesis of IL-1 and Type-I IFN-mediated disorders and point to an important role of excessive proinflammatory cytokine signaling, including interleukin (IL)-1 $\beta$ , Type-I interferons, IL-18, TNF and others in causing the organ specific immune dysregulation. The article discusses the concept of targeting proinflammatory cytokines and their signaling pathways with cytokine blocking treatments that have been life changing for some patients.

Published by Elsevier Inc.

DOI: 10.1016/j.det.2016.07.005

PMCID: PMC5147585

PMID: 27890235 [Indexed for MEDLINE]

967. Rheum Dis Clin North Am. 2017 Feb;43(1):15-26. doi: 10.1016/j.rdc.2016.09.004.

Barriers to Immunizations and Strategies to Enhance Immunization Rates in Adults with Autoimmune Inflammatory Diseases.

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For as long as there have been immunizations, there have been barriers to them. Immunization rates in the United States are below target. Rheumatologists and rheumatology practitioners need to understand the issues of immunizations in patients with autoimmune inflammatory disease to identify and overcome barriers to immunization. Several strategies for overcoming these barriers are discussed.

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DOI: 10.1016/j.rdc.2016.09.004

PMID: 27890171 [Indexed for MEDLINE]

968. Trends Immunol. 2017 Feb;38(2):79-93. doi: 10.1016/j.it.2016.11.001. Epub 2016 Nov 22.

ISG15: In Sickness and in Health.

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ISG15 is a type I interferon (IFN)-inducible gene encoding a protein with pleiotropic functions, acting both as a soluble molecule and as a protein modifier. Surprisingly, and despite the antiviral functions of ISG15 described in mice, humans born with inactivating mutations of ISG15 do not present with any overt viral phenotype, but are highly susceptible to environmental mycobacteria and have autoinflammatory disease presentations. In vitro, ISG15 deficiency also

leads to persistently high levels of type I IFN-stimulated gene expression and to increased resistance to all viruses tested to date. This suggests that ISG15 deficiency increases antiviral responses in humans, in stark contrast to expectations based on mouse experiments. We discuss here the roles of each of the forms of ISG15 in health and disease, as well as the differences between species.

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DOI: 10.1016/j.it.2016.11.001

PMID: 27887993 [Indexed for MEDLINE]

969. Best Pract Res Clin Rheumatol. 2016 Apr;30(2):296-303. doi: 10.1016/j.berh.2016.09.001. Epub 2016 Sep 21.

Approach to the patients with inadequate response to colchicine in familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is the most common form of monogenic autoinflammatory conditions, and response to colchicine has been considered as one of its distinctive features among other hereditary periodic fever disorders. Prophylactic colchicine has been shown to be effective in the prevention of inflammatory attacks and development of amyloidosis. However, the highest tolerable doses of colchicine may not be adequate enough to manage these goals in approximately 5% of FMF patients. Inadequate response to colchicine in fully compliant FMF patients may be associated with genetic and/or environmental factors affecting disease severity and colchicine bioavailability. Clarification of the molecular pathogenic mechanisms of FMF has revealed that interleukin-1 beta (IL-1 $\beta$ ) cytokine is the most likely target to attack, and several case reports and case series have already documented the efficacy and safety of available anti-IL-1 agents, such as anakinra, rilonacept, and canakinumab in those patients inadequately responding to colchicine. Characterization and early

identification of those FMF patients with uncontrolled inflammatory activity have become more important after the availability of new treatment options for the prevention of disease-associated complications and permanent damages.

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DOI: 10.1016/j.berh.2016.09.001

PMID: 27886801 [Indexed for MEDLINE]

970. Clin Rev Allergy Immunol. 2017 Apr;52(2):287-303. doi: 10.1007/s12016-016-8591-2.

An Update on the Use of Immunomodulators in Primary Immunodeficiencies.

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The genomic revolution in the past decade fuelled by breathtaking advances in sequencing technologies has defined several new genetic diseases of the immune system. Many of these newly characterized diseases are a result of defects in genes involved in immune regulation. The discovery of these diseases has opened a vista of new therapeutic possibilities. Immunomodulatory agents, a hitherto unexplored therapeutic option in primary immunodeficiency diseases have been tried in a host of these newly described maladies. These agents have been shown conclusively to favorably modulate immune responses, resulting in abatement of clinical manifestations both in experimental models and patients. While some of the treatment options have been approved for therapeutic use or have been shown to be of merit in open-label trials, others have been shown to be efficacious in a handful of clinical cases, animal models, and cell lines. Interferon  $\gamma$  is approved for use in chronic granulomatous disease (CGD) to reduce the burden of infection and has a good long-term efficacy. Recombinant human IL7 therapy has been shown increase the peripheral CD4 and CD8 T cell counts in patients with idiopathic CD4. Anti-IL1 agents are approved for the management of cryopyrin-related autoinflammatory syndrome, and their therapeutic efficacy is

being increasingly recognized in other autoinflammatory syndromes and CGD. Mammalian target of rapamycin (mTOR) inhibitors have been proven useful in autoimmune lymphoproliferative syndrome (ALPS) and in IPEX syndrome. Therapies reported to be potential use in case reports include abatacept in CTLA4 haploinsufficiency and LRBA deficiency, ruxolitinib in gain-of-function STAT1, tocilizumab in gain-of-function STAT3 defect, mTOR inhibitors in PIK3CD activation, magnesium in XMEN syndrome, and pioglitazone in CGD. Treatment options of merit in human cell lines include interferon  $\alpha$  and interferon  $\beta$  in TLR3 and UNC-93B deficiencies, anti-interferon therapy in SAVI, and Rho-kinase inhibitors in TTC7A deficiency. Anti-IL17 agents have show efficacy in animal models of leukocyte adhesion defect (LAD) and ALPS. This topical review explores the use of various immunomodulators and other biological agents in the context of primary immunodeficiency and autoinflammatory diseases.

DOI: 10.1007/s12016-016-8591-2

PMID: 27873163 [Indexed for MEDLINE]

971. Dermatology. 2016;232(5):534-540. doi: 10.1159/000449526. Epub 2016 Nov 22.

Autoinflammatory Skin Disease: A Review of Concepts and Applications to General Dermatology.

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We provide an up-to-date summary of important concepts of autoinflammation as well as describe important but rare monogenic autoinflammatory disorders that may present with cutaneous findings. Finally, of particular interest to a practicing general dermatology audience, we review concepts of autoinflammation as they apply to understanding the disease pathogenesis of common skin disorders.

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DOI: 10.1159/000449526

PMID: 27871068 [Indexed for MEDLINE]

972. J Clin Rheumatol. 2016 Dec;22(8):434.

The Expanding Mosaic of Autoinflammatory Disease.

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DOI: 10.1097/RHU.0000000000000471

PMID: 27870766

973. Br J Dermatol. 2017 Jul;177(1):72-83. doi: 10.1111/bjd.15193. Epub 2017 Jun 14.

Drug-induced pyoderma gangrenosum: a model to understand the pathogenesis of pyoderma gangrenosum.

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Pyoderma gangrenosum (PG) is a rare autoinflammatory condition in which the alteration of neutrophil function and the innate immune response play key roles in its pathogenesis. Cases of PG have been reported in patients being treated with certain medications, which may help us to understand some of the possible pathways involved in the aetiology of PG. The aim of this review is to review the cases of PG triggered by certain drugs and try to thoroughly understand the pathogenesis of the disease. To accomplish this, a PubMed search was completed using the following words: pyoderma gangrenosum, neutrophilic dermatosis, pathophysiology, drug-induced pyoderma gangrenosum. In total, we found 43 cases of drug-induced PG. Most of them were caused by colony-stimulating factors and

small-molecule tyrosine kinase inhibitors. We propose that drugs induce PG through various mechanisms such as dysfunctional neutrophil migration and function, dysregulated inflammatory response, promotion of keratinocyte apoptosis and alteration of epigenetic mechanisms. PG is a rare condition with complex pathophysiology and drug-induced cases are even more scarce; this is the main limitation of this review. Understanding the possible mechanisms of drug-induced PG, via abnormal neutrophil migration and function, abnormal inflammation, keratinocyte apoptosis and alteration of epigenetic mechanisms would help to better understand the pathogenesis of PG and ultimately to optimize targeted therapy.

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DOI: 10.1111/bjd.15193

PMID: 27864925 [Indexed for MEDLINE]

974. Neurology. 2017 Jan 3;88(1):93-100. doi: 10.1212/WNL.0000000000003432. Epub 2016 Nov 18.

Comorbidity between central disorders of hypersomnolence and immune-based disorders.

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**OBJECTIVE:** To assess and compare the frequencies of personal and family history of autoimmune diseases (AID), autoinflammatory disorders (ID), and allergies in a population of patients, adults and children, with narcolepsy type 1 (NT1), narcolepsy type 2 (NT2), and idiopathic hypersomnia (IH), 3 central hypersomnia disorders, and healthy controls.

**METHODS:** Personal and family history of AID, ID, and allergies were assessed by questionnaire and medical interview in a large cohort of 450 consecutive adult patients (206 NT1, 106 NT2, 138 IH) and 95 pediatric patients (80 NT1) diagnosed according to the third International Classification of Sleep Disorders criteria in national reference centers for narcolepsy in France and 751 controls (700 adults, 51 children) from the general population.

**RESULTS:** Ten adults with NT1 (4.9%) had a comorbid AID vs 3.4% of adult controls, without between-group differences in adjusted models. AID frequency did not differ between children with NT1 and controls. Conversely, compared with controls, AID frequency was higher in adults with NT2 ( $p = 0.002$ ), whereas ID ( $p = 0.0002$ ) and allergy ( $p = 0.003$ ) frequencies were higher in adults with IH. A positive family history of AID was found in the NT1 group and of ID in the IH group.

**CONCLUSIONS:** NT1 is not associated with increased risk of comorbid immune disorders, in favor of a potentially unique pathophysiology. Conversely, compared with controls, the frequency of autoimmune diseases was higher in adults with NT2, whereas allergies and autoinflammatory disorders were more common in adults with IH, suggesting an immune dysregulation mechanism in these conditions.

DOI: 10.1212/WNL.0000000000003432

PMID: 27864522 [Indexed for MEDLINE]

975. Arthritis Rheumatol. 2017 Apr;69(4):854-862. doi: 10.1002/art.39995.

Anakinra for Colchicine-Resistant Familial Mediterranean Fever: A Randomized, Double-Blind, Placebo-Controlled Trial.

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**OBJECTIVE:** Familial Mediterranean fever (FMF) is refractory to colchicine prophylaxis in 10-20% of patients. In a number of patient series, treatment with anakinra, an interleukin-1-blocking agent, prevented FMF attacks in those with colchicine-resistant FMF. This study was undertaken to evaluate the efficacy and safety of anakinra in the treatment of colchicine-resistant FMF, using a randomized controlled trial.

**METHODS:** Patients with colchicine-resistant FMF receiving colchicine (dosage  $\geq 1.5$  to  $\leq 3$  mg/day) were recruited and randomly assigned to receive anakinra or placebo (vehicle). The treatment duration was 4 months. Primary efficacy outcomes were the number of attacks per month, and the number of patients with a mean of  $<1$  attack per month. Quality of life was assessed using a 0-10-grade visual analog scale (VAS), and safety was assessed according to the number and severity of adverse events.

**RESULTS:** Twenty-five patients with colchicine-resistant FMF (14 women) were enrolled, of whom 12 were randomized to receive anakinra and 13 to receive placebo. The mean  $\pm$  SD number of attacks per patient per month was  $1.7 \pm 1.7$  in those receiving anakinra and  $3.5 \pm 1.9$  in those receiving placebo ( $P = 0.037$ ). Six patients in the anakinra group, compared to none in the placebo group, had  $<1$  attack per month ( $P = 0.005$ ). A beneficial effect of anakinra was noted in the number of attacks in the joints per month in patients receiving anakinra (mean  $\pm$  SD  $0.8 \pm 1.6$  versus  $2.1 \pm 1.1$  in the placebo group;  $P = 0.019$ ) and in

quality of life (mean  $\pm$  SD VAS score  $7.7 \pm 2.3$  in the anakinra group versus  $4.2 \pm 2.9$  in the placebo group;  $P = 0.045$ ). The number of adverse events per patient per month was comparable between the anakinra group and the placebo group (mean  $\pm$  SD  $2.03 \pm 1.75$  versus  $3.34 \pm 2.5$ ;  $P = 0.22$ ). There were no severe adverse events.

**CONCLUSION:** In this randomized controlled trial, anakinra appears to be an effective and safe treatment for colchicine-resistant FMF.

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DOI: 10.1002/art.39995

PMID: 27860460 [Indexed for MEDLINE]

976. Int J Rheum Dis. 2017 Sep;20(9):1286-1296. doi: 10.1111/1756-185X.12940. Epub 2016 Nov 9.

Clinical and genetic association, radiological findings and response to biological therapy in seven children from Qatar with non-bacterial osteomyelitis.

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**AIM:** We aim to report the clinical manifestations, genetic testing results, magnetic resonance imaging (MRI) findings and biologics used in the management of non-bacterial osteomyelitis in our center.

**METHODS:** We conducted a retrospective review of medical records. A previously proposed classification was implemented as follows: chronic recurrent multifocal osteomyelitis (CRMO), chronic non-bacterial osteomyelitis (CNBO) and acute non-bacterial osteomyelitis.

**RESULTS:** Four females and three males with a median age at presentation of 6 years (6 months-14 years) presented with arthralgia (7/7), back pain (4/7), arthritis (4/7) and bone pain (2/7). Six patients had CRMO and one patient had CNBO. Genetic testing revealed an apparent homozygote p.S734L LPIN2 mutation in

two siblings, a heterozygote p.M694V MEFV mutation in one patient with familial Mediterranean fever and heterozygote p.Q219H PSTPIPI variant of unknown significance in one patient. The most common lesions on MRI involved the tibia (6/7), talar bones (5/7), fibula (4/7) and sacroiliac joints (4/7). Three patients received infliximab. Two are in remission after 2 and 5 years, and the third was advanced after 5 years to canakinumab. Two other patients received canakinumab first. One patient with Majeed syndrome and dyserythropoietic anemia exhibited evidence of improvement, and one had partial improvement and was then treated with infliximab.

**CONCLUSION:** Non-bacterial osteomyelitis may coexist with other autoinflammatory diseases. MRI remains a favorable diagnostic tool and genetic testing may have a limited role in selected cases. Infliximab and canakinumab are associated with variable outcomes, and 6-week or less dosing intervals for both medications may be more effective.

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DOI: 10.1111/1756-185X.12940

PMID: 27860302 [Indexed for MEDLINE]

977. Medicine (Baltimore). 2016 Nov;95(44):e5065.

Marshall syndrome in a young child, a reality: Case report.

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**BACKGROUND:** Recurrent fever syndrome, known as the Marshall syndrome (MS), is a clinical entity that includes several clinical features, such as: fever (39-40°C) that occurs repeatedly at variable intervals (3-8 weeks) and in episodes of 3 to 6 days, cervical adenopathy, pharyngitis, and aphthous stomatitis. The diagnosis of MS is one of exclusions; laboratory data is nonspecific and no abnormalities

correlated with MS have been detected thus far.

**METHODS:** The authors report the case of a 2-year-old girl admitted to a tertiary pediatric center for repeated episodes of fever with aphthous stomatitis and laterocervical adenopathy.

**RESULTS:** The child's case history raised the suspicion of MS, which was subsequently confirmed by exclusion of all the other differential diagnoses (recurrent tonsillitis, juvenile idiopathic arthritis, Behçet's disease, cyclic neutropenia, hyperglobulinemia D syndrome). After the 3 febrile episodes, bilateral tonsillectomy was performed based on the parents' consent, with favorable immediate and remote postoperative clinical outcomes. The diagnosis of MS is one based on exclusion, as laboratory data is nonspecific. We took into consideration other causes of recurrent fever (recurrent tonsillitis, infectious diseases, juvenile idiopathic arthritis, Behçet's disease, cyclic neutropenia, Familial Mediterranean fever syndrome, hyperglobulinemia D syndrome). In our case, MS criteria were met through clinical examination and the child's outcome. Subsequently, laboratory data helped us establish the MS diagnosis.

**CONCLUSIONS:** Pediatricians should consider the MS diagnosis in the context of recurrent fever episodes associated with at least one of the following symptoms: pharyngitis, cervical adenopathy or aphthous stomatitis. Despite the indication for tonsillectomy in young children being controversial, in this case the surgery led to the total remission of the disease.

DOI: 10.1097/MD.00000000000005065

PMCID: PMC5591089

PMID: 27858841 [Indexed for MEDLINE]

978. Rheumatology (Oxford). 2016 Dec;55(suppl 2):ii23-ii29.

The challenge of autoinflammatory syndromes: with an emphasis on hyper-IgD syndrome.

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Autoinflammatory syndromes are disorders with an exaggerated inflammatory response, mostly in the absence of an appropriate trigger. Prototypic autoinflammatory syndromes are FMF, hyper-IgD syndrome (also known as mevalonate kinase deficiency), TNF receptor-associated periodic syndrome and cryopyrin-associated periodic syndrome. The clinical phenotypes partly overlap (with fever and acute phase response), but also differ between the various syndromes (e.g. regarding fever pattern, episodic vs chronic inflammation and accompanying clinical signs). In recent years, the genetic basis of quite a number of these relatively rare and mostly hereditary disorders has been elucidated. These genetic defects lead to either enhanced production of inflammatory mediators or to a lack of inhibition of these components of the innate immune system. Among these dysregulated inflammatory mediators, the pro-inflammatory cytokine IL-1 $\beta$  stands out. Hence, targeted treatment with blockers of IL-1 action, such as recombinant IL-1 receptor antagonist (IL-1Ra, anakinra) and mAb against IL-1 $\beta$  has met with impressive clinical results. In this article, hyper-IgD syndrome is discussed in more detail, based on 30 years of experience with this syndrome.

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DOI: 10.1093/rheumatology/kew351

PMID: 27856657 [Indexed for MEDLINE]

979. J Child Adolesc Psychopharmacol. 2016 Nov;26(9):847-850.

Obsessive-Compulsive Disorder, Tics, and Autoinflammatory Diseases: Beyond PANDAS.

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DOI: 10.1089/cap.2016.29118.bjc

PMID: 27854543 [Indexed for MEDLINE]

980. Clin Rheumatol. 2017 Jan;36(1):183-189. doi: 10.1007/s10067-016-3480-x. Epub 2016 Nov 16.

Efficacy and safety of adalimumab in Behçet's disease-related uveitis: a multicenter retrospective observational study.

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The study aim was to evaluate the efficacy of adalimumab (ADA) in a large series of Behçet's disease (BD)-related uveitis. We performed a multicenter retrospective observational study including 40 selected patients (66 eyes) receiving ADA. Clinical data were retrospectively analyzed at baseline, at 3 and 12 months of treatment. Primary end point was reduction of ocular inflammatory flares. Secondary end points were improvement of best corrected visual acuity (BCVA), reduction of macular thickness measured by optical coherence tomography (OCT), reduction in the occurrence of vasculitis assessed by fluorescein angiography (FA), and evaluation of statistically significant differences between patients treated with ADA monotherapy and those undergoing ADA plus DMARDs and in patients firstly treated with ADA compared to patients previously administered with other biologics; ADA steroid sparing effect was also evaluated. During the first 12 months of ADA therapy, the number of flares significantly decreased from 200 flares/100 patients/year to 8.5 flares/100 patients/year ( $p < 0.0001$ ). Similarly, BCVA improved if compared to baseline ( $7.4 \pm 2.9$  versus  $8.5 \pm 2.1$ ,  $p = 0.03$ ). OCT findings significantly improved showing a mean reduction of central macular thickness (CMT) of  $27.27 \pm 42.8 \mu\text{m}$  at the end of follow-up ( $p < 0.006$ ). FA identified retinal vasculitis in 22 cases at baseline (55%), 8 (20%) cases after 3 months, and in only one (2.5%) case at 12-month follow-up. FA improvement was highly significant at 3- and 12-month follow-up if compared to baseline ( $p < 0.0001$  and  $p = 0.006$ , respectively). ADA is highly effective and safe for the treatment of BD-related uveitis, providing a long-term control of ocular inflammation.

DOI: 10.1007/s10067-016-3480-x

PMID: 27853889 [Indexed for MEDLINE]

981. Ann Rheum Dis. 2017 May;76(5):e9. doi: 10.1136/annrheumdis-2016-210681. Epub 2016 Nov 16.

Criteria for CAPS, is it all in the name?

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DOI: 10.1136/annrheumdis-2016-210681

PMID: 27852576

982. J Clin Rheumatol. 2017 Jan;23(1):58-59. doi: 10.1097/RHU.0000000000000468.

Case of NOD2-Associated Autoinflammatory Disease Successfully Treated With Sulfasalazine.

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DOI: 10.1097/RHU.0000000000000468

PMID: 27851691 [Indexed for MEDLINE]

983. Clin Biochem. 2017 Mar;50(4-5):206-209. doi: 10.1016/j.clinbiochem.2016.11.008. Epub 2016 Nov 10.

Concordance between CRP and SAA in familial Mediterranean fever during attack-free period: A study of 218 patients.

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**INTRODUCTION:** Monitoring SAA level in attack-free FMF patients is recommended in order to adjust colchicine dose, and minimize the risk of AA amyloidosis. In countries where this test is not available, C-reactive protein (CRP), another acute phase reactant, is used instead. However, CRP is low and SAA is increased in some patients and vice versa.

**OBJECTIVES:** To determine the threshold of CRP corresponding to  $SAA < 10\text{mg/L}$  in patients with FMF and to assess their concordance at the patient level.

**PATIENTS AND METHODS:** Consecutive FMF patients in attack-free period and no other cause of intermittent inflammation including infections were recruited during their regular visits in the French reference center for FMF. Demographic and genetic data were recorded; CRP and SAA were tested simultaneously. The threshold value of CRP corresponding to  $10\text{mg/L}$  for SAA was determined and the concordance between the two markers was assessed with Cohen's kappa index.

**RESULTS:** 399 samples were obtained from 218 patients, mean age of 27years (33% under 18years old), 55% of female, from Sephardic Jewish origin in 71%. MEFV

mutation was M694V homozygous or compound heterozygous in 52%, and simple heterozygous in 18%. Six patients had AA amyloidosis. The appropriate CRP threshold was found to be 5mg/L in children and 8.75mg/L in adults. Global agreement with SAA<10mg/L was 84% [95% confidence interval: 82 to 86%], leading to a kappa index at 0.62 [95% confidence interval: 0.57 to 0.68].

CONCLUSION: CRP<5mg/L in FMF children or 8.75mg/L in FMF adults during attack-free periods might be a convenient substitute to guide therapeutic decisions when SAA is unavailable.

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DOI: 10.1016/j.clinbiochem.2016.11.008

PMID: 27838405 [Indexed for MEDLINE]

984. J Allergy Clin Immunol. 2017 Jun;139(6):1957-1965.e3. doi: 10.1016/j.jaci.2016.09.033. Epub 2016 Nov 7.

Endogenous polyclonal anti-IL-1 antibody responses potentiate IL-1 activity during pathogenic inflammation.

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BACKGROUND: Particular neutralizing mAbs to certain cytokines act as agonists in vivo through protection of the cytokine's active site and prolongation of its half-life. Although this principle might be useful for targeted immunotherapy, its role in the pathogenesis of inflammation and autoimmunity is unclear.

OBJECTIVE: We sought to determine whether slight, structurally nonrelevant modifications of the prototypic proinflammatory cytokine IL-1 $\beta$  during an immune response could elicit polyclonal anti-IL-1 $\beta$  antibody responses that modulated

IL-1 $\beta$ 's in vivo activity.

**METHODS:** We engineered 2 different IL-1 $\beta$  variants, thereby mimicking the process of cytokine modification occurring during inflammation, and conjugated them to virus-like particles, followed by immunization of mice. The resulting polyclonal anti-IL-1 $\beta$  antibody responses were assessed by using in vitro and in vivo assays, as well as 2 relevant (auto-) inflammatory murine models.

**RESULTS:** Although antibody responses generated to one variant were potentially inhibiting IL-1 $\beta$ , antibody responses induced by the other variant even potentiated the in vivo effects of IL-1 $\beta$ ; the latter led to enhanced morbidity in 2 different IL-1 $\beta$ -mediated mouse models, including a model of inflammatory bowel disease and an inflammatory arthritis model.

**CONCLUSION:** These data demonstrate that endogenous polyclonal anti-cytokine antibody responses can enhance the cytokine's activity in inflammatory and autoimmune diseases.

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DOI: 10.1016/j.jaci.2016.09.033

PMID: 27833025 [Indexed for MEDLINE]

985. An Bras Dermatol. 2016 Sep-Oct;91(5):566-578. doi: 10.1590/abd1806-4841.20165577.

Inflammasomes and dermatology.

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Inflammasomes are intracellular multiprotein complexes that comprise part of the innate immune response. Since their definition, inflammasome disorders have been linked to an increasing number of diseases. Autoinflammatory diseases refer to disorders in which local factors lead to the activation of innate immune cells, causing tissue damage when in the absence of autoantigens and autoantibodies.

Skin symptoms include the main features of monogenic inflammasomopathies, such as Cryopyrin-Associated Periodic Syndromes (CAPS), Familial Mediterranean Fever (FMF), Schnitzler Syndrome, Hyper-IgD Syndrome (HIDS), PAPA Syndrome, and

Deficiency of IL-1 Receptor Antagonist (DIRA). Concepts from other pathologies have also been reviewed in recent years, such as psoriasis, after the recognition of a combined contribution of innate and adaptive immunity in its pathogenesis. Inflammasomes are also involved in the response to various infections, malignancies, such as melanoma, autoimmune diseases, including vitiligo and lupus erythematosus, atopic and contact dermatitis, acne, hidradenitis suppurativa, among others. Inhibition of the inflammasome pathway may be a target for future therapies, as already occurs in the handling of CAPS, through the introduction of IL-1 inhibitors. This study presents a literature review focusing on the participation of inflammasomes in skin diseases.

DOI: 10.1590/abd1806-4841.20165577

PMCID: PMC5087212

PMID: 27828627 [Indexed for MEDLINE]

Conflict of interest statement: none

986. J Korean Med Sci. 2016 Dec;31(12):1902-1906. doi: 10.3346/jkms.2016.31.12.1902.

Decreased Chitotriosidase Activity and Levels in Familial Mediterranean Fever.

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Different studies have demonstrated changes in chitotriosidase (ChT) activity and concentrations in multiple diseases. However, changes in ChT activity and

concentrations have not been concurrently evaluated in patients with Familial Mediterranean Fever (FMF). In this study, we analyzed the changes in serum ChT activity and concentrations in patients with FMF. The study included a total of 80 patients with FMF and 80 healthy controls. ChT enzyme activity and concentrations were measured and then compared between the groups. ChT activity was measured by using fluorometric ELISA and ChT concentrations were measured by using colorimetric ELISA methods. The median ChT activity was 10.00 (6.00-15.00) nmol/mL/hr in the patients and 14.00 (6.25-20.75) nmol/mL/hr in the controls. There was a statistically significant difference in the ChT activity between the controls and patients ( $P = 0.027$ ). The median ChT concentrations were 65.40 (46.20-84.92) pg/mL and 125.00 (75.72-143.95) pg/mL in the patients and controls, respectively ( $P < 0.001$ ), which were expressed as median percentiles (25th-75th). Additionally, we found no correlation between C-reactive protein and ChT activity ( $P = 0.978$ ,  $r = 0.003$ ) and concentrations ( $P = 0.446$ ,  $r = -0.87$ ). Serum ChT enzyme activity and concentrations may not be considered as a biomarker in FMF patients taking colchicine. New studies are needed to evaluate the changes of enzyme activity and concentration in colchicine-negative patients.

DOI: 10.3346/jkms.2016.31.12.1902

PMCID: PMC5102852

PMID: 27822927 [Indexed for MEDLINE]

Conflict of interest statement: The authors have no potential conflicts of interest to disclose.

987. Strahlenther Onkol. 2017 Mar;193(3):229-233. doi: 10.1007/s00066-016-1065-x. Epub 2016 Nov 7.

Successful treatment of chronic recurrent multifocal osteomyelitis using low-dose radiotherapy : A case report.

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**BACKGROUND:** Chronic recurrent multifocal osteomyelitis (CRMO) is a rare autoinflammatory disease, which lacks an infectious genesis and predominantly involves the metaphysis of long bones. Common treatments range from nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids at first onset of disease, to immunosuppressive drugs and bisphosphonates in cases of insufficient remission. The therapeutic use of low-dose radiotherapy for CRMO constitutes a novelty.

**CASE REPORT:** A 67-year-old female patient presented with radiologically proven CRMO affecting the right tibia/talus and no response to immunosuppressive therapy. Two treatment series of radiation therapy were applied with an interval of 6 weeks. Each series contained six fractions (three fractions per week) with single doses of 0.5 Gy, thus the total applied dose was 6 Gy. Ten months later, pain and symptoms of osteomyelitis had completely vanished.

**CONCLUSION:** Radiotherapy seems to be an efficient and feasible complementary treatment option for conventional treatment refractory CRMO in adulthood. The application of low doses per fraction is justified by the inflammatory pathomechanism of disease.

DOI: 10.1007/s00066-016-1065-x

PMID: 27822735 [Indexed for MEDLINE]

988. Front Pharmacol. 2016 Oct 24;7:380. eCollection 2016.

A Snapshot on the On-Label and Off-Label Use of the Interleukin-1 Inhibitors in Italy among Rheumatologists and Pediatric Rheumatologists: A Nationwide Multi-Center Retrospective Observational Study.

Vitale A(1), Insalaco A(2), Sfriso P(3), Lopalco G(4), Emmi G(5), Cattalini M(6), Manna R(7), Cimaz R(8), Priori R(9), Talarico R(10), Gentileschi S(1), de Marchi G(11), Frassi M(12), Gallizzi R(13), Soriano A(14), Alessio M(15), Cammelli D(16), Maggio MC(17), Marcolongo R(18), La Torre F(19), Fabiani C(20), Colafrancesco S(9), Ricci F(6), Galozzi P(3), Viapiana O(21), Verrecchia E(7), Pardeo M(2), Cerrito L(7), Cavallaro E(11), Olivieri AN(22), Paolazzi G(23),

Vitiello G(24), Maier A(25), Silvestri E(5), Stagnaro C(10), Valesini G(9), Mosca M(10), de Vita S(11), Tincani A(12), Lapadula G(4), Frediani B(1), De Benedetti F(2), Iannone F(4), Punzi L(3), Salvarani C(14), Galeazzi M(1), Rigante D(26), Cantarini L(1).

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Background: Interleukin (IL)-1 inhibitors have been suggested as possible therapeutic options in a large number of old and new clinical entities characterized by an IL-1 driven pathogenesis. Objectives: To perform a nationwide snapshot of the on-label and off-label use of anakinra (ANA) and canakinumab (CAN) for different conditions both in children and adults. Methods: We retrospectively collected demographic, clinical, and therapeutic data from both adult and pediatric patients treated with IL-1 inhibitors from January 2008 to July 2016. Results: Five hundred and twenty-six treatment courses given to 475 patients (195 males, 280 females; 111 children and 364 adults) were evaluated. ANA was administered in 421 (80.04%) courses, CAN in 105 (19.96%). Sixty-two (32.1%) patients had been treated with both agents. IL-1 inhibitors were employed in 38 different indications (37 with ANA, 16 with CAN). Off-label use was more frequent for ANA than CAN ( $p < 0.0001$ ). ANA was employed as first-line biologic approach in 323 (76.7%) cases, while CAN in 37 cases (35.2%). IL-1 inhibitors were associated with corticosteroids in 285 (54.18%) courses and disease modifying anti-rheumatic drugs (DMARDs) in 156 (29.65%). ANA dosage ranged from 30 to 200 mg/day (or 1.0-2.0 mg/kg/day) among adults and 2-4 mg/kg/day among children; regarding CAN, the most frequently used posologies were 150mg every 8 weeks, 150mg every 4 weeks and 150mg every 6 weeks. The frequency of failure was higher among patients treated with ANA at a dosage of 100 mg/day than those treated with 2 mg/kg/day ( $p = 0.03$ ). Seventy-six patients (14.4%) reported an adverse event (AE) and 10 (1.9%) a severe AE. AEs occurred more frequently after the age of 65 compared to both children and patients aged between 16 and 65 ( $p = 0.003$  and  $p = 0.03$ , respectively). Conclusions: IL-1 inhibitors are mostly used off-label, especially ANA, during adulthood. The high frequency of good clinical responses suggests that IL-1 inhibitors are used with awareness of pathogenetic mechanisms; adult healthcare physicians generally employ standard dosages, while

pediatricians are more prone in using a weight-based posology. Dose adjustments and switching between different agents showed to be effective treatment strategies. Our data confirm the good safety profile of IL-1 inhibitors.

DOI: 10.3389/fphar.2016.00380

PMCID: PMC5076463

PMID: 27822185

989. Intern Emerg Med. 2017 Mar;12(2):269-270. doi: 10.1007/s11739-016-1570-z. Epub 2016 Nov 5.

Tumor necrosis factor inhibitors in tumor necrosis factor receptor-associated periodic syndrome: still a chance to work?

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DOI: 10.1007/s11739-016-1570-z

PMID: 27817124 [Indexed for MEDLINE]

990. Ann Rheum Dis. 2017 May;76(5):821-830. doi: 10.1136/annrheumdis-2016-210092. Epub 2016 Nov 3.

Development of the autoinflammatory disease damage index (ADDI).

Ter Haar NM(1)(2), Annink KV(3), Al-Mayouf SM(4), Amaryan G(5), Anton J(6), Barron KS(7), Benseler SM(8), Brogan PA(9), Cantarini L(10), Cattalini M(11), Cochino AV(12), De Benedetti F(13), Dedeoglu F(14), De Jesus AA(15), Della Casa Alberighi O(16), Demirkaya E(17), Dolezalova P(18), Durrant KL(19), Fabio G(20), Gallizzi R(21), Goldbach-Mansky R(15), Hachulla E(22), Hentgen V(23), Herlin T(24), Hofer M(25)(26), Hoffman HM(27), Insalaco A(28), Jansson AF(29), Kallinich T(30), Koné-Paut I(31), Kozlova A(32), Kuemmerle-Deschner JB(33), Lachmann HJ(34), Laxer RM(35), Martini A(36), Nielsen S(37), Nikishina I(38), Ombrello AK(39), Ozen S(40), Papadopoulou-Alataki E(41), Quartier P(42), Rigante D(43),

Russo R(44), Simon A(45), Trachana M(46), Uziel Y(47), Ravelli A(48), Gattorno M(49), Frenkel J(3).

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**OBJECTIVES:** Autoinflammatory diseases cause systemic inflammation that can result in damage to multiple organs. A validated instrument is essential to quantify damage in individual patients and to compare disease outcomes in clinical studies. Currently, there is no such tool. Our objective was to develop a common autoinflammatory disease damage index (ADDI) for familial Mediterranean fever, cryopyrin-associated periodic syndromes, tumour necrosis factor receptor-associated periodic fever syndrome and mevalonate kinase deficiency.

**METHODS:** We developed the ADDI by consensus building. The top 40 enrollers of patients in the Eurofever Registry and 9 experts from the Americas participated in multiple rounds of online surveys to select items and definitions. Further, 22 (parents of) patients rated damage items and suggested new items. A consensus meeting was held to refine the items and definitions, which were then formally weighted in a scoring system derived using decision-making software, known as 1000minds.

**RESULTS:** More than 80% of the experts and patients completed the online surveys. The preliminary ADDI contains 18 items, categorised in the following eight organ systems: reproductive, renal/amyloidosis, developmental, serosal, neurological, ears, ocular and musculoskeletal damage. The categories renal/amyloidosis and neurological damage were assigned the highest number of points, serosal damage the lowest number of points. The involvement of (parents of) patients resulted in the inclusion of, for example, chronic musculoskeletal pain.

**CONCLUSIONS:** An instrument to measure damage caused by autoinflammatory diseases is developed based on consensus building. Patients fulfilled a significant role

in this process.

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DOI: 10.1136/annrheumdis-2016-210092

PMID: 27811147 [Indexed for MEDLINE]

991. J Exp Med. 2016 Nov 14;213(12):2671-2689. Epub 2016 Oct 24.

--LUBAC deficiency perturbs TLR3 signaling to cause immunodeficiency and autoinflammation.

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The linear ubiquitin chain assembly complex (LUBAC), consisting of SHANK-associated RH-domain-interacting protein (SHARPIN), heme-oxidized IRP2 ubiquitin ligase-1 (HOIL-1), and HOIL-1-interacting protein (HOIP), is a critical regulator of inflammation and immunity. This is highlighted by the fact that patients with perturbed linear ubiquitination caused by mutations in the Hoip or Hoil-1 genes, resulting in knockouts of these proteins, may simultaneously suffer from immunodeficiency and autoinflammation. TLR3 plays a crucial, albeit controversial, role in viral infection and tissue damage. We identify a pivotal

role of LUBAC in TLR3 signaling and discover a functional interaction between LUBAC components and TLR3 as crucial for immunity to influenza A virus infection. On the biochemical level, we identify LUBAC components as interacting with the TLR3-signaling complex (SC), thereby enabling TLR3-mediated gene activation. Absence of LUBAC components increases formation of a previously unrecognized TLR3-induced death-inducing SC, leading to enhanced cell death. Intriguingly, excessive TLR3-mediated cell death, induced by double-stranded RNA present in the skin of SHARPIN-deficient chronic proliferative dermatitis mice (cpdm), is a major contributor to their autoinflammatory skin phenotype, as genetic coablation of Tlr3 substantially ameliorated cpdm dermatitis. Thus, LUBAC components control TLR3-mediated innate immunity, thereby preventing development of immunodeficiency and autoinflammation.

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DOI: 10.1084/jem.20160041

PMCID: PMC5110014

PMID: 27810922 [Indexed for MEDLINE]

992. Actas Dermosifiliogr. 2017 Mar;108(2):161-164. doi: 10.1016/j.ad.2016.09.006. Epub 2016 Oct 31.

Familial Mediterranean Fever: Diagnostic Difficulties in an Atypical Case.

[Article in English, Spanish]

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DOI: 10.1016/j.ad.2016.09.006

993. J Immunol. 2016 Dec 1;197(11):4266-4273. Epub 2016 Nov 2.

Suppression of IRAK1 or IRAK4 Catalytic Activity, but Not Type 1 IFN Signaling, Prevents Lupus Nephritis in Mice Expressing a Ubiquitin Binding-Defective Mutant of ABIN1.

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Polymorphisms in the TNIP1 gene encoding A20-binding inhibitor of NF- $\kappa$ B1 (ABIN1) predispose to lupus and other autoimmune diseases in at least eight human populations. We found previously that knock-in mice expressing a ubiquitin-binding-defective mutant of ABIN1 (ABIN1[D485N]) develop autoimmunity as they age and succumb to a disease resembling lupus nephritis in humans. In this article, we report that Flt3-derived dendritic cells from these mice overproduced type 1 IFNs upon stimulation with ligands that activate TLR7 or TLR9. However, crossing ABIN1[D485N] mice to IFNAR1-knockout mice that do not express the  $\alpha$ -subunit of the type 1 IFNR did not prevent splenomegaly, the appearance of high serum levels of autoantibodies and other Igs, or liver inflammation and only reduced kidney inflammation modestly. In contrast, crossing ABIN1[D485N] mice to knock-in mice expressing catalytically inactive mutants of IRAK1 or IRAK4 prevented splenomegaly, autoimmunity, and liver and kidney inflammation. Our results support the notion that IRAK1 and/or IRAK4 are attractive targets for the development of drugs to prevent, and perhaps treat, lupus nephritis and other autoinflammatory diseases caused by the decreased ability of ABIN1 or other proteins to restrict the strength of MyD88 signaling.



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DOI: 10.4049/jimmunol.1600788

PMCID: PMC5114882

PMID: 27807192 [Indexed for MEDLINE]

994. Nature. 2016 Nov 3;539(7627):124. doi: 10.1038/nature19837. Epub 2016 Sep 28.

Corrigendum: Noncanonical autophagy inhibits the autoinflammatory, lupus-like response to dying cells.

Martinez J, Cunha LD, Park S, Yang M, Lu Q, Orchard R, Li QZ, Yan M, Janke L, Guy C, Linkermann A, Virgin HW, Green DR.

Erratum for

Nature. 2016 May 5;533(7601):115-9.

DOI: 10.1038/nature19837

PMID: 27680703

995. J Rheumatol. 2016 Nov;43(11):1956-1964. Epub 2016 Sep 1.

Chronic Nonbacterial Osteomyelitis: Pathophysiological Concepts and Current Treatment Strategies.

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Chronic nonbacterial osteomyelitis (CNO) is an autoinflammatory bone disorder, covering a clinical spectrum with asymptomatic inflammation of single bones at the one end, and chronic recurrent multifocal osteomyelitis (CRMO) at the other end. The exact molecular pathophysiology of CNO remains largely unknown. Provided familial clusters and the association with inflammatory disorders of the skin and intestine suggest a genetic predisposition. Recently, profound dysregulation of cytokine responses was demonstrated in CRMO. Failure to produce antiinflammatory cytokines interleukin (IL)-10 and IL-19 contributes to activation of inflammasomes and subsequent IL-1 $\beta$  release. In IL-10-deficient and in CNO-prone chronic multifocal osteomyelitis mice, IL-1 $\beta$  was linked to bone inflammation. Further, alterations to the gut microbiome were suggested in contributing to IL-1 $\beta$  release from innate immune cells in mice, offering an interesting target in the search for molecular mechanisms in CNO. Here, we summarize clinical presentation and treatment options in CNO/CRMO, current pathophysiological

concepts, available mouse models, and promising future scientific directions.

DOI: 10.3899/jrheum.160256

PMID: 27585682 [Indexed for MEDLINE]

996. Ann Rheum Dis. 2017 Apr;76(4):e7. doi: 10.1136/annrheumdis-2016-210656. Epub 2016 Oct 31.

Why CAPS criteria are not diagnostic criteria?

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Comment in

Ann Rheum Dis. 2016 Apr;76(4):e8.

Comment on

Ann Rheum Dis. 2017 Jun;76(6):942-947.

DOI: 10.1136/annrheumdis-2016-210656

PMID: 27799158 [Indexed for MEDLINE]

997. Lupus. 2016 Dec;25(14):1623-1624. Epub 2016 Mar 23.

Comment on: Coexistence of systemic lupus erythematosus and familial Mediterranean fever in a pediatric patient.

Kelesoglu FM(1), Saracoglu B(2), Ciftkaya A(2), Durmus RB(2), Kaya S(2), Ozer S(2), Makar CC(2), Yilmaz Y(3), Acar A(4), Omeroglu R(2).

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DOI: 10.1177/0961203316641769

PMID: 27013664 [Indexed for MEDLINE]

998. Hautarzt. 2016 Dec;67(12):934-939.

[Pyoderma gangrenosum and Sweet's syndrome : Cutaneous manifestations of autoinflammatory disorders].

[Article in German]

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Pyoderma gangrenosum and Sweet's syndrome are rare diseases that belong to the group of neutrophilic dermatoses and share several common characteristics. Although the two disorders differ clinically from each other, both diseases show pronounced dermal infiltration of neutrophils without evidence of primary vasculitis and respond well to immunosuppressive drugs. In addition, both diseases are often associated with other systemic and hematological disorders. Recent findings show that the neutrophil dermatoses can be considered as cutaneous manifestations of autoinflammation, demonstrating an interesting new aspect in the development of the diseases and additional therapeutic avenues.

DOI: 10.1007/s00105-016-3888-x  
PMID: 27796411 [Indexed for MEDLINE]

999. Hautarzt. 2016 Nov;67(11):897-901.

[Severe acne in autoinflammatory diseases].

[Article in German]

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**BACKGROUND:** In recent years, acne has been described as a symptom of autoinflammatory diseases, such as PASH (pyoderma gangrenosum - PG, acne and suppurative hidradenitis - SH) and PAPASH (PG, acne, pyogenic arthritis, and SH). The pathogenesis of autoinflammatory diseases is not fully understood; however, based on the possible involvement of IL-1 $\beta$ , the recombinant human interleukin-1 receptor antagonist anakinra has been used in the treatment of certain autoinflammatory diseases.

**METHODS:** We describe two patients with severe acne and associated symptoms which led to the diagnosis PAPASH and PASH syndrome and who were treated with anakinra.

**RESULTS:** In the patient with PASH syndrome, inhibition of inflammation and almost complete healing of ulcers was observed. In the patient with PAPASH syndrome, partial response was achieved.

**CONCLUSION:** The therapeutic effect of anakinra in PASH syndrome and partly in PAPASH syndrome indicates an involvement of IL-1 $\beta$  in acne-associated autoinflammatory diseases.

DOI: 10.1007/s00105-016-3840-0

PMID: 27448064 [Indexed for MEDLINE]

1000. Nihon Naika Gakkai Zasshi. 2016 Nov;105(11):2237-44.

[A Case of FMF (Familial Mediterranean Fever) with HLA-B\*39 and HLA-B\*40 as Disease-promoting Factors].

[Article in Japanese]

Tokunaga T, Miyoshi S, Tamamoto S, Yamamoto S, Nishida A, Tanimoto T, Shoda H, Ishikawa N, Maeda H.

PMID: 30178986

1001. Hematol Oncol Stem Cell Ther. 2018 Sep;11(3):175-177. doi: 10.1016/j.hemonc.2016.09.001. Epub 2016 Oct 19.

A novel TNFRSF1A gene mutation in a patient with tumor necrosis factor receptor-associated periodic syndrome.

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Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is a periodic fever syndrome inherited in an autosomal dominant fashion. It stems from mutations in the TNFRSF1A (accession number: NM\_001065) gene expressing the receptor for tumor necrosis factor  $\alpha$ . A patient with TRAPS may present with prolonged episodes of fever attacks, abdominal pain, severe myalgia, and painful erythema on the trunk or extremities. Here, we report an 8-year-old boy with febrile attacks occurring every 1-2 months and continuing for 3-4 days. The patient experienced 40°C-fever attacks without chills. Approximately 80% of fever attacks were accompanied by abdominal manifestations. Direct sequencing analysis was used to assess the genomic DNA of the patient, and a heterozygous R426L mutation in exon 10 of the TNFRSF1A gene in an autosomal dominant inheritance fashion was identified. Further genetic analyses were also carried out on his parents. Due to the fact that the mutation was not inherited from the parents, it was likely that R426L was a de novo and novel mutation in the TNFRSF1A gene, which can trigger TRAPS or TRAPS-like symptoms.

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DOI: 10.1016/j.hemonc.2016.09.001

PMID: 27793577 [Indexed for MEDLINE]

1002. Arthritis Rheumatol. 2017 Feb;69(2):268-276. doi: 10.1002/art.39975.

Review: Found in Translation: International Initiatives Pursuing Interleukin-1 Blockade for Treatment of Acute Kawasaki Disease.

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DOI: 10.1002/art.39975

PMCID: PMC5274552

PMID: 27792871

1003. Clin Exp Rheumatol. 2016 Sep-Oct;34(6 Suppl 102):10-22. Epub 2016 Oct 13.

One year in review 2016: Behçet's syndrome.

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Several articles highlighting the epidemiology, pathogenesis, clinical features, treatment modalities and disease assessment of Behçet's syndrome (BS) have been published during the last year. Clinical and radiological features of lower extremity deep vein thrombosis due to BS can be quite different than those found in thrombosis due to other causes; additionally, frequency of post-thrombotic syndrome is significantly increased in BS. Some clinical and colonoscopic features are useful in differentiating BS from Crohn's disease. Barkhof criteria may be helpful in differentiating neurologic involvement due to BS from multiple sclerosis. Anatomical localization of papulopustular lesions but not histology has been found to be helpful in differentiating papulopustular lesions of BS from those found in acne vulgaris. Several studies looked at the ovarian reserve with contradicting results. A population-based cohort study found higher risk of hematological malignancies only among female BS patients living in Taiwan. The role of genetic factors and environment is discussed and both autoimmune and autoinflammatory features are underlined in the pathogenesis of BS. New data on the epistatic interactions between ERAP and HLA B51 is available and information on the microbiome have started to appear. New uncontrolled data suggest beneficial effects of anti-TNFs for refractory extra-ocular complications of BS such as pulmonary artery, gastrointestinal and central nervous system



involvement. Uncontrolled studies suggest promising results with interleukin-1 inhibition but gevokizumab, a humanised anti IL-1 $\beta$  antibody, failed to meet the primary endpoint of time to first ocular exacerbation in a phase III trial. The debate on anticoagulation continues with new observational data.

PMID: 27791958 [Indexed for MEDLINE]

1004. Clin Exp Rheumatol. 2016 Sep-Oct;34(6 Suppl 102):97-100. Epub 2016 Oct 17.

Familial Mediterranean fever gene mutation frequencies in a sample Turkish population.

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**OBJECTIVES:** Our knowledge about the frequencies of mutations in the Turkish population is based on the studies on the affected patients and hospital-based control groups. We aimed to determine the frequencies of MEFV gene mutations in a population-based field study in Turkey.

**METHODS:** Turkish citizens aged between 5 and 65 years were included in the study. Cities from seven regions of Turkey were studied. Blood samples were obtained from individuals who gave permission for laboratory experiments, and they were analysed for 10 MEFV gene mutations.

**RESULTS:** Among 500 participants, MEFV mutations were found in 74 (14.8%). Sixty four (12.8%), 7 (1.4%), and 3 (0.6%) participants were heterozygous, compound

heterozygous, and homozygous, respectively. Among inhabitants with heterozygous mutations, the most common heterozygous mutations were E148Q/- and M694V/-. Sixteen participants were found to be heterozygous for M694V, 2 were compound heterozygous for M694V/E148Q, and one was homozygous for M694V/M694V mutation; in total, the frequency of M694V allele was 4% (n=20). Twenty-three (4.6%) individuals were heterozygous for common mutations (M694V, M680I, V726A). Total allelic frequency was 8.4%.

**CONCLUSIONS:** Our study, which describes the MEFV mutational spectrum and distribution in a healthy Turkish population, found a carrier rate that is much higher than expected.

PMID: 27791953 [Indexed for MEDLINE]

1005. Clin Exp Rheumatol. 2016 Sep-Oct;34(6 Suppl 102):72-76. Epub 2016 Oct 25.

MEFV and SAA1 genotype associations with clinical features of familial Mediterranean fever and amyloidosis in Armenia.

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**OBJECTIVES:** Familial Mediterranean fever (FMF) is a hereditary periodic disease characterised by recurrent attacks of fever and serositis. The most devastating complication of FMF is amyloidosis (AA) affecting mainly the kidneys. Aim of the study is to search for correlations between the MEFV genotype and the SAA polymorphisms with the clinical manifestations of FMF and the occurrence of amyloidosis in a large cohort of Armenian patients.

**METHODS:** Information about the MEFV mutations, SAA polymorphisms and FMF clinical features, were obtained for 1017 FMF patients, from the database of the Center of Medical Genetics in Yerevan. For identifying probable correlation between the MEFV and SAA genotype and clinical features of FMF, regression logistic analyses were conducted between the genotype and phenotype of the patients.

**RESULTS:** Patients homozygous for M694V were highly associated with all the

clinical features of FMF and its complications - proteinuria and amyloidosis. None of the SAA1 polymorphisms had any correlation with FMF clinical features. However, homozygosis for SAA1  $\alpha/\alpha$  polymorphism was associated with proteinuria and amyloidosis whereas carrying the  $\beta/\beta$  polymorphism was found to be protective for amyloidosis.

CONCLUSIONS: The SAA1  $\alpha$  allele is strongly associated with amyloidosis in FMF patients. This observation is valid in inflammatory diseases other than FMF too. SAA1 polymorphism has no effect on the clinical features of FMF. M694V homozygosis is highly associated with typical features of FMF and with amyloidosis. FMF course in Armenia is similar to that in Middle Eastern countries where FMF disease is common.

PMID: 27791951 [Indexed for MEDLINE]

1006. Clin Exp Rheumatol. 2016 Sep-Oct;34(6 Suppl 102):129-135. Epub 2016 Oct 25.

A novel assessment tool for clinical care of patients with autoinflammatory disease: juvenile autoinflammatory disease multidimensional assessment report.

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**OBJECTIVES:** To develop and test a new multidimensional questionnaire for assessment of children with auto-inflammatory disease (AID) such as FMF, PFAPA, HIDS, TRAPS in standard clinical care.

**METHODS:** The juvenile auto-inflammatory disease multidimensional assessment report (JAIMAR) includes 16 parent or patient-centered measures and four dimensions that assess functional status, pain, therapeutic compliance and health-related quality of life (physical, social, school, emotional status) with disease outcome. It is proposed for use as both a proxy-report and a patient self-report, with the suggested age range of 8-18 years for use as a self-report.

**RESULTS:** 250 children with FMF were included in the study. Total of 179 forms were filled up by parents and patients, and 71 forms were filled up by parents having children less than 8 years. Completing and scoring the JAIMAR can be done in 15 minutes. For the JAIMAR's dimensions, the Cronbach's alpha coefficient for internal consistency was between 0.507-0.998. There was a significant and a positive correlation between the test-retest scale scores ( $ICC=0.607-0.966$ ). Concerning construct validity, all factors loadings were above 0.30. For the criterion validity, the correlation level between each dimension and the related scale ranged from medium ( $r=0.329$ ,  $p<0.0001$ ) to large ( $r=0.894$ ,  $p<0.0001$ ). The parents' proxy-reported and children's self-reported data were outstandingly concordant ( $r=0.770-0.989$ ).

**CONCLUSIONS:** The development of the JAIMAR introduces a new and multi-dimensional approach in paediatric rheumatology practice. It is a new tool for children with auto-inflammatory disease and it may help enhance their quality of care.

PMID: 27791950 [Indexed for MEDLINE]

1007. Clin Exp Rheumatol. 2016 Sep-Oct;34(6 Suppl 102):77-81. Epub 2016 Oct 25.

Demographic, clinical and therapeutic findings in a monocentric cohort of adult patients with suspected PFAPA syndrome.

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**OBJECTIVES:** Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenopathy (PFAPA) syndrome is a non-Mendelian autoinflammatory disorder until now considered to be specifically limited to paediatric age. Recently, an increasing number of reports seems to suggest that PFAPA syndrome, diagnosed by the Marshall criteria revised by Thomas et al., can also affect adults.

**METHODS:** The Marshall/Thomas criteria have been applied to 989 adult patients presenting for recurrent fever episodes: all patients enrolled were reviewed for demographic, clinical, and therapeutic data. Infectious, neoplastic, autoimmune

and other autoinflammatory diseases were ruled out.

**RESULTS:** We identified 30 adult patients (19 males, 11 females) with a suspected PFAPA syndrome: their mean age at disease onset was  $33.75 \pm 14.01$  years, mean age at diagnosis  $39.1 \pm 14.39$  years, and mean body temperature peak  $39.5 \pm 0.7^\circ\text{C}$ . In addition, the mean frequency of febrile episodes was  $11.58 \pm 8.97$  per year. More precisely, patients complained of pharyngitis (77%), cervical adenitis (73%), asthenia (63%), arthralgia (67%), oral aphthosis (50%), myalgia (54%), cephalalgia (43%), abdominal pain (27%), nausea/vomiting (17%), periorbital pain (17%), and arthritis (10%). Six out of 30 (20%) patients had suffered from PFAPA syndrome also during childhood, and the disease had reappeared in adulthood.

**CONCLUSIONS:** We provide the largest monocentric cohort of patients diagnosed with a suspected PFAPA syndrome in adulthood confirming that this syndrome can occur also during adulthood; moreover, due to the medical history of our patients and based on our experience, PFAPA syndrome might relapse during adulthood after a temporary remission reached in the course of paediatric age.

PMID: 27791949 [Indexed for MEDLINE]

1008. J Clin Lab Anal. 2016 Nov;30(6):978-981. doi: 10.1002/jcla.21966. Epub 2016 Apr 13.

Higher Pentraxin-3 Levels are Associated With Inflammation in Familial Mediterranean Fever.

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**BACKGROUND:** Circulating levels of Pentraxin-3 (PTX3) have been shown to increase in several inflammatory conditions. However, there is no information about the levels of PTX3 in patients with familial Mediterranean fever (FMF). This study was designed to evaluate the serum PTX3 levels in patients with FMF during attack and free-attack periods.

**METHODS:** Twenty FMF patients in attack and free-attack period, and 20 age-, sex-, and body mass index-matched healthy controls were included in the study. Blood samples were obtained within the first 24 h of the attack period and between attacks, and levels of white blood cell, erythrocyte sedimentation rate, Fibrinogen, high sensitive CRP, and PTX3 were determined.

**RESULTS:** PTX3 levels during the attack period were not significantly different from those in free-attack patients ( $4.9 \pm 4.6$  ng/ml vs.  $2.8 \pm 1.4$  ng/ml,  $P > 0.05$ ). However, both attack and free-attack patients had significantly higher PTX3 levels than healthy controls ( $4.9 \pm 4.6$  ng/ml vs.  $1.8 \pm 0.8$  ng/ml,  $P < 0.001$ ;  $2.8 \pm 1.4$  ng/ml vs.  $1.8 \pm 0.8$  ng/ml,  $P < 0.025$ , respectively).

**CONCLUSIONS:** PTX3 levels were not markedly affected from FMF attacks, but high level of PTX3 in free-attack period of FMF patients shows ongoing subclinical inflammation. However, further studies are needed to determine its usefulness as a marker in clinical practice.

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DOI: 10.1002/jcla.21966

PMID: 27790798 [Indexed for MEDLINE]

1009. Br J Dermatol. 2016 Nov;175(5):858. doi: 10.1111/bjd.14830.

The autoinflammatory pyoderma/acne (PA) syndromes: just interleukin-1-diseases?

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Comment on

Br J Dermatol. 2016 Nov;175(5):882-891.

DOI: 10.1111/bjd.14830

PMID: 27790678 [Indexed for MEDLINE]

1010. Science. 2016 Oct 28;354(6311):481-484. Epub 2016 Sep 29.

Aerobic glycolysis promotes T helper 1 cell differentiation through an epigenetic mechanism.

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Comment in

Science. 2016 Oct 28;354(6311):419-420.

Dev Cell. 2016 Nov 7;39(3):286-287.

Aerobic glycolysis (the Warburg effect) is a metabolic hallmark of activated T cells and has been implicated in augmenting effector T cell responses, including expression of the proinflammatory cytokine interferon- $\gamma$  (IFN- $\gamma$ ), via 3' untranslated region (3'UTR)-mediated mechanisms. Here, we show that lactate



dehydrogenase A (LDHA) is induced in activated T cells to support aerobic glycolysis but promotes IFN- $\gamma$  expression independently of its 3'UTR. Instead, LDHA maintains high concentrations of acetyl-coenzyme A to enhance histone acetylation and transcription of *Ifng*. Ablation of LDHA in T cells protects mice from immunopathology triggered by excessive IFN- $\gamma$  expression or deficiency of regulatory T cells. These findings reveal an epigenetic mechanism by which aerobic glycolysis promotes effector T cell differentiation and suggest that LDHA may be targeted therapeutically in autoinflammatory diseases.

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DOI: 10.1126/science.aaf6284

PMCID: PMC5539971

PMID: 27708054 [Indexed for MEDLINE]

1011. J Allergy Clin Immunol. 2017 Apr;139(4):1311-1320. doi: 10.1016/j.jaci.2016.07.041. Epub 2016 Sep 19.

Efficacy and safety of canakinumab in Schnitzler syndrome: A multicenter randomized placebo-controlled study.

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**BACKGROUND:** Schnitzler syndrome is an adult-onset autoinflammatory disease characterized by urticarial exanthema and monoclonal gammopathy accompanied by systemic symptoms such as fever, bone, and muscle pain. Up to now, approved treatment options are not available.

**OBJECTIVE:** We assessed effects of the anti-IL-1 $\beta$  mAb canakinumab on the clinical signs and symptoms of Schnitzler syndrome.

**METHODS:** In this phase II, randomized placebo-controlled multicenter study, 20 patients with active disease enrolled in 4 German study centers. Patients were randomly assigned to receive single subcutaneous canakinumab 150 mg or placebo injections for 7 days, followed by a 16-week open-label phase with canakinumab injections on confirmed relapse of symptoms. The primary end point was the proportion of patients with complete clinical response evaluated by physician global assessment at day 7. Key secondary end points included changes in patient-reported disease activity (Schnitzler activity score), inflammation markers (C-reactive protein and serum amyloid A), and quality-of-life assessments (Dermatology Life Quality Index and 36-item short form health survey).

**RESULTS:** The proportion of patients with complete clinical response at day 7 was significantly higher ( $P = .001$ ) in the canakinumab-treated group ( $n = 5$  of 7) than in the placebo group ( $n = 0$  of 13). Levels of inflammation markers C-reactive protein and serum amyloid A and quality-of-life scores were significantly reduced in canakinumab-treated but not in placebo-treated individuals. Positive effects continued up to 16 weeks. Adverse events were manageable and included respiratory tract infections, gastrointestinal symptoms, and hypertension.

**CONCLUSIONS:** In this first placebo-controlled study, canakinumab was effective in patients with Schnitzler syndrome, and thus canakinumab may be further evaluated as a therapeutic option for this rare disease.

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DOI: 10.1016/j.jaci.2016.07.041

PMID: 27658762 [Indexed for MEDLINE]

1012. Clin Exp Rheumatol. 2016 Sep-Oct;34(6 Suppl 102):S138. Epub 2016 Jul 27.

Unusual presentation of familial Mediterranean fever: atypical hyperaemic

recurrent skin lesions.

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PMID: 27463421 [Indexed for MEDLINE]

1013. Clin Exp Rheumatol. 2016 Sep-Oct;34(6 Suppl 102):S121-S128. Epub 2016 Jun 16.

Gene expression profile in TNF receptor-associated periodic syndrome reveals constitutively enhanced pathways and new players in the underlying inflammation.

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**OBJECTIVES:** Tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is a multisystemic autoinflammatory condition associated with heterozygous TNFRSF1A mutations, presenting with a variety of clinical symptoms, many of which yet unexplained. In this work, we aimed at deepening into TRAPS

pathogenic mechanisms sustained by monocytes.

**METHODS:** Microarray experiments were conducted to identify genes whose expression results altered in patients compared to healthy individuals, both under basal condition and following LPS stimulation.

**RESULTS:** An inflammatory state baseline, characterised by constitutive overexpression of IL1 $\beta$  and IL1R1 receptor, has been shown in TRAPS patients compared to controls, including in non-active disease phases. Following LPS stimulation, IL1RN up-regulation is stronger in controls than in patients and inflammatory pathways and microRNAs undergo differential regulation. Genes involved in post-translational modifications, protein folding and ubiquitination result constitutively up-regulated in TRAPS, while response to interferon types I and II is defective, failing to be up-regulated by LPS. TGF $\beta$  pathway is down-regulated in untreated TRAPS monocytes, while genes involved in redox regulation result constitutively over-expressed. Finally, additional molecular alterations seem to reflect organ failures sometime complicating the disease.

**CONCLUSIONS:** Gene expression profile in resting TRAPS monocytes has confirmed the patients' chronic inflammatory condition. In addition, pathways not yet associated with the disease have been disclosed, such as interferon types I and II response to LPS stimulation and a downregulation of the TGF $\beta$  pathway in basal condition. The role of miRNA, suggested by our results, deserves in-depth analyses in light of the possible development of targeted therapies.

PMID: 27310036 [Indexed for MEDLINE]

1014. Clin Exp Rheumatol. 2016 Sep-Oct;34(6 Suppl 102):S86-S91. Epub 2016 Jun 16.

CD11c is upregulated in CD8<sup>+</sup> T cells of patients with Behçet's disease.

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**OBJECTIVES:** Single nucleotide polymorphisms of CD11a and CD11c have been suggested as susceptibility loci in Korean patients with Behçet's disease (BD). As immunoregulatory roles of CD11c+CD8+T cells were previously observed in multiple autoimmune and autoinflammatory diseases, we aimed to investigate CD11a and CD11c in CD4+ and CD8+ subpopulation of BD patients.

**METHODS:** Peripheral-blood mononuclear cells were isolated from 21 patients with active BD, 26 patients with inactive BD, 20 patients with recurrent aphthous ulcers (RAU), and 23 healthy controls (HCs). The surface expression of CD11a and CD11c in CD4+ and CD8+ cell populations was analyzed by flow cytometry, and CD11a and CD11c mRNA and protein levels from purified CD8(+) T cells were analyzed using real-time polymerase chain reaction and western blot.

**RESULTS:** The frequencies of CD11a+ and CD11c+ cells were significantly increased in the CD4+ and CD8+ cell populations of active-BD patients, respectively, than that in the HCs. Additionally, both CD11a and CD11c mRNA and protein levels were significantly elevated in the CD8+ T cells of active-BD patients than that in the HCs.

**CONCLUSIONS:** The CD8+ T cells of BD patients exhibited increased CD11c expression levels. Upregulation of CD11c in CD8+ cells may contribute to BD pathogenesis.

PMID: 27309860 [Indexed for MEDLINE]

1015. Clin Exp Rheumatol. 2016 Sep-Oct;34(6 Suppl 102):S137. Epub 2016 May 24.

Increased frequency of psoriasis in the families of the children with familial Mediterranean fever.

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PMID: 27243382 [Indexed for MEDLINE]

1016. J Clin Lab Anal. 2016 Nov;30(6):1158-1163. doi: 10.1002/jcla.21997. Epub 2016 May 26.

Investigation of the Levels of Serum Amyloid A, YKL-40, and Pentraxin-3 in Patients with Familial Mediterranean Fever.

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**BACKGROUND:** Familial Mediterranean Fever (FMF) is an autosomal recessive form of recurrent episodes of fever and an autoinflammatory disease characterized by inflammation of the serous membranes. The clinical diagnosis is supported by the laboratory findings. This study investigated the relationship of Serum Amyloid A (SAA), YKL-40, and Pentraxin-3 (PTX-3) with the FMF disease.

**METHODS:** About 50 patients with FMF were enrolled in this study. Patients were divided into three groups according to disease severity score (mild, moderate, and severe). Thirty-seven healthy individuals were included as the control group. Serum SAA, YKL-40, and PTX-3 concentrations were measured using an ELISA kit.

**RESULTS:** Serum SAA and YKL-40 levels of FMF patients were significantly higher than in the control ( $P < 0.001$ ). PTX-3 levels were found to be higher in patients even though there was no significant difference ( $P = 0.113$ ). Whereas the positive predictive value was 71.9% for cut-off point of SAA, the positive predictive value was 83.3% for cut-off point of YKL-40. Whereas a significant correlation

was detected in SAA and PTX-3 with YKL-40 (respectively;  $P = 0.036$ ,  $P < 0.001$ ), there was no correlation between the PTX-3 with SAA ( $P = 0.219$ ).

CONCLUSIONS: YKL-40 can be used together with SAA to support the diagnosis of FMF and to monitor the severity of the disease. In this study, YKL-40 levels were examined for the first time in FMF patients and further studies are necessary using larger patient samples.

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DOI: 10.1002/jcla.21997

PMID: 27230955 [Indexed for MEDLINE]

1017. Clin Exp Rheumatol. 2016 Sep-Oct;34(6 Suppl 102):S52-S55. Epub 2016 Apr 21.

Semaphorin 3A, a potential immune regulator in familial Mediterranean fever.

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OBJECTIVES: Semaphorin 3A (sema3A) plays a regulatory role in immune responses with effects on both T and B regulatory cells. Familial Mediterranean fever (FMF) is an autoinflammatory disease, yet a possible role for regulatory T and B cells has been described.

METHODS: 17 FMF patients during attack and then in remission, 8 FMF patients with smoldering disease and 12 healthy controls were enrolled. Sema3A in serum and its expression on regulatory T and B cells was evaluated. Clinical parameters of FMF patients were assessed.

RESULTS: Semaphorin 3A serum level was lower in FMF patients during attack, smoldering disease or remission than healthy controls, ( $242.3 \pm 9.8$  ng/ml vs.  $258.9 \pm 11.5$  ng/ml vs.  $232.5 \pm 22.7$  ng/ml vs.  $323.3 \pm 160.2$  ng/ml, respectively

p<0.05). This decrease was specifically noted on regulatory B and T cells in FMF patients during attack and in smoldering disease and normalized in remission.  
CONCLUSIONS: Sema3A expression on T and B regulatory lymphocytes is low in FMF patients during attack and in smoldering disease compared to the expression in remission and healthy controls. These results are in line with previous descriptions suggesting a possible role of regulatory T cells in termination of FMF attacks. Further studies are needed to verify these preliminary findings.

PMID: 27157528 [Indexed for MEDLINE]

1018. Br J Dermatol. 2016 Nov;175(5):882-891. doi: 10.1111/bjd.14691. Epub 2016 Aug 23.

Pyoderma gangrenosum and its syndromic forms: evidence for a link with autoinflammation.

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Comment in

Br J Dermatol. 2016 Nov;175(5):858.

Pyoderma gangrenosum is a rare inflammatory neutrophilic dermatosis manifesting as painful ulcers with violaceous, undermined borders on the lower extremities. It may occur in the context of classic syndromes like PAPA (pyogenic arthritis,



pyoderma gangrenosum and acne) and SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis), as well as in a recently described entity named PASH (pyoderma gangrenosum, acne and suppurative hidradenitis). Pyoderma gangrenosum has recently been included within the spectrum of autoinflammatory diseases, which are characterized by recurrent episodes of sterile inflammation, without circulating autoantibodies and autoreactive T cells. In PAPA syndrome, different mutations involving the PSTPIP1 gene, via an increased binding affinity to pyrin, induce the assembly of inflammasomes. These are molecular platforms involved in the activation of caspase 1, a protease that cleaves inactive prointerleukin (pro-IL)-1 $\beta$  to its active isoform IL-1 $\beta$ . The overproduction of IL-1 $\beta$  triggers the release of a number of proinflammatory cytokines and chemokines, which are responsible for the recruitment and activation of neutrophils, leading to neutrophil-mediated inflammation. In SAPHO syndrome, the activation of the PSTPIP2 inflammasome has been suggested to play a role in inducing the dysfunction of the innate immune system. Patients with PASH have recently been reported to present alterations of genes involved in well-known autoinflammatory diseases, such as PSTPIP1, MEFV, NOD2 and NLRP3. Pyoderma gangrenosum and its syndromic forms can be regarded as a single clinicopathological spectrum in the context of autoinflammation.

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DOI: 10.1111/bjd.14691

PMID: 27106250 [Indexed for MEDLINE]

1019. J Clin Lab Anal. 2016 Nov;30(6):1003-1008. doi: 10.1002/jcla.21971. Epub 2016 Apr 19.

The Relationship Among the Level of Serum Amyloid A, High-Density Lipoprotein and Microalbuminuria in Patients With Familial Mediterranean Fever.

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**BACKGROUND:** Serum amyloid A (SAA), which is produced in the liver, acts as an apoprotein of high-density lipoprotein (HDL) accumulation in extracellular matrix of tissues and organs. SAA elevations play a significant role in the development of amyloidosis. Microalbuminuria (MAU) is the early period of amyloidosis in patients with familial Mediterranean fever (FMF). We assessed the association between SAA as an important factor for the development of amyloidosis in patients with FMF and cytokines, HDL, and MAU.

**METHODS:** A total of 40 FMF patients diagnosed with Tel-Hashomer criteria and making regular follow-up visits at the tertiary referral center from 2012 to 2013 were included in this study, besides 40 age- and sex-matched individuals as controls.

**RESULTS:** Compared with controls, FMF patients had higher SAA ( $25.20 \pm 45.78$  vs.  $1.68 \pm 0.63$  ng/ml;  $P = 0.002$ ). Also, FMF patients had higher MAU than controls ( $23.20 \pm 39.86$  vs.  $9.40 \pm 5.32$  mg/day;  $P = 0.036$ ). HDL was significantly lower in the patient group than in controls ( $39.35 \pm 10.45$  vs.  $47.82 \pm 15.31$  mg/dl;  $P = 0.023$ ). Interleukin-1 beta (IL-1), IL-6, and tumor necrosis factor alpha (TNF- $\alpha$ ) levels were higher in the FMF group than in controls ( $P < 0.0001$ ,  $P = 0.009$ ,  $P = 0.003$ , respectively).

**CONCLUSIONS:** Our results suggest that IL-1, IL-6, TNF- $\alpha$ , SAA, and HDL may serve as markers of subclinical inflammation in FMF patients. Due to increased plasma HDL levels, antiinflammatory and antioxidant effects may elevate in FMF patients.

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DOI: 10.1002/jcla.21971

PMID: 27094695 [Indexed for MEDLINE]

1020. Clin Exp Rheumatol. 2016 Sep-Oct;34(6 Suppl 102):S136. Epub 2016 Feb 9.

Effect of colchicine on serum lipid levels.

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PMID: 26885841 [Indexed for MEDLINE]

1021. Arthritis Rheumatol. 2017 Feb;69(2):447-459. doi: 10.1002/art.39960.

Identification of a High-Frequency Somatic NLRC4 Mutation as a Cause of Autoinflammation by Pluripotent Cell-Based Phenotype Dissection.

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**OBJECTIVE:** To elucidate the genetic background of a patient with neonatal-onset multisystem inflammatory disease (NOMID) with no NLRP3 mutation.

**METHODS:** A Japanese male child diagnosed as having NOMID was studied. The patient did not have any NLRP3 mutation, even as low-frequency mosaicism. We performed whole-exome sequencing on the patient and his parents. Induced pluripotent stem

cells (iPSCs) were established from the patient's fibroblasts. The iPSCs were then differentiated into monocyte lineage to evaluate the cytokine profile. RESULTS: We established multiple iPSC clones from a patient with NOMID and incidentally found that the phenotypes of monocytes from iPSC clones were heterogeneous and could be grouped into disease and normal phenotypes. Because each iPSC clone was derived from a single somatic cell, we hypothesized that the patient had somatic mosaicism of an interleukin-1 $\beta$ -related gene. Whole-exome sequencing of both representative iPSC clones and the patient's blood revealed a novel heterozygous NLRC4 mutation, p.T177A (c.529A>G), as a specific mutation in diseased iPSC clones. Knockout of the NLRC4 gene using the clustered regularly interspaced short palindromic repeat/Cas9 system in a mutant iPSC clone abrogated the pathogenic phenotype.

CONCLUSION: Our findings indicate that the patient has somatic mosaicism of a novel NLRC4 mutation. To our knowledge, this is the first case showing that somatic mutation of NLRC4 causes autoinflammatory symptoms compatible with NOMID. The present study demonstrates the significance of prospective genetic screening combined with iPSC-based phenotype dissection for individualized diagnoses.

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DOI: 10.1002/art.39960

PMID: 27788288 [Indexed for MEDLINE]

1022. Curr Opin Rheumatol. 2017 Jan;29(1):39-44.

Approach to cutaneous vasculitides with special emphasis on small vessel vasculitis: histopathology and direct immunofluorescence.

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PURPOSE OF REVIEW: The present review will focus on recent publications in cutaneous vasculitides.

RECENT FINDINGS: Some histopathological and clinical features, such as papillary dermal edema, perivascular C3 deposition, clinically evident edema, and lesions above the waist, may point out renal or gastrointestinal involvement in

Henoch-Schönlein purpura (HSP). HSP associated with familial Mediterranean fever differs from typical isolated HSP by showing no deposits of IgA, much younger age, and location of the lesions on the face or the trunk. Single-organ cutaneous small vessel vasculitis is a more restricted entity than hypersensitivity vasculitis and HSP. Because cutaneous polyarteritis nodosa and macular lymphocytic arteritis share some clinicopathologic features, the question is raised whether they are not two different entities. Several histopathological features defining IgG4-related disease are found in granuloma faciale and erythema elevatum diutinum, two localized chronic cutaneous vasculitis; however, in a recent series no diagnostic criteria for IgG4-related disease was detected in them.

**SUMMARY:** When a patient presents with skin lesions, in which necrotizing or leukocytoclastic vasculitis is confirmed histologically, irrespective of the size of the affected vessel, the possibility of systemic vasculitis, an infection, medication, or a systemic disease such as systemic lupus erythematosus must be searched before reaching definitive diagnosis.

DOI: 10.1097/BOR.0000000000000346

PMID: 27787337 [Indexed for MEDLINE]

1023. Arthritis Rheumatol. 2016 Nov;68(11):2760-2771. doi: 10.1002/art.39793.

Clinical and Genetic Features of Patients With TNFRSF1A Variants in Japan: Findings of a Nationwide Survey.

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**OBJECTIVE:** To elucidate the clinical and genetic features of patients with TNFRSF1A variants in Japan using data obtained from a nationwide survey conducted by the Ministry of Health, Labor, and Welfare of Japan study group for tumor necrosis factor receptor-associated periodic syndrome (TRAPS).

**METHODS:** Inquiries were sent to 2,900 departments of internal medicine and pediatrics in all hospitals with more than 200 beds in Japan, asking whether they had patients in whom TRAPS was suspected. Genetic tests for TNFRSF1A, MEFV, and MVK were performed on 169 patients. Cell surface expression of TNFRSF1A variants was assessed using 293T cells.

**RESULTS:** Ten patients from 10 independent families were found to have TNFRSF1A variants. We collected clinical and genetic information on 41 additional patients with TNFRSF1A variants and symptoms of inflammation from 23 independent families; 17 of these patients had not been described in the literature. The common clinical features of Japanese patients were fever of  $>38^{\circ}\text{C}$  (100% of patients), arthralgia (59%), and rash (55%). The prevalence of abdominal pain (36%), myalgia (43%), and amyloidosis (0%) was significantly lower in Japanese patients than in Caucasian patients. The most common variant was T61I (appearing in 49% of patients), and it was identified in 7 of 363 healthy controls. Defects in cysteine residues and the T50M variant were associated with decreased cell surface expression, while other variants, including T61I, were not.

**CONCLUSION:** Patients with TNFRSF1A variants are very rare in Japan, as in other countries, but there are a number of clinical and genetic differences between Japanese and Caucasian patients. The pathogenic significance of the T61I variant remains unclear.

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DOI: 10.1002/art.39793

PMID: 27332769 [Indexed for MEDLINE]

1024. Arthritis Rheumatol. 2016 Nov;68(11):2795-2805. doi: 10.1002/art.39763.

# The Phenotype and Genotype of Mevalonate Kinase Deficiency: A Series of 114 Cases From the Eurofever Registry.

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**OBJECTIVE:** Mevalonate kinase deficiency (MKD) is a rare metabolic disease characterized by recurrent inflammatory episodes. This study was undertaken to describe the genotype, phenotype, and response to treatment in an international cohort of MKD patients.

**METHODS:** All MKD cases were extracted from the Eurofever registry (Executive Agency for Health and Consumers project no. 2007332), an international, multicenter registry that retrospectively collects data on children and adults with autoinflammatory diseases.

**RESULTS:** The study included 114 MKD patients. The median age at onset was 0.5 years. Patients had on average 12 episodes per year. Most patients had gastrointestinal symptoms (n = 112), mucocutaneous involvement (n = 99), lymphadenopathy (n = 102), or musculoskeletal symptoms (n = 89). Neurologic symptoms included headache (n = 43), cerebellar syndrome (n = 2), and mental retardation (n = 4). AA amyloidosis was noted in 5 patients, almost twice as many as expected from findings in previous cohorts. Macrophage activation syndrome occurred in 1 patient. Patients were generally well between attacks, but 10-20% of the patients had constitutional symptoms, such as fatigue, between fever episodes. Patients with p.V377I/p.I268T compound heterozygosity had AA amyloidosis significantly more often. Patients without a p.V377I mutation more often had severe musculoskeletal involvement. Treatment with nonsteroidal antiinflammatory drugs relieved symptoms. Steroids given during attacks, anakinra, and etanercept appeared to improve symptoms and could induce complete remission in patients with MKD.

**CONCLUSION:** We describe the clinical and genetic characteristics of 114 MKD patients, which is the largest cohort studied so far. The clinical manifestations confirm earlier reports. However, the prevalence of AA amyloidosis is far higher than expected.

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DOI: 10.1002/art.39763

PMID: 27213830 [Indexed for MEDLINE]

1025. Ann N Y Acad Sci. 2018 Apr;1417(1):23-34. doi: 10.1111/nyas.13280. Epub 2016 Oct 26.



The emergence of the IL-36 cytokine family as novel targets for inflammatory diseases.

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The recently discovered interleukin (IL)-36 family of cytokines form part of the broader IL-1 family and are emerging as important mediators of inflammatory disease. The IL-36 subfamily consists of three ligands-IL-36 $\alpha$ , IL-36 $\beta$ , and IL-36 $\gamma$ -and the natural antagonist IL-36Ra. The cytokines exert their effects through a specific IL-36 receptor consisting of IL-36R and IL-1RAcP chains. IL-36 cytokines can direct both innate and adaptive immune responses by acting on parenchymal, stromal, and specific immune cell subsets. In humans, inactivating mutations in the gene encoding the IL-36R antagonist, which lead to unregulated IL-36R signaling, lead to an autoinflammatory condition termed deficiency of the IL-36R antagonist, which primarily manifests as a severe form of pustular psoriasis. While such discoveries have prompted deeper mechanistic studies highlighting the important role of IL-36 cytokines in psoriatic skin inflammation, it is now evident that IL-36 cytokines can also play important roles in inflammatory disorders in other organs, such as the gastrointestinal tract and the lungs. Given these emerging roles, strategies to specifically target the expression and activity of the IL-36 family have the potential to uncover novel therapeutic approaches aimed at treating inflammatory diseases in humans.

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DOI: 10.1111/nyas.13280

PMID: 27783881

1026. Clin Exp Rheumatol. 2017 May-Jun;35 Suppl 104(2):9. Epub 2016 Oct 25.

Familial Mediterranean fever patients may have unmet needs for treatment of erysipelas-like erythema.

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PMID: 27782864 [Indexed for MEDLINE]

1027. Curr Opin Allergy Clin Immunol. 2016 Dec;16(6):523-529.

Anticytokine autoantibodies in infection and inflammation: an update.

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**PURPOSE OF REVIEW:** Concise overview of the field of anticytokine autoantibodies with a focus on recent developments.

**RECENT FINDINGS:** Advances in particular in the analysis of autoantibodies to IFN $\gamma$ , granulocyte-macrophage colony-stimulating factor (GM-CSF) and type I IFN are presented. The target epitope for anti-IFN $\gamma$  autoantibodies has been found to have high homology to a protein from *Aspergillus* suggesting molecular mimicry as a mechanism of breaking self-tolerance. A treatment strategy using a recombinant, epitope-depleted version of IFN $\gamma$  is suggested. Autoantibodies to GM-CSF are associated with disseminated *Cryptococcus* and *Nocardia* infections thus expanding the spectrum of associated diseases beyond pulmonary alveolar proteinosis.

Detailed analysis of anti-GM-CSF autoantibody clones derived from pulmonary alveolar proteinosis patients show evidence of high somatic mutation suggesting T cell-dependent affinity maturation; full GM-CSF neutralization is achieved by

synergistic binding of antibodies targeting various distinct noncross-reactive epitopes and leading to antigen sequestration and Fc-mediated clearance. Single mAbs in contrast may lead to higher GM-CSF bioavailability. Anti type I IFN-specific autoantibodies derived from autoimmune polyglandular syndrome type I patients are of extreme high affinity and negatively correlate with the incidence of type I diabetes and may be thus considered to be protective. Hypomorphic severe combined immune deficiency may be associated with complex anticytokine patterns and the emergence of anti type I IFN autoantibodies correlates with severe viral infection histories.

SUMMARY: Anticytokine autoantibodies may cause susceptibility to infections. In autoimmune/autoinflammatory conditions, anticytokine autoantibodies may be protective or promote disease.

DOI: 10.1097/ACI.0000000000000316

PMID: 27755185 [Indexed for MEDLINE]

1028. Eur J Intern Med. 2017 Apr;39:75-78. doi: 10.1016/j.ejim.2016.10.011. Epub 2016 Oct 22.

Behçet's disease and familial Mediterranean fever: Two sides of the same coin or just an association? A cross-sectional study.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is a genetic disease, characterized by attacks of fever, arthritis, serositis and pain. Behçet's disease (BD) is an inflammatory disorder with a genetic basis, characterized by oral and genital ulcers, uveitis, pustular erythematous cutaneous lesions, arthritis, central nervous system involvement and possible vascular manifestations such as venous thrombosis, arteritis and aneurysms.

**OBJECTIVES:** To investigate the association and actual differentiation between these two entities in a large-scale population-based study.

**METHODS:** Data for this study was collected from the databases of "Clalit Health Services", the largest state-mandated health service organization in Israel. All adult members diagnosed with BD were included (n=892) and as well as their age- and sex-matched controls (n=4444), creating a cross-sectional population-based study. Medical records of all subjects were analyzed for documented FMF. A logistic regression model was done to estimate how BD, age, gender, BMI, ethnicity and socioeconomic status contributed as risk factors for FMF.

**RESULTS:** The proportion of FMF in patients with BD increased compared with those reported in controls (5.83% and 0.23%, respectively,  $P<0.001$ ). This coexistence was prominent among both sex groups but was much stronger among female BD patients (females with OR of 177 and of 8.4 in males,  $P<0.001$ ). In a multivariate analysis, BD was identified as an independent risk factor for FMF (OR 25.16, 95% CI 13-53.3).

**CONCLUSION:** BD diagnosis was found to be independently associated with higher incidence of FMF, especially in females, people of Arab descent and BMI>30. Our data imply that understating the differentiation between FMF and BD is not evident and clear in a real-life population of patients with BD.

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DOI: 10.1016/j.ejim.2016.10.011

PMID: 27776949 [Indexed for MEDLINE]

1029. J Acupunct Meridian Stud. 2016 Oct;9(5):264-266. doi: 10.1016/j.jams.2016.07.003. Epub 2016 Sep 10.

Evaluation of the Effectiveness of Acupuncture Therapy by Verbal Pain Scale in Patients with Abdominal Pain of Familial Mediterranean Fever.

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In this study, we evaluated the effectiveness of acupuncture therapy based on Verbal Pain Scale (VPS) scores in familial Mediterranean fever (FMF) patients admitted to the emergency department with attacks of abdominal pain. This observational study was conducted in Erzurum Regional Training and Research Hospital between August 2014 and December 2014. Twenty patients admitted to the emergency department with FMF attacks were included in the study. Acupuncture therapy was applied to three points including LI4 (Hegu), ST25 (Tianshu), and Ren12 (Zhongwan). The VPS test was applied to the patients before and after the treatment. Average VPS scores were found to be  $8.45 \pm 0.75$  before the treatment and  $2.10 \pm 0.85$  after the treatment. The difference of the VPS scores before and after treatment was statistically significant ( $p=0.001$ ). To our knowledge, this is the first study evaluating the effectiveness of acupuncture therapy in the treatment of FMF attacks. Our results suggest that acupuncture therapy can be used as an effective treatment method in patients with FMF attacks.

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DOI: 10.1016/j.jams.2016.07.003

PMID: 27776765 [Indexed for MEDLINE]

1030. J Invest Dermatol. 2016 Nov;136(11):2251-2259. doi: 10.1016/j.jid.2016.06.618. Epub 2016 Jul 5.

AP1S3 Mutations Cause Skin Autoinflammation by Disrupting Keratinocyte Autophagy and Up-Regulating IL-36 Production.

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Prominent skin involvement is a defining characteristic of autoinflammatory disorders caused by abnormal IL-1 signaling. However, the pathways and cell types that drive cutaneous autoinflammatory features remain poorly understood. We sought to address this issue by investigating the pathogenesis of pustular

psoriasis, a model of autoinflammatory disorders with predominant cutaneous manifestations. We specifically characterized the impact of mutations affecting AP1S3, a disease gene previously identified by our group and validated here in a newly ascertained patient resource. We first showed that AP1S3 expression is distinctively elevated in keratinocytes. Because AP1S3 encodes a protein implicated in autophagosome formation, we next investigated the effects of gene silencing on this pathway. We found that AP1S3 knockout disrupts keratinocyte autophagy, causing abnormal accumulation of p62, an adaptor protein mediating NF- $\kappa$ B activation. We showed that as a consequence, AP1S3-deficient cells up-regulate IL-1 signaling and overexpress IL-36 $\alpha$ , a cytokine that is emerging as an important mediator of skin inflammation. These abnormal immune profiles were recapitulated by pharmacological inhibition of autophagy and verified in patient keratinocytes, where they were reversed by IL-36 blockade. These findings show that keratinocytes play a key role in skin autoinflammation and identify autophagy modulation of IL-36 signaling as a therapeutic target.

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DOI: 10.1016/j.jid.2016.06.618

PMCID: PMC5070969

PMID: 27388993 [Indexed for MEDLINE]

1031. J Eur Acad Dermatol Venereol. 2016 Nov;30(11):e129-e131. doi: 10.1111/jdv.13407. Epub 2015 Oct 7.

Familial Mediterranean fever with onset in the 70s showing various neutrophilic dermatosis.

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DOI: 10.1111/jdv.13407

PMID: 26448397 [Indexed for MEDLINE]

1032. Ann Neurol. 2016 Dec;80(6):939-945. doi: 10.1002/ana.24806. Epub 2016 Nov 14.

Febrile infection-related epilepsy syndrome treated with anakinra.

Kenney-Jung DL(1)(2), Vezzani A(3), Kahoud RJ(1)(2), LaFrance-Corey RG(1), Ho ML(4), Muskardin TW(2), Wirrell EC(1)(2), Howe CL(1)(5)(6), Payne ET(1)(2).

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Febrile infection-related epilepsy syndrome (FIRES) is a devastating epileptic encephalopathy with limited treatment options and an unclear etiology. Anakinra is a recombinant version of the human interleukin-1 receptor antagonist used to treat autoinflammatory disorders. This is the first report of anakinra for treatment of a child with super-refractory status epilepticus secondary to FIRES. Anakinra was well tolerated and effective. Cerebral spinal fluid analysis revealed elevated levels of proinflammatory cytokines before treatment that normalized on anakinra, suggesting a potential pathogenic role for neuroinflammation in FIRES. Further studies are required to assess anakinra efficacy and dosing, and to further delineate disease etiology. Ann Neurol 2016;80:939-945.

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DOI: 10.1002/ana.24806

PMCID: PMC5225882

PMID: 27770579 [Indexed for MEDLINE]

1033. Immunobiology. 2017 Mar;222(3):483-493. doi: 10.1016/j.imbio.2016.10.012. Epub 2016 Oct 17.

In vivo anti-inflammatory activities of novel cytokine IL-38 in Murphy Roths Large (MRL)/lpr mice.

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The newly named interleukin (IL)-36 subfamily member IL-38 has been shown to exert anti-inflammatory activity. However, the in vivo immunomodulatory activity of IL-38 was poorly investigated in systemic lupus erythematosus (SLE). We have investigated the expression of CD4+IL-17+ Th17, CD4+IFN- $\gamma$ + Th1 and CD3+CD4-CD8-

double negative (DN) T cells and the related immunopathological mechanisms in female MRL/lpr mice model of spontaneous lupus-like disease, with or without IL-38 treatment. Intravenous administration of murine recombinant IL-38 into MRL/lpr mice can ameliorate the lupus-like clinical symptoms including proteinuria, leukocyturia and skin lesions. A remission of histopathology characteristics of skin and nephritis was also observed upon IL-38 treatment. Accordingly, IL-38 receptor was expressed on the cell surface of both CD4<sup>+</sup> Th and CD19<sup>+</sup> B lymphocytes. The splenic Th17 and DN T lymphocytes, the average mRNA level of epigenetically regulated gene expression of Th17 cells, and serum concentrations of IL-17 and IL-22 were significantly decreased upon the treatment of IL-38 (all  $p < 0.05$ ). The in vivo results suggest that IL-38 can ameliorate skin inflammation and nephritis in SLE mice probably via suppressing the formation of inflammatory cytokines such as IL-17 and IL-22, and pathogenic DN T cells. These findings may provide a biochemical basis for further investigation of the therapeutic mechanisms of IL-38 for the treatment of autoimmune-mediated inflammation.

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DOI: 10.1016/j.imbio.2016.10.012

PMID: 27769564 [Indexed for MEDLINE]

1034. Int J Pediatr Endocrinol. 2016;2016:18. Epub 2016 Oct 10.

Case report: recurrent abdominal symptoms in a child with panhypopituitarism - there is always a differential.

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BACKGROUND: We report the case of a 6 year old boy suffering from adenoypophysis

aplasia as well as ectopic neurohypophysis and delayed diagnosis of familial Mediterranean fever (FMF).

CASE PRESENTATION: The boy was diagnosed with panhypopituitarism during the neonatal period and suffered from recurrent episodes during the following years suggesting infections. He also showed signs of adrenal insufficiency. Finally, at the age of 6 years, an additional diagnosis of familial Mediterranean fever (FMF) was clinically suspected and later confirmed by molecular analysis.

CONCLUSION: The clinical pictures of panhypopituitarism and FMF can be overlapping. It is imperative to take a detailed and accurate history in order to find the right diagnosis, particularly a precise family history. In conditions like FMF an early diagnosis is crucial, as initiation of treatment with colchicine is important to prevent long-term complications due to amyloid fibril deposition.

DOI: 10.1186/s13633-016-0037-3

PMCID: PMC5057440

PMID: 27766107

1035. Autoimmun Rev. 2017 Jan;16(1):34-47. doi: 10.1016/j.autrev.2016.09.023. Epub 2016 Sep 23.

Role of galectin-3 in autoimmune and non-autoimmune nephropathies.

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Galectins are evolutionary conserved  $\beta$ -galactoside binding proteins with a carbohydrate-recognition domain (CRD) of approximately 130 amino acids. In mammals, 15 members of the galectin family have been identified and classified into three subtypes according to CRD organization: prototype, tandem repeat-type and chimera-type galectins. Galectin-3 (gal-3) is the only chimera type galectin in vertebrates containing one CRD linked to an unusual long N-terminal domain

which displays non-lectin dependent activities. Although recent studies revealed unique, pleiotropic and context-dependent functions of gal-3 in both extracellular and intracellular space, gal-3 specific pathways and its ligands have not been clearly defined yet. In the kidney gal-3 is involved in later stages of nephrogenesis as well as in renal cell cancer. However, gal-3 has recently been associated with lupus glomerulonephritis, with Familial Mediterranean Fever-induced proteinuria and renal amyloidosis. Gal-3 has been studied in experimental acute kidney damage and in the subsequent regeneration phase as well as in several models of chronic kidney disease, including nephropathies induced by aging, ischemia, hypertension, diabetes, hyperlipidemia, unilateral ureteral obstruction and chronic allograft injury. Because of the pivotal role of gal-3 in the modulation of immune system, wound repair, fibrosis and tumorigenesis, it is not surprising that gal-3 can be an intriguing prognostic biomarker as well as a promising therapeutic target in a great variety of diseases, including chronic kidney disease, chronic heart failure and cardio-renal syndrome. This review summarizes the functions of gal-3 in kidney pathophysiology focusing on the reported role of gal-3 in autoimmune diseases.

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DOI: 10.1016/j.autrev.2016.09.023

PMID: 27666815 [Indexed for MEDLINE]

1036. Clin Exp Rheumatol. 2016 Sep-Oct;34(5 Suppl 101):S11-S16. Epub 2016 Oct 18.

Information technology in paediatric rheumatology.

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Information technology in paediatric rheumatology has seen several exciting developments in recent years. The new multidimensional questionnaires for juvenile idiopathic arthritis, juvenile dermatomyositis, and juvenile autoinflammatory diseases integrate all major parent- and child-reported outcomes (PCROs) used in these diseases into a single tool, and provide an effective guide to manage, document change in health, assess effectiveness of therapeutic interventions, and verify the parent and child satisfaction with illness outcome. The Pharmachild registry is aimed to gain information concerning the long-term effectiveness and safety of the medications currently used in juvenile idiopathic arthritis, particularly biologic agents, through collection of prospective data in a large, multinational sample of patients. Children and their parents are directly involved in the data collection by means of the regular completion of a digital version of a multidimensional questionnaire. The Patient-Reported Outcomes Measurement Information System (PROMIS) employs modern measurement science to advance assessment of PCROs, particularly HRQL, and offers multidimensional profile measures. The conceptual link of paediatric PROMIS with adult instruments facilitates harmonisation of assessments made in children and adolescents with those carried out in young adults in the process of transition of medical care. Development of electronic versions of questionnaires that permit their completion through smartphones or touch-screen devices will revolutionise information collection from parents and children, foster the regular collection of PCROs in routine care, and ultimately improve the quality of self-reported health data, and patient outcomes.

PMID: 27762188 [Indexed for MEDLINE]

1037. Clin Rheumatol. 2017 Feb;36(2):469-475. doi: 10.1007/s10067-016-3453-0. Epub 2016 Oct 20.

Myositis-specific autoantibodies and their association with malignancy in Italian patients with polymyositis and dermatomyositis.

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This study aims to characterize myositis-specific antibodies in a well-defined cohort of patients with idiopathic inflammatory myopathy and to determine their association with cancer. Sera from 40 patients with polymyositis, dermatomyositis, and controls were tested by protein and RNA immunoprecipitation to detect autoantibodies, and immunoprecipitation-Western blot was used for anti-MJ/NXP-2, anti-MDA5, and anti-TIF1 $\gamma$ / $\alpha$  identification. Medical records were re-evaluated with specific focus on cancer. Anti-MJ/NXP-2 and anti-TIF1 $\gamma$ / $\alpha$  were the most common antibodies in dermatomyositis. In six dermatomyositis cases, we found five solid forms of cancer and one Hodgkin's lymphoma in long-term remission. Among patients with cancer-associated dermatomyositis, three were positive for anti-TIF1 $\gamma$ / $\alpha$ , two for anti-Mi-2, and one for anti-MJ/NXP-2. The strongest positivity of anti-TIF1 $\gamma$  was seen in two active forms of cancer, and this antibody was either negative or positive at low titers in the absence of cancer or in the 7-year remission Hodgkin's lymphoma. Four out of twenty (20 %) patients with polymyositis had solid cancer, but no specific association with autoantibodies was identified; further, none of the four cases of antisynthetase syndrome had a history of cancer. No serum myositis-associated autoantibody was observed in control sera, resulting in positive predictive value 75 %, negative predictive value 78.5 %, sensitivity 50 %, specificity 92 %, and area under the ROC curve 0.7083 for the risk of paraneoplastic DM in anti-TIF1 $\gamma$ / $\alpha$  (+) patients. Myositis-specific autoantibodies can be identified thanks to the use of immunoprecipitation, and their association with cancer is particularly clear for anti-TIF1 $\gamma$ / $\alpha$  in dermatomyositis. This association should be evaluated in a prospective study by immunoprecipitation in clinical practice.

DOI: 10.1007/s10067-016-3453-0

PMID: 27761751 [Indexed for MEDLINE]

Secondary bladder amyloidosis with familial Mediterranean fever in a living donor kidney transplant recipient: a case report.

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**BACKGROUND:** Secondary bladder amyloidosis is an extremely rare disease, resulting from a chronic systematic inflammatory disorder associated with amyloid deposits.

Although uncommon in Japan, familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease characterized by recurrent episodes of fever of short duration and serositis and is frequently associated with systemic amyloidosis.

Here, we present a case of a Japanese patient complaining of fever and macroscopic hematuria after a living donor renal transplantation. Consequently, he was diagnosed with secondary bladder amyloidosis with FMF.

**CASE PRESENTATION:** A 64-year-old Japanese male received a living ABO-incompatible kidney transplant from his wife. The postoperative clinical course was normal, and the patient was discharged 21 days after the transplantation with a serum creatinine level of 0.78 mg/dl. The patient frequently complained of general fatigue and fever of unknown origin. Six months later, the patient presented with continuous general fatigue, macroscopic hematuria, and fever. Cystoscopic examination of the bladder showed an edematous region with bleeding, and a transurethral biopsy revealed amyloid deposits. His wife stated that the patient had a recurrent high fever since the age of 40 years and that his younger brother was suspected to have a familial autoinflammatory syndrome; thus, the patient was

also suspected to have a familial autoinflammatory syndrome. Based on his brother's medical history and the genetic tests, which showed a homozygous mutation (M694V/M694V) for the Mediterranean fever protein, he was diagnosed with FMF. Although colchicine treatment for FMF was planned, the patient had an untimely death due to heart failure. We re-evaluated the pathological findings of the various tissue biopsies obtained during the treatment after the renal transplantation. Immunohistochemistry revealed amyloid deposits in the bladder region, renal allograft, and myocardium and the condition was diagnosed as AA amyloidosis associated with FMF.

**CONCLUSION:** We presented a case of systemic amyloidosis with FMF, involving the bladder region, myocardium, and renal allograft, diagnosed after renal transplantation. Bladder amyloidosis should be considered in patients with macroscopic hematuria, particularly in the kidney transplant recipients with idiopathic chronic renal disease. Diagnosis of secondary bladder amyloidosis may result in the early detection of underlying diseases, which may contribute to patient prognosis.

DOI: 10.1186/s13104-016-2273-2

PMCID: PMC5070197

PMID: 27760547 [Indexed for MEDLINE]

1039. JAMA Dermatol. 2017 Jan 1;153(1):66-70. doi: 10.1001/jamadermatol.2016.3601.

Pityriasis Rubra Pilaris Type V as an Autoinflammatory Disease by CARD14 Mutations.

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**Importance:** We found CARD14 mutations (2 de novo novel mutations and another previously reported mutation) in 3 of 3 patients with pityriasis rubra pilaris (PRP) type V, but not in patients with PRP of other types. Our findings, combined with the published literature, suggest that type V PRP, both familial and sporadic, can be caused by CARD14 mutations. Detailed clinical observation revealed that all 3 patients displayed unique patchy macular brown hyperpigmentation.

**Objective:** To further determine how often patients with PRP have pathogenic mutations in CARD14 and to elucidate which clinical subtype of PRP is caused by CARD14 mutations.

**Design, Setting, and Participants:** We sequenced the entire coding regions of CARD14 in genomic DNA from patients with 5 clinical subtypes of PRP. The detailed clinical features were analyzed in all the patients. The pathogenicity of each mutation was evaluated by several computational predictions. PRP was classified into 6 subgroups, types I to VI, based on clinical criteria. We categorized all the patients with PRP into the clinical subtypes using the classic PRP classification; 22 cases of PRP with varying subtypes were studied.

**Main Outcomes and Measures:** The prevalence of CARD14 mutations in each subtype of

PRP was evaluated. Clinical features and characteristics of patients with PRP with CARD14 mutations were analyzed.

Results: Overall 22 patients with PRP were included in our study (12 men, 10 women; mean [SD] age, 26 [18] years). Among 3 patients with PRP type V, all were found to have CARD14 mutations: 2 de novo novel mutations (p.Cys127Ser and p.Gln136Leu), and another previously reported mutation (p.Gly117Ser). All were close to the reported pathogenic domains. In silico analysis of all 3 mutations suggested that they are functionally relevant to pathogenesis. All 3 patients displayed unique patchy macular brown hyperpigmentation additionally to other typical features of PRP. Patients with PRP type I and type IV, 1 patient each, had the rare variants in CARD14.

Conclusions and Relevance: Pityriasis rubra pilaris type V is a distinct variant of PRP that is caused by CARD14 mutations. In addition, a rare variant of CARD14 might also be implicated in the pathophysiology of other forms of PRP.

DOI: 10.1001/jamadermatol.2016.3601

PMID: 27760266 [Indexed for MEDLINE]

1040. Folia Med (Plovdiv). 2016 Sep 1;58(3):211-214. doi: 10.1515/folmed-2016-0025.

First Case of TNF-Receptor-Associated Autoinflammatory Syndrome (TRAPS) in Bulgaria.

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TRAPS is a very rare disease with an estimated prevalence of about one per million. We present a 53-year-old patient from Bulgaria. The clinical features of the disease are periodic fever, arthralgia, myalgia, rash, abdominal pain and hepatosplenomegaly. Laboratory studies yield leukocytosis, highly elevated levels of CRP, significantly high ESR. Secondary amyloidosis AA is determined. The genetic analysis found a heterozygous T>C nucleotide substance (c.250T>C) in exon 3 of TNFRSF1A gene which is associated with TRAPS (MIM\*191190). The presented

case of genetic changes and clinical manifestations in the autoinflammatory syndrome TRAPS due to a mutation in the gene encoding the receptor for tumour necrosis factor alpha (TNFRSF1A) is the first documented case of the disease reported in Bulgaria.

DOI: 10.1515/folmed-2016-0025

PMID: 27760004 [Indexed for MEDLINE]

1041. Curr Opin Rheumatol. 2017 Jan;29(1):4-11.

Vasculitis in the autoinflammatory diseases.

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**PURPOSE OF REVIEW:** This article addresses the prevalence and relationship between autoinflammatory diseases and vasculitis.

**RECENT FINDINGS:** Autoimmune diseases (AIDs) are a group of syndromes characterized by episodes of unprovoked inflammation due to dysregulation of the innate immune system. Despite the common occurrence of rashes and other skin lesions in these diseases, vasculitis is reported in only a few. On the other hand, neutrophilic dermatoses are more prevalent. Large vessel vasculitis is reported in patients with Behcet's and Blau's syndromes. Small and medium size vasculitides are reported in familial Mediterranean fever mainly as Henoch-Schonlein purpura and polyarteritis nodosa, respectively. It is rarely described in hyper IgD with periodic fever syndrome, cryopyrin associated periodic syndromes, TNF receptor-associated periodic syndrome, deficiency of interleukin-1 receptor antagonist and pyoderma gangrenosum and acne syndrome. In most AID where bones and skin are mainly involved (CRMO, Majeed syndrome, Cherubism and DITRA) - vasculitis has not been described at all. In AID small vessel vasculitis affects mainly the skin with no involvement of internal organs.

**SUMMARY:** In AID, neutrophilic dermatoses are more common and prominent than vasculitis. This may reflect a minor role for interleukin-1 in the pathogenesis of vasculitis. The rarity of vasculitis in AID suggests that in most reported cases its occurrence has been probably coincidental rather than being an integral

feature of the disease.

DOI: 10.1097/BOR.0000000000000347

PMID: 27755121 [Indexed for MEDLINE]

1042. Arthritis Rheumatol. 2017 Feb;69(2):253-256. doi: 10.1002/art.39961.

Editorial: It Just Takes One: Somatic Mosaicism in Autoinflammatory Disease.

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DOI: 10.1002/art.39961

PMCID: PMC5538189

PMID: 27748054

1043. Eur J Rheumatol. 2016 Sep;3(3):118-121. Epub 2016 Sep 1.

The role of MEFV mutations in the concurrent disorders observed in patients with familial Mediterranean fever.

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OBJECTIVE: This study aimed to investigate the frequency in which familial Mediterranean fever (FMF) coexists with other diseases and determine whether Mediterranean fever (MEFV) gene mutations are involved in such coexistence.

**MATERIAL AND METHODS:** In total, 142 consecutive patients with FMF investigated for MEFV mutation were enrolled in this study [Female: 87; Male: 55, mean age  $32\pm 12$  years (11-62)]. All the patients were questioned for the presence of concurrent disorders, and the medical records of these patients were revised retrospectively. A previous diagnosis of inflammatory disorder other than FMF was considered true if it met the relevant criteria. MEFV mutations were divided into 2 groups, namely M694V and its subgroup (homozygous or heterozygous) (Group I) and others (Group II). Compound heterozygosity for M694V mutation was included in Group II to form a homogeneous group for Group I. Group I and Group II were compared according to phenotypical features. The presence of MEFV mutation was investigated in exons 2, 3, 5, and 10 by the multiplex-PCR reverse hybridization method.

**RESULTS:** Concomitant disorders were found in 17 of 73 patients with FMF (23%) in Group I and 5 of 56 patients (8.9%) in Group II ( $p=0.04$ ). Concomitant disorders in Group I were as follows: 7 cases of amyloidosis, 2 cases of Behcet's disease (BD), 4 cases of ankylosing spondylitis (AS), 1 case of antiphospholipid syndrome, 1 case of Henoch-Schonlein purpura (HSP), 1 case of combination of psoriatic arthritis, HSP, and membranoproliferative glomerulonephritis, and 1 case of AS and amyloidosis. In Group II, the following disorders were found: 1 case of amyloidosis, 1 case of BD, 1 case of AS, 1 case of ulcerative colitis, and 1 case of vitiligo.

**CONCLUSION:** The presence of M694V mutation may predispose patients with FMF to developing other inflammatory disorders.

DOI: 10.5152/eurjrheum.2016.16012

PMCID: PMC5058450

PMID: 27733942

Conflict of interest statement: No conflict of interest was declared by the authors.

1044. Hosp Pharm. 2015 Nov;50(10):859-867. Epub 2015 Nov 19.

Beyond Gout: Colchicine Use in the Cardiovascular Patient.

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Colchicine is one of the oldest medications still in use today and is commonly used for the treatment of gout and familial Mediterranean fever. Its anti-inflammatory properties have raised the question of its utility in managing several cardiovascular diseases, including postoperative atrial fibrillation and pericarditis. This article will review the evidence for colchicine in these conditions and provide recommendations for use.

DOI: 10.1310/hpj5010-859

PMCID: PMC5057191

PMID: 27729672

1045. Intern Med. 2016;55(19):2889-2892. Epub 2016 Oct 1.

Familial Mediterranean Fever with Rheumatoid Arthritis Complicated by Pulmonary Paragonimiasis.

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A 42-year-old woman presented with an intermittent fever and chest and back pain, and an abnormal chest shadow was detected. She was diagnosed with paragonimiasis caused by *Paragonimus westermani*. Praziquantel therapy improved the abnormal chest shadow, but did not relieve her symptoms. She was also diagnosed with familial Mediterranean fever (FMF), and colchicine therapy resolved her symptoms. She subsequently developed arthralgia and morning stiffness in her hands. We also diagnosed the patient with rheumatoid arthritis (RA), and corticosteroid and salazosulfapyridine therapy improved her symptoms. The existence of paragonimiasis complicated the diagnosis of FMF. The coexistence of FMF and RA is

very rare, but does exist.

DOI: 10.2169/internalmedicine.55.6999

PMCID: PMC5088556

PMID: 27725555 [Indexed for MEDLINE]

1046. Swiss Med Wkly. 2016 Oct 10;146:w14352. doi: 10.4414/smw.2016.14352. eCollection 2016.

Neutrophil extracellular traps in health and disease.

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Polymorphonuclear neutrophil granulocytes are the first responders of the immune system to threats by invading microorganisms. In the traditional view, they combat the intruders by phagocytosis and externalisation of granules containing lytic and microbicidal factors. A dozen years ago, this concept was expanded by the observation that neutrophils may react to bacteria by extruding their nuclear chromosomal DNA with attached nuclear and cytoplasmic constituents to form extracellular reticular structures. Since they trapped and immobilised the microbes, they were designated neutrophil extracellular traps (NETs), and their ensuing cell death NETosis. Subsequently, the NETs were shown to act against different types of pathogens, including viruses, and an intricate interplay between the NETs and countermeasures of the pathogens became apparent. The NETs were also found to induce inflammatory responses in the host that contributed to the pathophysiology of autoinflammatory and even autoimmune diseases. Of special interest is the direct link that NETs provide to infections that may initiate and maintain inflammation without the participation of adaptive immunity. In contrast, neutrophils seem capable of activating B cells to produce antibodies relevant to autoimmunity independently of T cell help. Further results imply NETs in the occurrence of thrombosis of the veins and recently also in the generation

of arterial plaque. Data from the studies on the defence against pathogens and the pathophysiology of inflammation and thrombosis have started to drive applications to modulate NET formation and its effects and may provide opportunities to optimise current diagnostic and therapeutic concepts.

DOI: 10.4414/smw.2016.14352

PMID: 27723901 [Indexed for MEDLINE]

1047. Arthritis Care Res (Hoboken). 2017 Apr;69(4):578-586. doi: 10.1002/acr.23120. Epub 2017 Mar 3.

International Retrospective Chart Review of Treatment Patterns in Severe Familial Mediterranean Fever, Tumor Necrosis Factor Receptor-Associated Periodic Syndrome, and Mevalonate Kinase Deficiency/Hyperimmunoglobulinemia D Syndrome.

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**OBJECTIVE:** Periodic fever syndrome (PFS) conditions are characterized by recurrent attacks of fever and localized inflammation. This study examined the diagnostic pathway and treatments at tertiary centers for familial Mediterranean fever (FMF), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), and mevalonate kinase deficiency (MKD)/hyperimmunoglobulinemia D syndrome (HIDS).

**METHODS:** PFS specialists at medical centers in the US, the European Union, and the eastern Mediterranean participated in a retrospective chart review, providing de-identified data in an electronic case report form. Patients were treated between 2008 and 2012, with at least 1 year of followup; all had clinical and/or genetically proven disease and were on/eligible for biologic treatment.

**RESULTS:** A total of 134 patients were analyzed: FMF (n = 49), TRAPS (n = 47), and MKD/HIDS (n = 38). Fever was commonly reported as severe across all indications. Other frequently reported severe symptoms were serositis for FMF patients and elevated acute-phase reactants and gastrointestinal upset for TRAPS and MKD/HIDS. A long delay from disease onset to diagnosis was seen within TRAPS and MKD/HIDS (5.8 and 7.1 years, respectively) compared to a 1.8-year delay in FMF patients. An equal proportion of TRAPS patients first received anti-interleukin-1 (anti-IL-1) and anti-tumor necrosis factor (anti-TNF) biologic agents, whereas IL-1 blockade was the main choice for FMF patients resistant to colchicine and MKD/HIDS patients. For TRAPS patients, treatment with anakinra versus anti-TNF treatments as first biologic agent resulted in significantly higher clinical and biochemical responses ( $P = 0.03$  and  $P < 0.01$ , respectively). No significant differences in responses were observed between biologic agents among other cohorts.

**CONCLUSION:** Referral patterns and diagnostic delays highlight the need for greater awareness and improved diagnostics for PFS. This real-world treatment assessment supports the need for further refinement of treatment practices.

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DOI: 10.1002/acr.23120

PMID: 27723279 [Indexed for MEDLINE]

1048. Vnitr Lek. Fall 2016;62(9):713-727.

[Schnitzlers Syndrome Differential diagnostics, an overview of therapeutic options and description of 5 cases treated with anakinra].

[Article in Czech]

Adam Z, Šedivá A, Koukalová R, Řehák Z, Petrášová H, Szturz P, Adamová Z, Vetešníková E, Pour L, Krejčí M, Sandecká V, Pourová E, Čermáková Z, Ševčíková S, Král Z, Mayer J.

Schnitzlers syndrome is an acquired auto-inflammatory disease of still unclear origin. The Strasbourg criteria were adopted (non-infectious fever, chronic urticaria, changes in the bone structure, leukocytosis and higher values of inflammatory markers - CRP and presence of monoclonal immunoglobulin mostly of type IgM, very rarely of IgG) to establish this diagnosis. The first-choice therapy for this disease is the blocking of interleukin-1 effects. In practice, the interleukin-1 receptor antagonist, anakinra, is the most commonly used. Currently reports also appear of the use of other medicines blocking the effect of interleukin-1, namely canakinumab and rilonacept. We have been treating 5 patients with anakinra (108, 72, 33, 32 and 1 months) on a long-term basis. In all the patients, we commenced administration of anakinra in a dose of 100 mg once a day. As a result of 100 mg being administered once a day, all symptoms went away completely in 4 patients, while they receded by about 75 % in 1 patient, without disappearing completely. This patient needs an increased dose of 2 ampoules per day on the days of spontaneously intensified medical ailments. After one year of treatment it turned out for one of the four patients whose symptoms had completely disappeared when administered the 100mg daily dose, that he only needed the respective dose of anakinra at 48-hour intervals. However this patient does not tolerate further extension of the intervals between dose administrations. We have not recorded any adverse effects of anakinra in the course of the treatment, and no decline in the efficiency of anakinra has been observed: it acts as effectively now as it did at the beginning of the treatment. The text discusses the differential diagnostics of the Schnitzler syndrome. Key words: anakinra - auto-inflammatory diseases - canakinumab - fever of unknown origin - FUO - interleukin 1 - cryopyrin-associated autoinflammatory syndrome (CAPS) - monoclonal gammopathy - rilonacept - Schnitzlers Syndrome - Adult Stills disease.

PMID: 27715073 [Indexed for MEDLINE]

1049. JAAD Case Rep. 2016 Sep 28;2(5):366-368. eCollection 2016 Sep.

The role of interleukin-1 $\beta$  in pyoderma gangrenosum.

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DOI: 10.1016/j.jdcr.2016.07.007

PMCID: PMC5043387

PMID: 27709123

1050. Eur J Rheumatol. 2016 Jun;3(2):61-64. Epub 2016 Apr 5.

Relationship between endothelial dysfunction and microalbuminuria in familial Mediterranean fever.

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**OBJECTIVE:** The aim of our study is to investigate the relationship between microalbuminuria and flow-mediated dilatation in familial Mediterranean fever (FMF) patients.

**MATERIAL AND METHODS:** In our study, there were two groups consisting of 54 patients who were out of the attack period (43 of whom had no microalbuminuria and 11 of whom had microalbuminuria) and 40 healthy controls (M/F: 12/28).

**RESULTS:** There was no statistically difference between patient and control groups'age (25.06 $\pm$ 8.07, 22.89 $\pm$ 6.00 years, respectively). Flow-mediated dilatation (FMD) percentages were significantly different between the three groups (p=0.01). It was observed that there was a correlation between microalbuminuria and FMD percentage.

CONCLUSION: Endothelial dysfunction and renal damage occurred as a result of low-grade chronic inflammation. Microalbuminuria, which is the indicator of renal damage and endothelial dysfunction, and FMD show that endothelial functions can be used in the following of early detection of renal damage and endothelial functions in FMF patients.

DOI: 10.5152/eurjrheum.2016.15079

PMCID: PMC5042232

PMID: 27708973

1051. Ann Rheum Dis. 2017 Jun;76(6):942-947. doi: 10.1136/annrheumdis-2016-209686. Epub 2016 Oct 4.

Diagnostic criteria for cryopyrin-associated periodic syndrome (CAPS).

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Comment in

Ann Rheum Dis. 2016 Apr;76(4):e7.

Ann Rheum Dis. 2016 Apr;76(4):e8.

Cryopyrin-associated periodic syndrome (CAPS) is a rare, heterogeneous disease entity associated with NLRP3 gene mutations and increased interleukin-1 (IL-1) secretion. Early diagnosis and rapid initiation of IL-1 inhibition prevent organ damage. The aim of the study was to develop and validate diagnostic criteria for CAPS. An innovative process was followed including interdisciplinary team building, item generation: review of CAPS registries, systematic literature review, expert surveys, consensus conferences for item refinement, item reduction and weighting using 1000Minds decision software. Resulting CAPS criteria were tested in large cohorts of CAPS cases and controls using correspondence analysis. Diagnostic models were explored using sensitivity analyses. The international team included 16 experts. Systematic literature and registry review identified 33 CAPS-typical items; the consensus conferences reduced these to 14. 1000Minds exercises ranked variables based on importance for the diagnosis. Correspondence analysis determined variables consistently associated with the diagnosis of CAPS using 284 cases and 837 controls. Seven variables were significantly associated with CAPS ( $p < 0.001$ ). The best diagnosis model included: Raised inflammatory markers (C-reactive protein/serum amyloid A) plus  $\geq$ two of six CAPS-typical symptoms: urticaria-like rash, cold-triggered episodes, sensorineural hearing loss, musculoskeletal symptoms, chronic aseptic meningitis and skeletal abnormalities. Sensitivity was 81%, specificity 94%. It performed well for all

CAPS subtypes and regardless of NLRP3 mutation. The novel approach integrated traditional methods of evidence synthesis with expert consensus, web-based decision tools and innovative statistical methods and may serve as model for other rare diseases. These criteria will enable a rapid diagnosis for children and adults with CAPS.

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DOI: 10.1136/annrheumdis-2016-209686

PMID: 27707729 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: JBK-D performed clinical studies with Novartis and received speaking honoraria from Novartis and SOBI.

1052. Rev Clin Esp. 2017 Mar;217(2):108-116. doi: 10.1016/j.rce.2016.08.004. Epub 2016 Oct 1.

Autoinflammatory diseases in adults. Clinical characteristics and prognostic implications.

[Article in English, Spanish]

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Autoinflammatory diseases are clinical conditions with inflammatory manifestations that present in a periodic or persistent manner and are caused by acquired or hereditary disorders of the innate immune response. In general, these diseases are more common in childhood, but cases have been reported in adults and

are therefore important for all specialists. There are few references on these diseases in adults due to their low prevalence and underdiagnosis. The aim of this study is to review the scientific literature on these disorders to systematise their clinical, prognostic and treatment response characteristics in adults.

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DOI: 10.1016/j.rce.2016.08.004

PMID: 27702442

1053. *Pediatr Dermatol*. 2016 Nov;33(6):602-614. doi: 10.1111/pde.12984. Epub 2016 Oct 4.

Newly Described Autoinflammatory Diseases in Pediatric Dermatology.

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Specific gene mutations leading to dysregulation of innate immune response produce the expanding spectrum of monogenic autoinflammatory diseases (AIDs). They are characterized by seemingly unprovoked, recurrent episodes of systemic inflammation in which a myriad of manifestations usually affect skin. Novel genetic technologies have led to the discovery of new AIDs and phenotypes that were not previously clinically described. Consequently the number of AIDs is continuously growing and their recognition and the disclosure of their pathophysiology will prompt early diagnosis and targeted treatment of affected patients. The objective of the present work is to review those newly described AIDs with prominent dermatologic manifestations that may constitute a major criterion for their diagnosis.

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DOI: 10.1111/pde.12984

1054. JCI Insight. 2016 May 5;1(6):e86336.

Anakinra as a diagnostic challenge and treatment option for systemic autoinflammatory disorders of undefined etiology.

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**BACKGROUND:** Some adult patients presenting with unexplained pyrexia, serositis, skin rashes, arthralgia, myalgia, and other symptoms commonly found in autoinflammatory disorders may not fit a specific diagnosis, either because their clinical phenotype is nondiagnostic or genetic tests are negative. We used the term undifferentiated systemic autoinflammatory disorder (uSAID) to describe such cases. Given that well-defined autoinflammatory diseases show responses to IL-1 blockade, we evaluated whether anakinra was useful for both diagnosing and treating uSAID patients.

**METHODS:** We performed a retrospective analysis of consecutive patients presenting with uSAID between 2012-2015 who were treated with the recombinant IL-1 receptor antagonist anakinra. uSAID was diagnosed after excluding malignancy, infection, and pathogenic mutations in known hereditary fever syndromes (HFS) genes and where clinical criteria for adult onset Still's disease (AOSD) were not met.

**RESULTS:** A total of 11 patients presented with uSAID (5 males and 6 females),



with a mean time to diagnosis of 3.5 years (1-8 years). Patients were unresponsive or only partially controlled on disease-modifying antirheumatic drug (DMARD)/steroid treatment. Anakinra controlled symptoms within 4-6 weeks of starting treatment in 9 of 11 cases. Two patients discontinued therapy - one due to incomplete response and another due to severe injection-site reactions.

**CONCLUSION:** This retrospective case series demonstrates that the spectrum of poorly defined autoinflammatory disorders that show responsiveness to anakinra is considerable. Anakinra seems a viable treatment option for these patients, who are unresponsive to standard steroid/DMARD treatments. Moreover, given the mechanisms of action, response to anakinra implicates underlying IL-1 dysregulation in the disease pathogenesis of responding uSAIDs patients.

DOI: 10.1172/jci.insight.86336

PMCID: PMC5033915

PMID: 27699261 [Indexed for MEDLINE]

1055. Clin Med (Lond). 2016 Oct;16(5):488-490.

Lesson of the month 1: Autoinflammatory syndromes - an unusual cause of pyrexia of unknown origin.

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Autoinflammatory diseases are disorders of innate immunity and are characterised by recurring and unprovoked episodes of inflammation. We present a case of episodic pyrexia, associated with a significant inflammatory response, in a young man in whom the cause had remained unexplained since infancy. He was eventually diagnosed with hyperimmunoglobulinaemia D syndrome (HIDS); one of the autoinflammatory syndromes.

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DOI: 10.7861/clinmedicine.16-5-488  
PMID: 27697817 [Indexed for MEDLINE]

1056. J Immunol. 2016 Nov 1;197(9):3481-3489. Epub 2016 Sep 30.

Inositol-Triphosphate 3-Kinase C Mediates Inflammasome Activation and Treatment Response in Kawasaki Disease.

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Comment in

Nat Rev Rheumatol. 2016 Dec;12 (12 ):693.

Kawasaki disease (KD) is a multisystem vasculitis that predominantly targets the coronary arteries in children. Phenotypic similarities between KD and recurrent fever syndromes point to the potential role of inflammasome activation in KD. Mutations in NLRP3 are associated with recurrent fever/autoinflammatory syndromes. We show that the KD-associated genetic polymorphism in inositol-triphosphate 3-kinase C (ITPKC) (rs28493229) has important functional consequences, governing ITPKC protein levels and thereby intracellular calcium,

which in turn regulates NLRP3 expression and production of IL-1 $\beta$  and IL-18. Analysis of transcript abundance, protein levels, and cellular response profiles from matched, serial biospecimens from a cohort of genotyped KD subjects points to the critical role of ITPKC in mediating NLRP3 inflammasome activation. Treatment failure in those with the high-risk ITPKC genotype was associated with the highest basal and stimulated intracellular calcium levels and with increased cellular production of IL-1 $\beta$  and IL-18 and higher circulating levels of both cytokines. Mechanistic studies using Itpkc-deficient mice in a disease model support the genomic, cellular, and clinical findings in affected children. Our findings provide the mechanism behind the observed efficacy of rescue therapy with IL-1 blockade in recalcitrant KD, and we identify that regulation of calcium mobilization is fundamental to the underlying immunobiology in KD.

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DOI: 10.4049/jimmunol.1600388

PMID: 27694492 [Indexed for MEDLINE]

1057. Clin Rheumatol. 2016 Nov;35(11):2631-2638. Epub 2016 Sep 30.

Different roles of TNF inhibitors in acute anterior uveitis associated with ankylosing spondylitis: state of the art.

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The purpose of the present review was to provide a comprehensive picture of the efficacy of the different tumor necrosis factor (TNF)- $\alpha$  inhibiting agents in the treatment of acute anterior uveitis (AAU), the most common extra-articular

manifestation of ankylosing spondylitis (AS). AS related, AAU may lead to severe visual impairment, due to frequent flare recurrences, anterior, and posterior segment complications and traditional treatment side effects. Considerably higher levels of tumor necrosis factor (TNF) have been assessed in the aqueous humor and inflamed joints of patients with AS. Anti-TNF drugs have shown efficacy in preventing relapses of rheumatological manifestations of spondyloarthropathies. Several studies have underlined the sustained efficacy of the monoclonal anti-TNF antibodies also in reducing the recurrence of anterior chamber flares in patients with AS-related AAU. On the other hand, retrospective studies and observational reports have indicated lower effectiveness and some paradoxical occurrence of uveitis following treatment with the soluble receptor agent etanercept. Growing evidence suggests that a prophylactic strategy could be advocated in subjects with frequent and recalcitrant attacks of AS-AAU. In this regard, the administration of monoclonal anti-TNF antibodies such as adalimumab (ADA) has been shown to significantly reduce the rate of AAU recurrences. Indeed, during ADA treatment about 90 % of patients have shown to remain completely free of attacks for the entire follow-up period, in most studies. Further studies are needed to confirm the long-term efficacy of TNF inhibitors in AS related AAU and also their role in preventing ocular complications and visual impairment.

DOI: 10.1007/s10067-016-3426-3

PMID: 27686662 [Indexed for MEDLINE]

1058. Semin Immunol. 2016 Oct;28(5):425-430. doi: 10.1016/j.smim.2016.09.002. Epub 2016 Sep 27.

Immunometabolic circuits in trained immunity.

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The classical view that only adaptive immunity can build immunological memory has recently been challenged. Both in organisms lacking adaptive immunity as well as in mammals, the innate immune system can adapt to mount an increased resistance to reinfection, a de facto innate immune memory termed trained immunity. Recent studies have revealed that rewiring of cellular metabolism induced by different immunological signals is a crucial step for determining the epigenetic changes underlying trained immunity. Processes such as a shift of glucose metabolism from oxidative phosphorylation to aerobic glycolysis, increased glutamine metabolism and cholesterol synthesis, play a crucial role in these processes. The discovery of trained immunity opens the door for the design of novel generations of vaccines, for new therapeutic strategies for the treatment of immune deficiency states, and for modulation of exaggerated inflammation in autoinflammatory diseases.

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DOI: 10.1016/j.smim.2016.09.002

PMID: 27686054 [Indexed for MEDLINE]

1059. Cytometry B Clin Cytom. 2017 Nov;92(6):541-549. doi: 10.1002/cyto.b.21484. Epub 2017 Feb 10.

Image analysis of neutrophil nuclear morphology: Learning about phenotypic range and its reliable analysis from patients with pelger-Huët-anomaly and treated with colchicine.

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The nuclear morphology of neutrophils depends on different endogenous and exogenous factors, which can lead to hypo- or hypersegmentation of the normally 2-4 segmented nucleus. Hyposegmentation can be due to mutations in the LBR-gene (Pelger-Huët-Anomaly) or can be induced, for example, by colchicine treatment. The range of this phenotypic variation is known as "norm of reaction," which can be of major relevance for clinical diagnosis and therapeutic intervention. In this project, we studied the norm of reaction in 26 subjects with 0-3 wild type LBR alleles. In addition, the phenotypic variation was analyzed in 3 patients with Familial Mediterranean Fever (FMF), before and after colchicine treatment. We measured the phenotype nuclear segmentation of neutrophils based on two conventional qualitative methods, the "rule of threads" and the "rule of thirds." In addition, we tested a morphometric quantitative approach, the "circularity index." The circularity index was superior in cases with hyposegmentation; the rule of thirds with respect to hypersegmentation. Approximately 65% of the observed phenotypic variance was explainable by the number of LBR wild type alleles. The gene-dosage effect followed a non-additive, hysteresis-like characteristic with lower and upper plateaus. Colchicine treatment had a clear, although minor phenotypic effect compared to the number of LBR wild type genes or the mutation type. Thus, the nuclear morphology of granulocytes and its norm of reaction can be regarded as an excellent model both for detailing the interplay between endogenous and exogenous factors and for clinical diagnostic purposes. © 2016 International Clinical Cytometry Society.

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DOI: 10.1002/cyto.b.21484

PMID: 27684937 [Indexed for MEDLINE]

1060. J Pathol. 2017 Jan;241(2):123-139. doi: 10.1002/path.4812. Epub 2016 Nov 11.

The burgeoning field of innate immune-mediated disease and autoinflammation.

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Immune-mediated autoinflammatory diseases are occupying an increasingly prominent position among the pantheon of debilitating conditions that afflict humankind.

This review focuses on some of the key developments that have occurred since the original description of autoinflammatory disease in 1999, and focuses on underlying mechanisms that trigger autoinflammation. The monogenic autoinflammatory disease range has expanded considerably during that time, and now includes a broad spectrum of disorders, including relatively common conditions such as cystic fibrosis and subsets of systemic lupus erythematosus. The innate immune system also plays a key role in the pathogenesis of complex inflammatory disorders. We have proposed a new nomenclature to accommodate the rapidly increasing number of monogenic disorders, which predispose to either autoinflammation or autoimmunity or, indeed, combinations of both. This new terminology also encompasses a wide spectrum of genetically determined autoinflammatory diseases, with variable clinical manifestations of immunodeficiency and immune dysregulation/autoimmunity. We also explore some of the ramifications of the breakthrough discovery of the physiological role of pyrin and the search for identifiable factors that may serve to trigger attacks of autoinflammation. The evidence that pyrin, as part of the pyrin inflammasome, acts as a sensor of different inactivating bacterial modification Rho GTPases, rather than interacting directly with these microbial products, sets the stage for a better understanding of the role of microorganisms and infections in the autoinflammatory disorders. Finally, we discuss some of the triggers of autoinflammation as well as potential therapeutic interventions aimed at enhancing autophagy and proteasome degradation pathways. Copyright © 2016 Pathological Society of Great Britain and Ireland. Published by John Wiley & Sons, Ltd.

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DOI: 10.1002/path.4812

1061. BMJ Case Rep. 2016 Sep 28;2016. pii: bcr2016216922. doi: 10.1136/bcr-2016-216922.

XIAP deficiency and MEFV variants resulting in an autoinflammatory lymphoproliferative syndrome.

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A 16-year-old boy of Caucasian ethnicity was evaluated for recurrent febrile episodes occurring during most of his life without establishment of any microbial aetiology. During febrile episodes he developed extensive splenomegaly, lymphadenopathy, anaemia, severe abdominal pain and general malaise. Lymph node biopsies demonstrated inflammation and sinus histiocytosis but no malignancy or granuloma. The patient underwent seroconversion for Epstein-Barr virus (EBV) infection during the hospitalisation. Genetic testing identified a hemizygous frameshift mutation in the X linked inhibitor of apoptosis (XIAP)-gene as well as variants in the MEFV gene indicating Familial Mediterranean Fever (FMF). XIAP expression was markedly reduced in the patient, while a functional assay assessing tumour necrosis factor (TNF) $\alpha$  production of monocytes in response to NOD2 stimulation displayed reduced activity. We suggest that the heterozygous MEFV variants and the hemizygous XIAP variant in combination triggered the prolonged and pathological inflammatory response to EBV infection.

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DOI: 10.1136/bcr-2016-216922

PMCID: PMC5051366

PMID: 27681353



1062. Clin Rheumatol. 2017 Feb;36(2):421-425. doi: 10.1007/s10067-016-3421-8. Epub 2016 Sep 27.

Discontinuing colchicine in symptomatic carriers for MEFV (Mediterranean FeVer) variants.

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Familial Mediterranean fever (FMF) is inherited autosomal recessively; however, heterozygotes may express FMF phenotype. We aimed to define the characteristics of FMF patients heterozygous for MEFV (Mediterranean FeVer) mutations in whom colchicine was stopped after a period of treatment, with close follow-up. We reviewed the charts of 182 children who were heterozygous for MEFV variants. We excluded the patients (n = 34) heterozygous for MEFV variants of unknown significance and patients with typical periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome (n = 2). All patients were followed up with their routine analysis and serum amyloid A levels every 6 months while on colchicine treatment and every 3-6 months thereafter. MEFV gene variant analysis was performed with Sanger sequencing. Twenty-two out of 146 heterozygotes initially had FMF phenotype, but colchicine was discontinued after a treatment period. The most common MEFV variant was M694V (86.3 %). The median age at diagnosis/initiation of colchicine was 76 (24-144) months. The median duration of colchicine treatment was 36 (24-110) months. The median age at colchicine cessation was 120 (55-172) months. At the time of colchicine cessation, the median attack- and inflammation-free period was 27 (24-84) months. The median follow-up after colchicine cessation was 22.5 (6-102) months. We re-started colchicine in only two patients because of recurrence of symptoms. Individuals with one mutation only can display FMF phenotype and require colchicine for the clinical and laboratory inflammation. However, in some of these patients, colchicine may be discontinued with very careful follow-up.

DOI: 10.1007/s10067-016-3421-8

PMID: 27679472 [Indexed for MEDLINE]

1063. Clin Rheumatol. 2017 Feb;36(2):451-455. doi: 10.1007/s10067-016-3417-4. Epub 2016 Sep 27.

Adalimumab effectiveness in Behçet's disease: short and long-term data from a multicenter retrospective observational study.

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Our aim was to evaluate the effectiveness of adalimumab (ADA) during a 24-month study period in patients affected with Behçet's disease (BD). Clinical and therapeutic data from 100 consecutive BD patients treated with ADA were retrospectively collected and statistically analyzed. At 12-week follow-up, ADA induced clinical efficacy in 81 patients, with a mean time to response of  $7.63 \pm 3.43$  weeks; 25 (30.9 %) patients underwent a disease relapse after  $22.17 \pm 1.57$  months, but treatment adjustments allowed a recovery of efficacy in 11 cases. At 24-month follow-up, 67/100 patients were still on ADA therapy despite concomitant treatments. No differences were identified between ADA

monotherapy and co-treatment with DMARDs about efficacy ( $p = 0.09$ ), time to response ( $p = 0.61$ ), relapses ( $p = 0.36$ ), and ADA discontinuation ( $p = 0.40$ ). No differences existed in patients switched from other tumor necrosis factor (TNF)- $\alpha$  inhibitors about efficacy at 12 weeks ( $p = 0.13$ ) and rapidity of response ( $p = 0.93$ ) while relapses ( $p = 0.01$ ) and ADA discontinuation at 24 months ( $p = 0.001$ ) were significantly more common. Adverse events occurred in 10 patients. ADA confirmed its effectiveness in BD. Combination therapy with DMARDs seems not significantly superior to monotherapy. Frequency and time to response for ADA was not conditioned by a previous lack or loss of efficacy to other TNF- $\alpha$  inhibitors, but long-term loss of efficacy seemed more likely in patients switched from other anti-TNF agents.

DOI: 10.1007/s10067-016-3417-4

PMID: 27679471 [Indexed for MEDLINE]

1064. J Mol Med (Berl). 2016 Oct;94(10):1111-1127. Epub 2016 Sep 27.

Insights from Mendelian Interferonopathies: Comparison of CANDLE, SAVI with AGS, Monogenic Lupus.

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Autoinflammatory disorders are sterile inflammatory conditions characterized by episodes of early-onset fever and disease-specific patterns of organ inflammation. Recently, the discoveries of monogenic disorders with strong type I interferon (IFN) signatures caused by mutations in proteasome degradation and

cytoplasmic RNA and DNA sensing pathways suggest a pathogenic role of IFNs in causing autoinflammatory phenotypes. The IFN response gene signature (IGS) has been associated with systemic lupus erythematosus (SLE) and other autoimmune diseases. In this review, we compare the clinical presentations and pathogenesis of two IFN-mediated autoinflammatory diseases, CANDLE and SAVI, with Aicardi Goutières syndrome (AGS) and monogenic forms of SLE (monoSLE) caused by loss-of-function mutations in complement 1 (C1q) or the DNA nucleases, DNASE1 and DNASE1L3. We outline differences in intracellular signaling pathways that fuel a pathologic type I IFN amplification cycle. While IFN amplification is caused by predominantly innate immune cell dysfunction in SAVI, CANDLE, and AGS, autoantibodies to modified RNA and DNA antigens interact with tissues and immune cells including neutrophils and contribute to IFN upregulation in some SLE patients including monoSLE, thus justifying a grouping of "autoinflammatory" and "autoimmune" interferonopathies. Understanding of the differences in the cellular sources and signaling pathways will guide new drug development and the use of emerging targeted therapies.

DOI: 10.1007/s00109-016-1465-5

PMCID: PMC5094849

PMID: 27678529 [Indexed for MEDLINE]

1065. J Dermatol. 2017 Aug;44(8):981-982. doi: 10.1111/1346-8138.13619. Epub 2016 Sep 26.

Rapid desensitization to anakinra-related delayed reaction: Need for a standardized protocol.

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DOI: 10.1111/1346-8138.13619

PMID: 27667671

1066. BMJ Case Rep. 2016 Sep 22;2016. pii: bcr2016216941. doi: 10.1136/bcr-2016-216941.

Severe liver involvement in two patients with long-term history of fever:  
remember familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is characterised by recurrent, self-limited fever attacks and serositis. Severe liver involvement has rarely been reported. We present two FMF cases of a 55-year-old man and a 20-year-old woman in whom the prevailing manifestations were recurrent unexplained episodes of anicteric hepatitis (man) and recurrent severe jaundice (woman). A long-term history of recurrent self-limited episodes of fever was also claimed in both. After exclusion of infectious, malignant, autoimmune, and liver and biliary diseases, a diagnosis of FMF as confirmed by molecular analysis was established. The patients started colchicine 1 mg/day with immediate resolution of symptoms. During follow-up, no new episodes of fever and exacerbation of liver biochemical parameters have been recorded for 5 and 1 years. Physicians must keep FMF in mind in patients with recurrent episodes of unexplained severe liver impairment and fever and especially in regions like Mediterranean basin where hereditary periodic fever syndromes are common.

2016 BMJ Publishing Group Ltd.

DOI: 10.1136/bcr-2016-216941

1067. Rev Med Interne. 2018 Apr;39(4):265-270. doi: 10.1016/j.revmed.2016.08.019. Epub 2016 Sep 19.

[Mevalonate kinase deficiency in 2016].

[Article in French]

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Mevalonate kinase deficiency is a rare, autosomal recessive, auto-inflammatory disease. This results from mutations in the gene MVK coding for the enzyme mevalonate kinase. This enzyme is involved in cholesterol and isoprenoids synthesis. Depending partially of the residual activity of the mevalonate kinase, the clinical spectrum realizes a continuum which extends from the mild phenotype of the hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) to a lethal form of mevalonic aciduria. The HIDS is characterized by recurrent episodes of fever with an intense inflammatory syndrome, accompanied with lymphadenopathy, abdominal pain, diarrhea, arthralgia, hepatomegaly, splenomegaly and skin rash. The first attack more frequently takes place in the first year of life, even

during the neonatal period, where it can be confused with a maternofetal infection. There is furthermore in mevalonate aciduria a psychomotor retardation, a failure to thrive, a cerebellar ataxia, a dysmorphic syndrome and a reduction of the visual acuity. The diagnosis is based on the mevalonic aciduria during febrile attack. Genetics confirm the diagnosis in more than 80 % of the cases. The dosage of IgD, low sensitive and specific, has no interest. There is no reference treatment. The less severe forms can be treated by non-steroidal anti-inflammatory drugs or steroids during febrile attacks. The most severe patients can be treated by biotherapy: antagonists of IL-1, TNF- $\alpha$  and IL-6.

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DOI: 10.1016/j.revmed.2016.08.019  
PMID: 27659743 [Indexed for MEDLINE]

1068. J Genet. 2016 Sep;95(3):667-74.

Prevalence of common MEFV mutations and carrier frequencies in a large cohort of Iranian populations.

Beheshtian M(1), Izadi N, Kriegshauser G, Kahrizi K, Mehr EP, Rostami M, Hosseini M, Azad M, Montajabiniat M, Kariminejad A, Nemeth S, Oberkanins C, Najmabadi H.

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Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disorder caused by mutations in the MEFV gene. The disease is especially common among Armenian, Turkish, Jewish and Middle East Arab populations. To identify the frequency and the spectrum of common MEFV mutations in different Iranian populations, we investigated a cohort of 208 unselected asymptomatic individuals and 743 FMF patients. Nine hundred and fifty-one samples were analysed for the presence of 12 MEFV mutations by PCR and reverse-hybridization (FMF StripAssay, ViennaLab, Vienna, Austria). Confirmatory dideoxy sequencing of all MEFV gene exons was performed for 39 patients. Fifty-seven (27.4%) healthy individual

carried mutant MEFV alleles. Three hundred and ninety-one (52.6%) FMF patients were found positive for either one (172/743; 23.1%), two or three MEFV mutations. Using dideoxy sequencing, three novel variants, A66P, R202W and H300Q, could be identified. Our analysis revealed an allele frequency and carrier rate of 15.6 and 27.4%, respectively, among healthy Iranians. Still moderate compared to neighbouring Armenia, but higher than in Turkey or Iraq, these data suggest that FMF is remarkably common among Iranian populations. E148Q was most frequent in the group of healthy individuals, whereas M694V was the most common mutation among FMF patients, thereby corroborating previous studies on MEFV mutational spectra in the Middle East. Accordingly, MEFV mutations are frequent in healthy Iranian individuals across different ethnic groups. Based on this finding, the awareness for FMF and the implementation of augmented carrier screening programmes considering the multiethnic nature of the Iranian population should be promoted.

PMID: 27659338 [Indexed for MEDLINE]

1069. Neuropediatrics. 2017 Apr;48(2):79-85. doi: 10.1055/s-0036-1593374. Epub 2016 Sep 22.

Neurological Manifestations in Familial Mediterranean Fever: Results of 22 Children from a Reference Center in Kayseri, an Urban Area in Central Anatolia, Turkey.

Canpolat M(1), Gumus H(1), Gunduz Z(2), Dusunsel R(2), Kumandas S(1), Bayram AK(1), Yel S(3), Poyrazoglu HG(1), Yilmaz K(3), Doganay S(4), Yikilmaz A(4), Dundar M(5), Per H(1).

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Erratum in

Neuropediatrics. 2017 Oct;48(5):402.

**Background** Familial Mediterranean fever (FMF) is an inherited inflammatory disorder characterized by attacks of fever with polyserositis. **Objective** The purpose of this study was to evaluate pediatric patients with FMF who had central nervous system (CNS) findings. **Materials and Methods** Our medical records database for 2003 to 2014 was screened retrospectively. In total, 104 patients with FMF were identified, 22 of whom had undergone neurological examination for CNS symptoms. **Results** Neurological findings included headache in 16 patients (72.7%), epilepsy in 6 patients (27.3%), pseudotumor cerebri in 2 patients (9.1%), tremor in 2 patients (9.1%), and multiple sclerosis in 1 patient (4.5%). The most common MEFV gene mutation was homozygous M694V (40.9%). **Conclusions** Patients with FMF can present with various CNS manifestations. Further studies that include large populations are needed to elucidate the neurological manifestations of FMF.

Georg Thieme Verlag KG Stuttgart · New York.

DOI: 10.1055/s-0036-1593374

PMID: 27656843 [Indexed for MEDLINE]

1070. Evid Based Complement Alternat Med. 2016;2016:6356871. doi: 10.1155/2016/6356871.  
Epub 2016 Aug 30.

Xianfanghuomingyin, a Chinese Compound Medicine, Modulates the Proliferation and Differentiation of T Lymphocyte in a Collagen-Induced Arthritis Mouse Model.

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In traditional Chinese medicine (TCM), xianfanghuomingyin (XFHM) is used to treat autoimmune diseases, including rheumatoid arthritis (RA). Here, we studied the mechanisms underlying its treatment effects, especially its anti-inflammatory effects in a collagen-induced arthritis (CIA) mouse model. We found that cartilage destruction and pannus formation were alleviated by treatment with XFHM. The abnormal differentiation of Th1 and Th17 cells was downregulated significantly by XFHM, and Th2 and Treg cells were upregulated. Moreover, the expression levels of specific cytokines and transcription factors related to Th1 cells (interferon  $\gamma$  [IFN $\gamma$ ], T-bet) and Th17 cells (interleukin- [IL-] 17) and the nuclear receptor retinoic acid receptor-related orphan receptor-gamma (ROR $\gamma$ ) were downregulated. Serum IL-4 and GATA-3, which contribute to Th2 cells differentiation, increased significantly after XFHM administration. These results indicate that XFHM can restore the balance of T lymphocytes and reestablish the immunological tolerance to inhibit autoinflammatory disorder of RA. Taken together, XFHM can be used as a complementary or alternative traditional medicine to treat RA.

DOI: 10.1155/2016/6356871

PMCID: PMC5021507

PMID: 27656238

1071. J Am Vet Med Assoc. 2016 Oct 1;249(7):755-7. doi: 10.2460/javma.249.7.755.

Pathology in Practice.

Philips BH, Loria KO, Sirivelu MP, Jaber SM, Allen-Worthington KH, Veeder CL, Brice AK.

DOI: 10.2460/javma.249.7.755

PMID: 27654161 [Indexed for MEDLINE]

1072. J Paediatr Child Health. 2016 Sep;52(9):865-71. doi: 10.1111/jpc.13326.

Periodic fevers and autoinflammatory syndromes in childhood.

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Recurrent fever is a common presentation in paediatric practice and can be caused by a wide variety of diseases including autoinflammatory conditions. The innate immune system plays an essential role in the 'first line' response to infection through mediation of inflammatory responses. Inflammasomes are part of the regulatory process for this system and result in the production of the powerful pro-inflammatory cytokine interleukin-1 $\beta$ . Dysregulation of inflammasomes, and Interleukin 1 production, contributes to the pathogenesis of autoinflammatory diseases. This review focuses on described periodic fever syndromes (PFS) which are now collectively referred to as autoinflammatory syndromes. Conditions discussed include periodic fever aphthous stomatitis pharyngitis and cervical adenopathy, familial Mediterranean fever, tumour necrosis factor receptor-associated periodic syndromes, hyperimmunoglobulinaemia D and the cryopyrin-associated periodic syndromes. Presenting features, complications, diagnostic and treatment approaches for these conditions are discussed. Nonetheless, as most of these conditions are rare and may have significant long-term complications, it is recommended that they be managed in consultations with a physician experienced in managing PFS.

© 2016 Paediatrics and Child Health Division (The Royal Australasian College of Physicians).

DOI: 10.1111/jpc.13326

1073. J Clin Pathol. 2017 Jan;70(1):1-8. doi: 10.1136/jclinpath-2016-203810. Epub 2016 Sep 19.

Autoinflammatory diseases: update on classification diagnosis and management.

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The spectrum of systemic autoinflammatory disorders broadens continually. In part, this is due to the more widespread application of massive parallel sequencing, helping with novel gene discovery in this and other areas of rare diseases. Some of the conditions that have been described fit neatly into a conventional idea of autoinflammation. Others, such as interferon-mediated autoinflammatory diseases, are broadening the concept which we consider to be autoinflammatory disorders. There is also a widening of the clinical phenotypes associated with certain genetic mutations, as genetic testing is used more regularly and increasing numbers of patients are screened. It is also increasingly evident that both autoinflammatory and autoimmune problems are frequently seen as complications of primary immunodeficiency disorders. The aim of this review is to provide an update on some recently discovered conditions and to discuss how these disorders help to define the concept of autoinflammation. The review will also cover recent discoveries in the biology of innate-immune-mediated inflammation and describe how this has provided the biological rationale for using anti-interleukin-1 therapies in the treatment of many such conditions. Finally, we discuss the importance of recognising somatic mutations as causes of autoinflammatory clinical phenotypes and provide practical advice on how this could be tackled in everyday clinical practice.

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DOI: 10.1136/jclinpath-2016-203810

PMID: 27646526 [Indexed for MEDLINE]

1074. Rev Med Interne. 2018 Apr;39(4):233-239. doi: 10.1016/j.revmed.2016.07.007. Epub 2016 Sep 14.

[Interleukin-1, inflammasome and autoinflammatory diseases].

[Article in French]

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Interleukin-1 is a major cytokine of innate immunity and inflammation. It exerts various systemic effects during the inflammatory response, such as fever induction, thrombopoiesis and granulopoiesis, or leukocyte recruitment. Its involvement has been demonstrated in many inflammatory-mediated diseases, such as diabetes or gout. Moreover, interleukin-1 plays a pivotal role in some autoinflammatory diseases, such as cryopyrinopathies or familial Mediterranean fever. In these diseases, a constitutional defect of the inflammasome, a protein complex responsible for the activation of interleukin-1, explains the hypersecretion of interleukin-1. Other autoinflammatory diseases have a more complex pathophysiology involving deregulation of the interleukin-1 pathway, upstream or downstream of the inflammasome, or through more complex mechanisms. In this review, we are detailing the synthesis, the activation, the signalling,

and the regulation of interleukin-1. We then describe the autoinflammatory diseases or related-diseases where the pathological role of interleukin-1 has been demonstrated.

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DOI: 10.1016/j.revmed.2016.07.007  
PMID: 27639913 [Indexed for MEDLINE]

1075. Scand J Rheumatol. 2017 Mar;46(2):165-166. doi: 10.1080/03009742.2016.1218930.  
Epub 2016 Sep 16.

Anti-Müllerian hormone levels are not reduced in patients with adult autoinflammatory diseases compared to healthy controls.

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DOI: 10.1080/03009742.2016.1218930  
PMID: 27636858 [Indexed for MEDLINE]

1076. J Cell Physiol. 2017 Jun;232(6):1326-1336. doi: 10.1002/jcp.25602. Epub 2016 Dec 20.

Differential Expression of miR-4520a Associated With Pyrin Mutations in Familial Mediterranean Fever (FMF).

Latsoudis H(1)(2), Mashreghi MF(3), Grün JR(4), Chang HD(3), Stuhlmüller B(5), Repa A(6), Gergiannaki I(6), Kabouraki E(6), Vlachos GS(7), Häupl T(3), Radbruch A(3), Sidiropoulos P(6), Doukoumetzidis K(7), Kardassis D(2)(8), Niewold TB(9),

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Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent, acute, and self-limiting attacks of fever. Mutations in MEFV gene encoding pyrin account for FMF, but the high number of heterozygote patients with typical symptoms of the disease has driven a number of alternative aetiopathogenic hypotheses. The MEFV gene was knocked down in human myelomonocytic cells that express endogenous pyrin to identify deregulated microRNAs (miRNAs). Microarray analyses revealed 29 significantly differentially expressed miRNAs implicated in pathways associated with cellular integrity and survival. Implementation of in silico gene network prediction algorithms and bioinformatics analyses showed that miR-4520a is predicted to target genes implicated in autophagy through regulation of RHEB/mTOR signaling. Differential expression levels of RHEB were confirmed by luciferase reporter gene assays providing further evidence that is directly targeted by miR-4520a. Although the relative expression levels of miR-4520a were variable among FMF patients, the statistical expression of miR-4520a was different between FMF mutation carriers and controls ( $P = 0.0061$ ), indicating an association between miR-4520a expression

and MEFV mutations. Comparison between FMF patients bearing the M694V mutation, associated with severe disease, and healthy controls showed a significant increase in miR-4520a expression levels ( $P = 0.00545$ ). These data suggest that RHEB, the main activator of mTOR signaling, is a valid target of miR-4520a with the relative expression levels of the latter being significantly deregulated in FMF patients and highly dependent on the presence of pyrin mutations, especially of the M694V type. These results suggest a role of deregulated autophagy in the pathogenesis of FMF. *J. Cell. Physiol.* 232: 1326-1336, 2017. © 2016 Wiley Periodicals, Inc.

© 2016 Wiley Periodicals, Inc.

DOI: 10.1002/jcp.25602

PMID: 27636101 [Indexed for MEDLINE]

1077. *Clin Rheumatol.* 2017 Jul;36(7):1661-1667. doi: 10.1007/s10067-016-3410-y. Epub 2016 Sep 16.

NLRP12 autoinflammatory disease: a Chinese case series and literature review.

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As one of the systemic autoinflammatory diseases (SAIDs), the nucleotide-binding oligomerization domain-like receptor protein (NLRP)12 autoinflammatory disease (NLRP12-AD) is an autosomal dominant disorder associated with NLRP12 mutation. SAIDs have been hardly reported in the Chinese population, and NLRP12-AD has been reported only in Caucasians. We report the first case series of NLRP12-AD in the Chinese population coupled with literature review. Three Han Chinese adult patients with clinical phenotype suggestive of NLRP12-AD carrying NLRP12 variants were treated by the authors in 2015. Their phenotype and genotype were carefully studied. A PubMed search for SAIDs was conducted between January, 1990 and January, 2016, and we focused on NLRP12-AD. All three adult patients developed periodic disease in adulthood. They presented with recurrent fever (n = 3), polyarthralgia (n = 3), myalgia (n = 3), urticaria (n = 2), lymphadenopathy (n = 2), and erythema nodosa (n = 1). All patients carry the NLRP12 mutation F402L. Based upon our analysis of a total of 26 patients with NLRP12-AD in the literature, both familial and sporadic cases were equally reported and late-onset cases accounted for 28 %. NLRP12-AD patients typically present with periodic fever, urticaria-like rash, arthralgia/arthritis, myalgia, and lymphadenopathy. Genotyping identifies the NLRP12 gene mutations, notably F402L (55 %). Relative to the literature reports, our patients had the similar phenotypic and genotypic features. Patients with NLRP12-AD usually respond to glucocorticoid therapy. Our report is the first to confirm the presence of NLRP12-AD in the Chinese population. It highlights the importance of screening NLRP12 in patients with unexplained periodic fever syndrome.

DOI: 10.1007/s10067-016-3410-y

PMID: 27633793 [Indexed for MEDLINE]

1078. *Pediatr Neonatol*. 2017 Aug;58(4):378-379. doi: 10.1016/j.pedneo.2016.03.012. Epub 2016 Aug 21.

Familial Mediterranean Fever Presenting with Recurrent Aseptic Meningitis: A Case Report.

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DOI: 10.1016/j.pedneo.2016.03.012

PMID: 27622671

1079. Neuropsychiatr Dis Treat. 2016 Aug 29;12:2225-32. doi: 10.2147/NDT.S109414. eCollection 2016.

Association between sequence variations of the Mediterranean fever gene and the risk of migraine: a case-control study.

Coşkun S(1), Varol S(2), Özdemir HH(2), Çelik SB(3), Balduz M(4), Camkurt MA(5), Çim A(1), Arslan D(2), Çevik MU(2).

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Migraine pathogenesis involves a complex interaction between hormones, neurotransmitters, and inflammatory pathways, which also influence the migraine phenotype. The Mediterranean fever gene (MEFV) encodes the pyrin protein. The major role of pyrin appears to be in the regulation of inflammation activity and the processing of the cytokine pro-interleukin-1 $\beta$ , and this cytokine plays a part in migraine pathogenesis. This study included 220 migraine patients and 228 healthy controls. Eight common missense mutations of the MEFV gene, known as M694V, M694I, M680I, V726A, R761H, K695R, P369S, and E148Q, were genotyped using real-time polymerase chain reaction with 5' nuclease assays, which include sequence specific primers, and probes with a reporter dye. When mutations were evaluated separately among the patient and control groups, only the heterozygote E148Q carrier was found to be significantly higher in the control group than in the patient group ( $P=0.029$ , odds ratio [95% confidence interval] =0.45 [0.21-0.94]). In addition, the frequency of the homozygote and the compound

heterozygote genotype carrier was found to be significantly higher in patients (n=8, 3.6%) than in the control group (n=1, 0.4%) (P=0.016, odds ratio [95% confidence interval] =8.57 [1.06-69.07]). However, there was no statistically significant difference in the allele frequencies of MEFV mutations between the patients and the healthy control group (P=0.964). In conclusion, the results of the present study suggest that biallelic mutations in the MEFV gene could be associated with a risk of migraine in the Turkish population. Moreover, MEFV mutations could be related to increased frequency and short durations of migraine attacks (P=0.043 and P=0.021, respectively). Future studies in larger groups and expression analysis of MEFV are required to clarify the role of the MEFV gene in migraine susceptibility.

DOI: 10.2147/NDT.S109414

PMCID: PMC5010163

PMID: 27621632

1080. Chest. 2016 Sep;150(3):e65-71. doi: 10.1016/j.chest.2016.02.682.

Severe Pulmonary Fibrosis as the First Manifestation of Interferonopathy (TMEM173 Mutation).

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We report three cases of pulmonary disease suggesting fibrosis in two familial and one sporadic case. Pulmonary symptoms were associated with various clinical features of systemic inflammation and vasculitis involving the skin, and appeared at different ages. A strong interferon signature was found in all three cases. Disease was not responsive to corticosteroids, and lung transplantation was considered for all three subjects at an early age. One of them underwent double-lung transplantation, but she immediately experienced a primary graft dysfunction and died soon after. Recognized causes of familial interstitial lung disease were all excluded. All three subjects had a mutation in the previously described autoinflammatory disease called SAVI (stimulator of interferon genes [STING]-associated vasculopathy with onset in infancy). These cases emphasize the need to consider this possibility in children and young adults with lung fibrosis after common causes have been ruled out.

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DOI: 10.1016/j.chest.2016.02.682

PMID: 27613991 [Indexed for MEDLINE]

1081. Semin Arthritis Rheum. 2016 Dec;46(3):367-371. doi: 10.1016/j.semarthrit.2016.07.007. Epub 2016 Jul 20.

Autoinflammatory associated vasculitis.

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Autoinflammatory diseases are characterized by recurrent episodes of fever and localized or systemic inflammation and are caused by monogenic defects of innate immunity. The skin is commonly involved with various manifestations including erysipelas like rash and urticaria. Although vasculitis has been described in many autoinflammatory diseases, it has not been recognized as a characteristic feature of these diseases and autoinflammatory diseases are not listed as an etiology for vasculitis associated with a systemic disease in the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. We describe herein 3 patients with different autoinflammatory diseases in whom leukocytoclastic vasculitis was one of the major and presenting symptoms. A review of the vast evidence in the literature for vasculitis in the spectrum of autoinflammatory diseases and a suggested pathophysiology is presented. We suggest the term autoinflammatory associated vasculitis to describe vasculitis associated with autoinflammatory diseases. Autoinflammatory diseases should be considered within the differential diagnosis of vasculitis.

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DOI: 10.1016/j.semarthrit.2016.07.007

PMID: 27612399 [Indexed for MEDLINE]

1082. *Pediatr Rheumatol Online J.* 2016 Sep 8;14(1):51. doi: 10.1186/s12969-016-0111-7.

Monogenic polyarteritis: the lesson of ADA2 deficiency.

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The deficiency of Adenosine Deaminase 2 (DADA2) is a new autoinflammatory disease characterised by an early onset vasculopathy with livedoid skin rash associated with systemic manifestations, CNS involvement and mild immunodeficiency. This condition is secondary to autosomal recessive mutations of CECR1 (Cat Eye Syndrome Chromosome Region 1) gene, mapped to chromosome 22q11.1, that encodes for the enzymatic protein adenosine deaminase 2 (ADA2). By now 19 different mutations in CECR1 gene have been detected. The pathogenetic mechanism of DADA2 is still unclear. ADA2 is a secreted protein mainly expressed by cells of the myeloid lineage; its enzymatic activity is higher in conditions of hypoxia, inflammation and oncogenesis. Moreover ADA2 is able to induce macrophages proliferation and differentiation; its deficiency is in fact associated with a reduction of anti-inflammatory macrophages (M2). The deficiency of ADA2 is also associated with an up-regulation of neutrophils-expressed genes and an increased secretion of pro-inflammatory cytokines. The mild immunodeficiency detected in many DADA2 patients suggests a role of this protein in the adaptive immune response; an increased mortality of B cells and a reduction in the number of memory B cells, terminally differentiated B cells and plasmacells has been described in many patients. The lack of the protein is associated with endothelium damage; however the function of this protein in the endothelial homeostasis is still unknown. From the clinical point of view, this disease is characterized by a wide spectrum of severity. Chronic or recurrent systemic inflammation with fever, elevation of acute phase reactants and skin manifestations (mainly represented by livedo reticularis) is the typical clinical picture. While in some patients the disease is mild and skin-limited, others present a severe, even lethal, disease with multi-organ involvement; the CNS involvement is rather common with ischemic or hemorrhagic strokes. In many patients not only the clinical picture but also the histopathologic features are undistinguishable from those of systemic polyarteritis nodosa (PAN). Of note, patients with an unusual phenotype, mainly dominated by clinical manifestations suggestive for an immune-destructive condition, have been described. Due to its rarity, the response to treatment of DADA2 is still anecdotal. While steroids can control the disease's manifestations at high dosage, none of the common immunosuppressive drugs turned out to be effective. Biologic drugs have been used only in few patients, without a clear effectiveness; anti-TNF drugs are those associated to a better clinical response. Hematopoietic stem cells transplantation was effective in patients with a severe phenotype.

PMCID: PMC5015262

PMID: 27609179 [Indexed for MEDLINE]

1083. Eur Rev Med Pharmacol Sci. 2016 Aug;20(16):3427-33.

P wave and QT dispersion in familial mediterranean fever.

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Comment in

Eur Rev Med Pharmacol Sci. 2016 Nov;20(22):4623-4625.

**OBJECTIVE:** Familial mediterranean fever (FMF) is the most common auto-inflammatory disease that is characterized by recurrent, self-limited attacks of fever and serous membrane inflammation. Patients with inflammatory rheumatic diseases are considered to have a raised cardiovascular diseases risk. The aim of this study was to investigate; by means of P wave dispersion (Pd) and QT dispersion (QTd) parameters detected by simple standard electrocardiogram (ECG), atrial and ventricular repolarization changes in pregnant women with and without FMF.

**PATIENTS AND METHODS:** In this case-control study including 37 pregnant women with FMF who already put on colchicine treatment and 40 healthy, uncomplicated pregnancy cases, were prospectively assessed using 12-lead ECG and echocardiography.

**RESULTS:** No differences in Pd and corrected QT values were found between the groups. Epicardial fat thickness values were significantly higher in the FMF group compared with the control group ( $p = 0.015$ ). A positive correlation was found between FMF duration and epicardial fat thickness ( $r = 0.350$ ,  $p = 0.042$ ).

**CONCLUSIONS:** Pd, a non-invasive marker of potential atrial arrhythmia and QT-d, a non-invasive marker of potentially lethal ventricular tachyarrhythmia, constitute a recent contribution to the field of noninvasive electrocardiology. Pd and QT-d values were not altered in pregnant women with FMF who already put on colchicine treatment, with no increased risk of atrial or ventricular arrhythmias indicated.

Colchicine may have a cardio-protective effect beyond the effect mediated through suppression of inflammation.

PMID: 27608902 [Indexed for MEDLINE]

1084. J Assoc Physicians India. 2015 Aug;63(8):71-4.

Patient with Recurrent Polyserositis (Familial Mediterranean Fever).

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Familial Mediterranean fever (FMF) is a hereditary autosomal recessive ,systemic, auto-inflammatory disorder characterized by sporadic, unpredictable attacks of fever and serosal inflammation. FMF is caused by mutations in MEFV, a gene located on the short arm of chromosome 16 (16p13) which encodes a protein 'Pyrin'. The disorder has been given various names including familial paroxysmal polyserositis, periodic peritonitis, recurrent polyserositis, benign paroxysmal peritonitis, and periodic disease or periodic fever, As the name indicates, FMF occurs within families and is much more common in individuals of Mediterranean descent than in persons of any other ethnicity. It has been described in several ethnic groups including Sephardic Jews, Armenians, Turks, North Africans, Arabs, Greeks, and Italians. However, the disease is not restricted to these groups and sporadic cases have been reported. Diagnosis is usually clinical and it classically presents with unprovoked, recurrent attacks of fever and painful polyserositis mainly affecting the peritoneum (most common), synovium, and pleura that usually (but not always) begin in childhood. We present a atypical case of FMF with type 1 Diabetes Mellitus and FMF who had no fever, Mediterranean ancestry or family history and discuss his clinical features,diagnosis and management.



PMID: 27604438 [Indexed for MEDLINE]

1085. Med Res Rev. 2017 Jan;37(1):180-216. doi: 10.1002/med.21406. Epub 2016 Sep 8.

The Role of Interleukin-1 in Inflammatory and Malignant Human Skin Diseases and the Rationale for Targeting Interleukin-1 Alpha.

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Inflammation plays a major role in the induction and progression of several skin diseases. Overexpression of the major epidermal proinflammatory cytokines interleukin (IL) 1 alpha (IL-1 $\alpha$ ) and 1 beta (IL-1 $\beta$ ) is positively correlated with symptom exacerbation and disease progression in psoriasis, atopic dermatitis, neutrophilic dermatoses, skin phototoxicity, and skin cancer. IL-1 $\beta$  and the interleukin-1 receptor I (IL-1RI) have been used as a therapeutic target for some autoinflammatory skin diseases; yet, their system-wide effects limit their clinical usage. Based on the local effects of extracellular IL-1 $\alpha$  and its precursor, pro-IL-1 $\alpha$ , we hypothesize that this isoform is a promising drug target for the treatment and prevention of many skin diseases. This review provides an overview on IL-1 $\alpha$  and IL-1 $\beta$  functions, and their contribution to inflammatory and malignant skin diseases. We also discuss the current treatment regimens, and ongoing clinical trials, demonstrating the potential of targeting IL-1 $\alpha$ , and not IL-1 $\beta$ , as a more effective strategy to prevent or treat the onset and progression of various skin diseases.

DOI: 10.1002/med.21406

PMID: 27604144 [Indexed for MEDLINE]

1086. Expert Opin Biol Ther. 2016 Nov;16(11):1425-1434. Epub 2016 Sep 19.

Canakinumab investigated for treating familial Mediterranean fever.

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**INTRODUCTION:** Familial Mediterranean fever (FMF) is the most common hereditary autoinflammatory syndrome. The treatment of choice is colchicine. However, ~40% of patients are only partial responders and 5-10% are non-responders. Advances in the understanding of the role of pyrin in the regulation of interleukin (IL)-1 $\beta$  activation has led to use of anti-IL-1 agents for colchicine-resistant FMF.

**AREAS COVERED:** The authors performed a literature search of anti-IL-1 treatment for FMF, particularly canakinumab, a humanized IL-1 $\beta$  antibody, by searching PubMed/Medline/Scopus since 2001 and proceedings of major rheumatologic conferences since 2011 for unpublished studies.

**EXPERT OPINION:** Many reports of successful treatments with anti-IL-1 agents were published since 2007. In 2011, the first case reports of successful treatment with canakinumab were reported. Successful phase II trials reported in 2014 and 2015 led to a double-blind, randomized, placebo-controlled phase III trial in patients with colchicine-resistant FMF. Significantly more canakinumab treated patients attained the very stringent primary outcome measure and secondary outcomes vs. those treated with placebo. The safety profile was similar to canakinumab trials for other indications. Canakinumab appears to be an excellent alternative for the vast majority of patients with colchicine-resistant FMF, with an adequate safety profile.

DOI: 10.1080/14712598.2016.1233963

PMID: 27603969

1087. Arkh Patol. 2016 Jul-Aug;78(4):64-68. doi: 10.17116/patol201678464-68.

[Immunomorphological characteristics of the synovial membrane in rheumatic diseases].

[Article in Russian; Abstract available in Russian from the publisher]

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The synovial membrane is frequently a target in rheumatic diseases. A search for diagnostic criteria and determination of changes in the pathological process necessitate standardized biopsy diagnostic techniques and quantification of morphological changes using digital imaging methods. The paper considers main methods for obtaining synovial membrane samples. It presents major morphological and immunohistochemical variations in synovitis in the presence of rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis. It shows different immunological and autoinflammatory mechanisms of these diseases. Synovial membrane inflammation in rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis is characterized by different components of morphogenesis, which is proven by the expression of different cell markers. Rheumatoid synovitis is an autoinflammatory process; synovitis in ankylosing spondylitis is characterized by autoinflammatory processes; biomechanical factors as joint inflammation triggers are leading in osteoarthritis.

Publisher: Синовиальная оболочка часто является мишенью при ревматических заболеваниях. Поиск критериев диагностики и определение динамики патологического процесса обуславливают необходимость стандартизации методов биопсийной диагностики и количественной оценки морфологических изменений с применением цифровых методов визуализации. Рассмотрены основные методы получения образцов синовиальной оболочки. Представлены основные морфологические и иммуногистохимические различия синовитов при ревматоидном артрите, анкилозирующем спондилите и остеоартрозе. Показаны различные иммунологические и

аутовоспалительные механизмы развития этих заболеваний. Воспаление в синовиальной оболочке при ревматоидном артрите, анкилозирующем спондилите и остеоартрозе характеризуется различными звеньями морфогенеза, что доказывается экспрессией различных клеточных маркеров. Ревматоидный синовит является аутоиммунным процессом, для синовита при анкилозирующем спондилите характерны аутовоспалительные процессы, а при остеоартрозе ведущими являются биомеханические

факторы, как инициаторы воспаления в суставе.

DOI: 10.17116/patol201678464-68

PMID: 27600785 [Indexed for MEDLINE]

1088. Mol Cell Pediatr. 2016 Dec;3(1):33. doi: 10.1186/s40348-016-0058-2. Epub 2016 Aug 15.

The experience of canakinumab in renal amyloidosis secondary to Familial Mediterranean fever.

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**INTRODUCTION:** Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by self-limited recurrent attacks of fever and serositis. Patients may develop renal amyloidosis. Colchicine prevents attacks and renal amyloidosis. Five to 10 % of the patients with FMF are resistant or intolerant to colchicine.

**CASE DESCRIPTION:** Herein, we reported our experience with clinical-laboratory features and treatment responses of a pediatric FMF patient with amyloidosis treated with canakinumab. We observed a significant decrease in proteinuria and increase growth in the patient.

**DISCUSSION AND EVALUATION:** The most serious complication of FMF is the development of AA type amyloidosis which is characterized by proteinuria. Colchicine is the prototype drug that decreases production of amyloidogenic precursor protein. Occasionally, colchicine inadequate patient is observed, as in our case. Canakinumab is a human anti-IL-1 $\beta$  monoclonal antibody. Previously, canakinumab efficacy were shown in a limited number of studies.

**CONCLUSIONS:** Our data, though limited to only one patient, emphasize that therapeutic intervention with canakinumab seems to be improve kidney function in colchicine-resistant FMF with renal amyloidosis.

DOI: 10.1186/s40348-016-0058-2

PMCID: PMC5010548

PMID: 27590627

1089. Vet Immunol Immunopathol. 2016 Oct 15;179:32-5. doi: 10.1016/j.vetimm.2016.08.003. Epub 2016 Aug 3.

Serum levels of innate immunity cytokines are elevated in dogs with metaphyseal osteopathy (hypertrophic osteodystrophy) during active disease and remission.

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Metaphyseal osteopathy (MO) (hypertrophic osteodystrophy) is a developmental disorder of unexplained etiology affecting dogs during rapid growth. Affected dogs experience relapsing episodes of lytic/sclerotic metaphyseal lesions and systemic inflammation. MO is rare in the general dog population; however, some

breeds (Weimaraner, Great Dane and Irish Setter) have a much higher incidence, supporting a hereditary etiology. Autoinflammatory childhood disorders of parallel presentation such as chronic recurrent multifocal osteomyelitis (CRMO), and deficiency of interleukin-1 receptor antagonist (DIRA), involve impaired innate immunity pathways and aberrant cytokine production. Given the similarities between these diseases, we hypothesize that MO is an autoinflammatory disease mediated by cytokines involved in innate immunity. To characterize immune dysregulation in MO dogs we measured serum levels of inflammatory markers in 26 MO and 102 control dogs. MO dogs had significantly higher levels (pg/ml) of serum Interleukin-1 $\beta$  (IL-1 $\beta$ ), IL-18, IL-6, Granulocyte-macrophage colony stimulating factor (GM-CSF), C-X-C motif chemokine 10 (CXCL10), tumor necrosis factor (TNF), and IL-10. Notably, recovered MO dogs were not different from dogs during active MO disease, providing a suggestive mechanism for disease predisposition. This is the first documentation of elevated immune markers in MO dogs, uncovering an immune profile similar to comparable autoinflammatory disorders in children.

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DOI: 10.1016/j.vetimm.2016.08.003

PMCID: PMC5570445

PMID: 27590423 [Indexed for MEDLINE]

1090. Rheumatol Int. 2016 Nov;36(11):1585-1589. Epub 2016 Sep 1.

Prevalence and significance of MEFV gene mutations in patients with gouty arthritis.

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Gouty arthritis is a chronic erosive autoinflammatory disease. Pyrin has anti-inflammatory effects in the regulation of inflammasome and is encoded by the MEFV gene. The relationship between different rheumatic diseases and the MEFV gene mutations was demonstrated. The aim of this study was to determine the frequency of MEFV gene mutations in patients with gouty arthritis and identify a possible correlation with disease phenotype. Ninety-three patients with gouty arthritis and 102 healthy controls, compatible with age, gender and ethnicity, were included in the study. MEFV gene mutations were investigated by PCR method. Out of 93 patients with gouty arthritis, 36 (38.7 %) showed MEFV gene mutations carriage, whereas 20.6 % in healthy control group. Distribution of mutations identified in patients with gouty arthritis was as; R202Q in 18 (19.3 %), E148Q in 5 (5.4 %), K695R in 4 (4.3 %), M680I in 2 (2.1 %), V726A in 2 (2.1 %), P369S in 2 (2.1 %), R408Q in 2 (2.1 %), M694 V in 1 (1.1 %), respectively. Three patients were identified with compound heterozygosity. Distribution of MEFV gene mutations carriage in healthy controls was; E148Q in 11 (10.7 %), M694 V in 2 (1.9 %), M694I in 1 (0.9 %), M680I in 2 (1.9 %), V726A in 1 (0.9 %), A744S in 1 (0.9 %), K695R in 2 (1.9 %), and P369S in 1 (0.9 %) patients, respectively. Higher MEFV gene mutations carrier frequency was observed in patients with gouty arthritis, compared with the control group ( $p = 0.009$ ). Heterozygous R202Q was the most common mutation detected in patients with gouty arthritis, while heterozygous E148Q in healthy control group. Statistically significant difference was not detected between clinical findings of gouty arthritis and the MEFV gene mutations ( $p > 0.05$ ). We determined higher prevalence of MEFV gene mutations in patients with gouty arthritis compared with the healthy control group. The most frequently detected mutation was heterozygous R202Q, whereas E148Q in healthy controls. High carriage rates of MEFV gene mutations in gouty arthritis suggest that it may play an important role in the pathogenesis of the disease and predisposition to the disease.

DOI: 10.1007/s00296-016-3560-x

PMID: 27587294 [Indexed for MEDLINE]

1091. Cephalalgia. 2017 Oct;37(12):1135-1144. doi: 10.1177/0333102416665870. Epub 2016 Sep 1.

Comparison of comorbidities of migraine and tension headache in a pediatric headache clinic.

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**Objective** To compare comorbidities between migraine and tension headache in patients treated in a tertiary pediatric headache clinic. **Methods** Files of patients with migraine or tension headache attending a pediatric headache clinic were retrospectively reviewed for the presence of organic comorbidities. Additionally, patients were screened with the self-report Strengths and Difficulties Questionnaire to identify nonorganic comorbidities. If necessary, patients were referred to a pediatric psychiatrist, psychologist or social worker for further evaluation. **Results** The study cohort comprised 401 patients: 200 with migraine and 201 with tension headache. The main organic comorbidities were atopic disease, asthma, and first-reported iron-deficiency anemia; all occurred with statistical significance more often with migraine than with tension headache (Familial Mediterranean fever was six times more frequent in the migraine group than in the tension headache group, but the difference was not statistically significant. Nonorganic comorbidities (psychiatric, social stressors) were associated significantly more often with tension headache than with migraine (48.3% versus 33%;  $p = 0.03$ ). **Conclusions** Children and adolescents with migraine or tension headache treated in a dedicated clinic have high rates of organic and nonorganic comorbidities. In this setting, patients with migraine have significantly more organic comorbidities, and patients with tension headache, significantly more nonorganic comorbidities.

DOI: 10.1177/0333102416665870

PMID: 27586882 [Indexed for MEDLINE]

1092. Clin Exp Rheumatol. 2016 Jul-Aug;34(4 Suppl 98):12-6. Epub 2016 Jul 21.

Autophagy, NLRP3 inflammasome and auto-inflammatory/immune diseases.



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Loss of homeostasis, as a result of pathogen invasion or self imbalance, causes tissue damage and inflammation. In addition to its well-established role in promoting clearance of pathogens or cell corpses, inflammation is also key to drive tissue repair and regeneration. Conserved from flies to humans, a transient, well-balanced inflammatory response is critical for restoration of tissue homeostasis after damage. The absence of such a response can result in failure of tissue repair, leading to the development of devastating immunopathologies and degenerative diseases. Studies in the past decade collectively suggest that a malfunction of NLRP3 inflammasome, a key tissue damage sensor, is a dominant driver of various autoinflammatory and autoimmune diseases, including gout, rheumatoid arthritis, and lupus. It is therefore crucial to understand the biology and regulation of NLRP3 inflammasome and determine its affect in the context of various diseases. Of note, various studies suggest that autophagy, a cellular waste removal and rejuvenation process, serves an important role as a macrophage-intrinsic negative regulator of NLRP3 inflammasome. Here, we review recent advances in understanding how autophagy regulates NLRP3 inflammasome activity and discuss the implications of this regulation on the pathogenesis of autoinflammatory and autoimmune diseases.

PMID: 27586797 [Indexed for MEDLINE]

1093. J Clin Immunol. 2016 Nov;36(8):764-773. Epub 2016 Aug 31.

Autoimmune and Inflammatory Manifestations in 247 Patients with Primary Immunodeficiency-a Report from the Slovenian National Registry.

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An abnormal regulation of immune responses leads to autoimmune and inflammatory manifestations in patients with primary immunodeficiencies (PIDs). The objective of our study was to evaluate the frequency of non-infectious and non-malignant manifestations in a large cohort of patients included in the Slovenian national PID registry and to assess the time of manifestation onset with respect to the time of PID diagnosis. Medical records of registered patients were reviewed. Data on autoimmunity, lymphoproliferation, autoinflammation, allergies, PID diagnosis, and underlying genetic defects were collected and analyzed. The time of each manifestation onset was determined and compared with the time of PID diagnosis. As of May 2015, 247 patients with 50 different PIDs were registered in the Slovenian national PID registry (147 males, 100 females; mean age 20 years). Mean disease duration was 14 years; 78 % of patients were younger than 18 years; and 22 % of patients were adults. Diagnosis of PID was genetically confirmed in 51 % of patients. Non-infectious and non-malignant manifestations were present in 69/235 (29 %) patients, including autoimmune manifestations in 52/235 (22 %), lymphoproliferative/granulomatous in 28/235 (12 %), autoinflammatory in 12/247 (5 %), and allergic manifestations in 10/235 (4 %) of all registered patients. Autoimmune manifestations were present in all patients whose PIDs were classified as diseases of immune dysregulation, 47 % of patients with chronic granulomatous

disease, and 38 % of patients with predominantly antibody immune deficiencies. A high prevalence of non-infectious and non-malignant manifestations among patients in the Slovenian national PID registry suggests common genetic factors of autoimmunity, inflammation, and immunodeficiency. Patients with PID should be routinely screened for autoimmune and inflammatory manifestations at the time of PID diagnosis and during the long-term follow up.

DOI: 10.1007/s10875-016-0330-1

PMID: 27582173 [Indexed for MEDLINE]

1094. Immunotargets Ther. 2016 Aug 22;5:69-80. doi: 10.2147/ITT.S89795. eCollection 2016.

Toll-like receptors in the pathogenesis of autoimmune diseases: recent and emerging translational developments.

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Autoinflammatory diseases are defined as the loss of self-tolerance in which an inflammatory response to self-antigens occurs, which are a significant global burden. Toll-like receptors are key pattern recognition receptors, which integrate signals leading to the activation of transcription factors and ultimately proinflammatory cytokines. Recently, it has become apparent that these are at the nexus of autoinflammatory diseases making them viable and attractive drug targets. The aim of this review was to evaluate the role of innate immunity in autoinflammatory conditions alongside the role of negative regulation while suggesting possible therapeutic targets.

DOI: 10.2147/ITT.S89795

PMCID: PMC5001654

PMID: 27579291

1095. Immunol Cell Biol. 2016 Nov;94(10):935-942. doi: 10.1038/icb.2016.81.

T-cell exhaustion: understanding the interface of chronic viral and autoinflammatory diseases.

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During acute viral infection CD8 T cells rapidly expand before contracting down to a persistent memory population that confers long-lasting immunity. However when the antigen persists, such as during chronic viral infection, a dysfunctional process termed 'exhaustion' limits the antiviral response, facilitating ongoing viraemia and poor clinical outcome. CD8 T-cell exhaustion was originally identified in lymphocytic choriomeningitis virus infection of mice; however, new evidence has shown that exhaustion is associated with the control of a wide range of human chronic inflammatory states, including chronic viral infection, autoimmunity and cancer. Consequently, an understanding of the mechanisms controlling exhaustion during chronic infection may also indicate new strategies for controlling other chronic inflammatory diseases. In particular, the success of immune checkpoint blockade as a form of cancer immunotherapy has prompted renewed efforts to understand how T-cell immunity to chronic antigenic stimulation might similarly be measured or modulated in autoimmune diseases. Here we summarise the mechanisms controlling T-cell exhaustion and how they relate to the control of autoimmune responses, providing a future perspective on measuring or manipulating exhaustion to personalise therapy.

DOI: 10.1038/icb.2016.81

PMID: 27577866 [Indexed for MEDLINE]

1096. *Pediatr Rheumatol Online J*. 2016 Aug 30;14(1):47. doi: 10.1186/s12969-016-0109-1.

Chronic recurrent multifocal osteomyelitis (CRMO) - advancing the diagnosis.

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**BACKGROUND:** Chronic recurrent multifocal osteomyelitis (CRMO) is a little known inflammatory bone disease occurring primarily in children and adolescents. Delays in referral and diagnosis may lead to prolonged courses of antibiotics with in-patient care, unnecessary radiation exposure from multiple plain radiographs or bone scans and repeated surgery including bone biopsies. Children (aged < 18 years) diagnosed with CRMO between January 2005 and December 2012, reviewed at Bristol Royal Hospital for Children were included and all available data collected. Information regarding CRMO was sent to all orthopaedic surgeons in the region in 2009. The aim of the study was to examine the features of the cohort, to examine the length of time to diagnosis and to explore the criteria used for diagnosis with and without biopsy.

**FINDINGS:** Over an 8 year period, 41 patients were diagnosed with CRMO. Symptom onset occurred at a median of 9 years of age and time to diagnosis had a median of 15 months (range 0-92). Correlation coefficient analysis for time to diagnosis by year showed statistical significance with a decreasing trend. From the cohort data, diagnostic criteria were developed; applied retrospectively, 34 (83 %) children may have been diagnosed using the criteria, without a biopsy.

**CONCLUSIONS:** The data suggest that increasing knowledge of this condition may shorten time to diagnosis. Use of the Bristol diagnostic criteria by an experienced clinician may obviate the need for biopsy in some patients.

DOI: 10.1186/s12969-016-0109-1

PMCID: PMC5006369

PMID: 27576444 [Indexed for MEDLINE]

Spondyloarthritis associated with familial Mediterranean fever: successful treatment with anakinra.

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DOI: 10.1093/rheumatology/kew290

PMID: 27576367 [Indexed for MEDLINE]

1098. Inflamm Bowel Dis. 2016 Oct;22(10):2499-512. doi: 10.1097/MIB.0000000000000889.

Helminth Regulation of Immunity: A Three-pronged Approach to Treat Colitis.

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By reputation, the parasite is a pariah, an unwelcome guest. Infection with helminth parasites evokes stereotypic immune responses in humans and mice that are dominated by T helper (Th)-2 responses; thus, a hypothesis arises that

infection with helminths would limit immunopathology in concomitant inflammatory disease. Although infection with some species of helminths can cause devastating disease and affect the course of microbial infections, analyses of rodent models of inflammatory disease reveal that infection with helminth parasites, or treatment with helminth extracts, can limit the severity of autoinflammatory disease, including colitis. Intriguing, but fewer, studies show that adoptive transfer of myeloid immune cells treated with helminth products/extracts in vitro can suppress inflammation. Herein, 3 facets of helminth therapy are reviewed and critiqued: treatment with viable ova or larvae, treatment with crude extracts of the worm or purified molecules, and cellular immunotherapy. The beneficial effect of helminth therapy often converges on the mobilization of IL-10 and regulatory/alternatively activated macrophages, while there are reports on transforming growth factor (TGF)- $\beta$ , regulatory T cells and dendritic cells, and recent data suggest that helminth-evoked changes in the microbiota should be considered when defining anticolic mechanisms. We speculate that if the data from animal models translate to humans, noting the heterogeneity therein, then the choice between use of viable helminth ova, helminth extracts/molecules or antigen-pulsed immune cells could be matched to disease management in defined cohorts of patients with inflammatory bowel disease.

DOI: 10.1097/MIB.0000000000000889

PMID: 27575495 [Indexed for MEDLINE]

1099. Ann Rheum Dis. 2017 Feb;76(2):468-472. doi: 10.1136/annrheumdis-2016-209841. Epub 2016 Aug 26.

Familial chilblain lupus due to a gain-of-function mutation in STING.

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Comment in

Ann Rheum Dis. 2016 Dec;75(12):e75.

Ann Rheum Dis. 2016 Dec;75(12):e76.

**OBJECTIVES:** Familial chilblain lupus is a monogenic form of cutaneous lupus erythematosus caused by loss-of-function mutations in the nucleases TREX1 or SAMHD1. In a family without TREX1 or SAMHD1 mutation, we sought to determine the causative gene and the underlying disease pathology.

**METHODS:** Exome sequencing was used for disease gene identification. Structural analysis was performed by homology modelling and docking simulations. Type I interferon (IFN) activation was assessed in cells transfected with STING cDNA using an IFN- $\beta$  reporter and Western blotting. IFN signatures in patient blood in response to tofacitinib treatment were measured by RT-PCR of IFN-stimulated genes.

**RESULTS:** In a multigenerational family with five members affected with chilblain lupus, we identified a heterozygous mutation of STING, a signalling molecule in the cytosolic DNA sensing pathway. Structural and functional analyses indicate that mutant STING enhances homodimerisation in the absence of its ligand cGAMP resulting in constitutive type I IFN activation. Treatment of two affected family members with the Janus kinase (JAK) inhibitor tofacitinib led to a marked suppression of the IFN signature.

**CONCLUSIONS:** A heterozygous gain-of-function mutation in STING can cause familial chilblain lupus. These findings expand the genetic spectrum of type I IFN-dependent disorders and suggest that JAK inhibition may be of therapeutic value.

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DOI: 10.1136/annrheumdis-2016-209841

PMID: 27566796 [Indexed for MEDLINE]



1100. Immunol Cell Biol. 2016 Nov;94(10):943-948. doi: 10.1038/icb.2016.76. Epub 2016 Oct 11.

Rare phenotypes in the understanding of autoimmunity.

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The study of rare phenotypes has a long history in the description of autoimmune disorders. First Mendelian syndromes of idiopathic tissue destruction were defined more than 100 years ago and were later revealed to result from immune-mediated reactivity against self. In the past two decades, continuous advances in sequencing technology and particularly the advent of next-generation sequencing have allowed to define the genetic basis of an ever-growing number of Mendelian forms of autoimmunity. This has provided unique insight into the molecular pathways that govern immunological homeostasis and that are indispensable for the prevention of self-reactive immune-mediated tissue damage and 'horror autotoxicus'. Here we will discuss selected examples of past and recent investigations into rare phenotypes of autoimmunity that have delineated pathways critical for central and peripheral control of the adaptive immune system. We will outline the implications of these findings for rare and common forms of autoimmunity and will discuss the benefits and potential pitfalls of the integration of next-generation sequencing into algorithms for clinical diagnostics. Because of the concise nature of this review, we will focus on syndromes caused by defects in the control of adaptive immunity as innate immune-mediated autoinflammatory disorders have been covered in excellent recent

reviews on Mendelian and polygenic forms of autoimmunity.

DOI: 10.1038/icb.2016.76

PMCID: PMC5371426

PMID: 27562064 [Indexed for MEDLINE]

1101. Praxis (Bern 1994). 2016 Aug;105(17):1033-6. doi: 10.1024/1661-8157/a002450.

Immer wieder dieses Fieber ....

[Article in German]

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DOI: 10.1024/1661-8157/a002450

PMID: 27560818 [Indexed for MEDLINE]

1102. Proc Natl Acad Sci U S A. 2016 Sep 6;113(36):10127-32. doi: 10.1073/pnas.1612594113. Epub 2016 Aug 24.

Biallelic hypomorphic mutations in a linear deubiquitinase define otulipenia, an early-onset autoinflammatory disease.

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Systemic autoinflammatory diseases are caused by mutations in genes that function in innate immunity. Here, we report an autoinflammatory disease caused by loss-of-function mutations in OTULIN (FAM105B), encoding a deubiquitinase with linear linkage specificity. We identified two missense and one frameshift mutations in one Pakistani and two Turkish families with four affected patients. Patients presented with neonatal-onset fever, neutrophilic dermatitis/panniculitis, and failure to thrive, but without obvious primary immunodeficiency. HEK293 cells transfected with mutated OTULIN had decreased enzyme activity relative to cells transfected with WT OTULIN, and showed a substantial defect in the linear deubiquitination of target molecules. Stimulated patients' fibroblasts and peripheral blood mononuclear cells showed evidence for increased signaling in the canonical NF- $\kappa$ B pathway and accumulated linear ubiquitin aggregates. Levels of proinflammatory cytokines were significantly increased in the supernatants of stimulated primary cells and serum samples. This discovery adds to the emerging spectrum of human diseases caused by defects in the ubiquitin pathway and suggests a role for targeted cytokine therapies.

PMID: 27559085 [Indexed for MEDLINE]

Conflict of interest statement: Conflict of interest statement: S.Ö. received royalties for consulting and speaking from Novartis and SOBI. All other authors declare no conflict of interest.

1103. J Allergy Clin Immunol. 2017 Feb;139(2):597-606.e4. doi: 10.1016/j.jaci.2016.06.021. Epub 2016 Jul 16.

Clinical spectrum and features of activated phosphoinositide 3-kinase  $\delta$  syndrome: A large patient cohort study.

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**BACKGROUND:** Activated phosphoinositide 3-kinase  $\delta$  syndrome (APDS) is a recently described combined immunodeficiency resulting from gain-of-function mutations in PIK3CD, the gene encoding the catalytic subunit of phosphoinositide 3-kinase  $\delta$  (PI3K $\delta$ ).

**OBJECTIVE:** We sought to review the clinical, immunologic, histopathologic, and radiologic features of APDS in a large genetically defined international cohort.

**METHODS:** We applied a clinical questionnaire and performed review of medical notes, radiology, histopathology, and laboratory investigations of 53 patients with APDS.

**RESULTS:** Recurrent sinopulmonary infections (98%) and nonneoplastic lymphoproliferation (75%) were common, often from childhood. Other significant complications included herpesvirus infections (49%), autoinflammatory disease (34%), and lymphoma (13%). Unexpectedly, neurodevelopmental delay occurred in 19% of the cohort, suggesting a role for PI3K $\delta$  in the central nervous system; consistent with this, PI3K $\delta$  is broadly expressed in the developing murine central nervous system. Thoracic imaging revealed high rates of mosaic attenuation (90%) and bronchiectasis (60%). Increased IgM levels (78%), IgG deficiency (43%), and CD4 lymphopenia (84%) were significant immunologic features. No immunologic marker reliably predicted clinical severity, which ranged from asymptomatic to

death in early childhood. The majority of patients received immunoglobulin replacement and antibiotic prophylaxis, and 5 patients underwent hematopoietic stem cell transplantation. Five patients died from complications of APDS.

CONCLUSION: APDS is a combined immunodeficiency with multiple clinical manifestations, many with incomplete penetrance and others with variable expressivity. The severity of complications in some patients supports consideration of hematopoietic stem cell transplantation for severe childhood disease. Clinical trials of selective PI3K $\delta$  inhibitors offer new prospects for APDS treatment.

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DOI: 10.1016/j.jaci.2016.06.021

PMCID: PMC5292996

PMID: 27555459 [Indexed for MEDLINE]

1104. Lakartidningen. 2016 Aug 22;113. pii: DZFY.

Familjär medelhavsfeber - viktig sjukdom i en globaliserad värld - Särskilt vanlig hos personer från östra Medelhavsområdet.

[Article in Swedish]

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Familial Mediterranean fever - an important disease in a globalised world  
Familial Mediterranean fever (FMF) is characterized by recurrent febrile attacks during 1/2-3 days associated with peritonitis, pleuritis and arthritis. FMF is the most common monogenic autoinflammatory disease in the world, with over 100 000 affected individuals. It is particularly common in individuals with an origin in the eastern Mediterranean Basin, where the disease has a prevalence of 100-200 per 100 000. The gene for FMF (MEFV) was identified in 1997 with an autosomal recessive inheritance; however, a significant proportion ( $\approx 25\%$ ) of clinical patients lack two mutations. MEFV codes for the protein pyrin, whose exact function still needs to be defined. The most serious complication of FMF is amyloid A amyloidosis, in particular renal amyloidosis. FMF is efficiently treated with daily doses of colchicine resulting in an almost normal life expectancy and amyloidosis confined to non-compliant patients. In today's globalized world we need to adapt to a new context that includes inherited conditions, which have historically been uncommon in our part of the world. One of these conditions is FMF, that should primarily be suspected in individuals with an origin in the eastern Mediterranean Basin and recurrent attacks of fever.

PMID: 27551868 [Indexed for MEDLINE]

1105. Rheumatology (Oxford). 2017 Jul 1;56(7):1060-1068. doi: 10.1093/rheumatology/kew301.

Transforming growth factor  $\beta$  activated kinase 1: a potential therapeutic target for rheumatic diseases.

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Pro-inflammatory cytokines such as IL-1 $\beta$ , IL-6 and TNF- $\alpha$  are central regulators of autoinflammatory diseases. While targeting these cytokines has proven to be a

successful clinical strategy, the long-term challenges such as drug resistance, lack of efficacy and poor clinical outcomes in some patients are some of the limitations faced by these therapies. This has ignited strategies to reduce inflammation by potentially targeting a variety of molecules, including cell surface receptors, signalling proteins and/or transcription factors to minimize cytokine-induced inflammation and tissue injury. In this regard, transforming growth factor  $\beta$  activated kinase 1 (TAK1) is activated in the inflammatory signal transduction pathways in response to IL-1 $\beta$ , TNF- $\alpha$  or toll-like receptor stimulation. Because of its ideal position upstream of mitogen-activated protein kinases and the I $\kappa$ B kinase complex in signalling cascades, targeting TAK1 may be an attractive strategy for treating diseases characterized by chronic inflammation. Here, we discuss the emerging role of TAK1 in mediating the IL-1 $\beta$ , TNF- $\alpha$  and toll-like receptor mediated inflammatory responses in diseases such as RA, OA, gout and SS. We also review evidence suggesting that TAK1 inhibition may have potential therapeutic value. Finally, we focus on the current status of the development of TAK1 inhibitors and suggest further opportunities for testing TAK1 inhibitors in rheumatic diseases.

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DOI: 10.1093/rheumatology/kew301

PMCID: PMC5850516

PMID: 27550296 [Indexed for MEDLINE]

1106. J Pharm Sci. 2016 Nov;105(11):3453-3457. doi: 10.1016/j.xphs.2016.07.008. Epub 2016 Aug 17.

Tip-Loaded Dissolvable Microneedle Arrays Effectively Deliver Polymer-Conjugated Antibody Inhibitors of Tumor-Necrosis-Factor-Alpha Into Human Skin.

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Autoinflammatory skin diseases are characterized by a disequilibrium of cytokines in the local skin microenvironment, suggesting that local delivery of therapeutics, including anticytokine antibodies, may provide benefit without the unwanted off-target effects of systemically delivered therapies. Rapid diffusion of therapeutics away from the target site has been a challenge to the development of local therapies. Conjugation of high molecular weight hydrophilic polymers to cytokine neutralizing mAbs has been shown to be an effective strategy for local control of inflammation in healing burn wounds. However, the burn application is unique because the skin barrier is already breached. For the treatment of autoinflammatory skin diseases, the major challenge for local delivery lies in penetrating the stratum corneum. Here, we investigate a new therapeutic approach combining the use of tip-loaded dissolvable microneedle arrays (TL-dMNAs) for

local application of polymer-conjugated antibody inhibitors of tumor-necrosis-factor-alpha (TNF- $\alpha$ ). Specifically, intradermal delivery and pharmacokinetics of (anti-TNF- $\alpha$ -Ab)-(high molecular weight hyaluronic acid [HA]) conjugates from tip-loaded, obelisk-shaped dissolvable microneedle arrays were investigated in living human skin. The results indicate (1) TL-dMNAs can be successfully fabricated to integrate (anti-TNF- $\alpha$ -Ab)-HA at the tip portion of the microneedles while preserving the biological activity necessary for antibody ligand binding; (2) (anti-TNF- $\alpha$ -Ab)-HA can be effectively delivered into human skin using obelisk-shaped TL-dMNAs; and (3) polymer conjugation effectively inhibits antibody diffusion from the delivery site. Taken together, these results support the evaluation of microneedle array-based delivery of varying polymer-antibody conjugates for the treatment of inflammatory skin diseases.

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DOI: 10.1016/j.xphs.2016.07.008

PMID: 27544434 [Indexed for MEDLINE]

1107. J Invest Dermatol. 2016 Sep;136(9):1747-1748. doi: 10.1016/j.jid.2016.05.102. Epub 2016 Jul 20.

The Association between Hidradenitis Suppurativa and Crohn's Disease: in Search of the Missing Pathogenic Link.

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Comment on

J Invest Dermatol. 2016 Aug;136(8):1716-8.

Hidradenitis suppurativa is a chronic, autoinflammatory skin disease. Shalom et al. demonstrate in a large cross-sectional study an association between Crohn's disease and hidradenitis suppurativa, but not with ulcerative colitis. This association supports the hypothesis that a similar pathogenic mechanism contributes to both diseases, providing new possibilities for functional studies and therapy development.

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DOI: 10.1016/j.jid.2016.05.102

PMID: 27542293 [Indexed for MEDLINE]

1108. Clin Immunol. 2016 Oct;171:65-66. doi: 10.1016/j.clim.2016.08.016. Epub 2016 Aug 15.

Mutations in pyrin masquerading as a primary immunodeficiency.

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Whole exome sequencing is increasingly used in the diagnosis of primary immunodeficiencies due to the overlapping and atypical presentations of these disorders. We report two patients who presented with recurrent infections and early onset colitis. They were investigated by whole exome sequencing due to suspicion of primary immunodeficiency and found to have mutations in pyrin known

to cause familial Mediterranean fever.

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DOI: 10.1016/j.clim.2016.08.016

PMID: 27538774 [Indexed for MEDLINE]

1109. Arch Rheumatol. 2016 Aug 17;32(1):10-14. doi: 10.5606/ArchRheumatol.2017.5791. eCollection 2017 Mar.

Prevalence of Mediterranean FeVer Gene Mutations in Turkish Cypriot Population.

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**Objectives:** This study aims to determine the carrier frequency and the most common mutations of the Mediterranean FeVer (MEFV) gene in healthy Cypriot population of Turkish origin.

**Patients and methods:** A total of 296 healthy participants (102 males, 194 females; median age 30 years; range 1 to 81 years) were evaluated. The exon 2, 3, 5 and 10 of MEFV genes were amplified by polymerase chain reaction.

**Results:** The participants demonstrated an extremely high carrier rate (12.5%). Most commonly detected mutations were E148Q and A74S, with rates of 7.3% and 2.8%, respectively.

**Conclusion:** Mediterranean FeVer gene mutation types and carrier rates in Turkish Cypriot population are different than other Mediterranean populations in the region. MEFV mutation carriage is frequent in North Cyprus and familial Mediterranean fever might be one of the causes for end stage renal disease in

Turkish Cypriots.

DOI: 10.5606/ArchRheumatol.2017.5791

PMCID: PMC5900430

PMID: 29901013

Conflict of interest statement: Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

1110. Cell. 2016 Aug 25;166(5):1215-1230.e20. doi: 10.1016/j.cell.2016.07.019. Epub 2016 Aug 11.

The Deubiquitinase OTULIN Is an Essential Negative Regulator of Inflammation and Autoimmunity.

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Methionine-1 (M1)-linked ubiquitin chains regulate the activity of NF- $\kappa$ B, immune homeostasis, and responses to infection. The importance of negative regulators of M1-linked chains in vivo remains poorly understood. Here, we show that the M1-specific deubiquitinase OTULIN is essential for preventing TNF-associated systemic inflammation in humans and mice. A homozygous hypomorphic mutation in human OTULIN causes a potentially fatal autoinflammatory condition termed OTULIN-related autoinflammatory syndrome (ORAS). Four independent OTULIN mouse models reveal that OTULIN deficiency in immune cells results in cell-type-specific effects, ranging from over-production of inflammatory cytokines and autoimmunity due to accumulation of M1-linked polyubiquitin and spontaneous NF- $\kappa$ B activation in myeloid cells to downregulation of M1-polyubiquitin signaling by degradation of LUBAC in B and T cells. Remarkably, treatment with anti-TNF neutralizing antibodies ameliorates inflammation in ORAS patients and rescues mouse phenotypes. Hence, OTULIN is critical for restraining life-threatening spontaneous inflammation and maintaining immune homeostasis.

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DOI: 10.1016/j.cell.2016.07.019

PMCID: PMC5002269

PMID: 27523608 [Indexed for MEDLINE]

1111. Immunol Res. 2017 Feb;65(1):285-292. doi: 10.1007/s12026-016-8851-5.

Rapidly progressive diffuse systemic sclerosis after local vitamins A, D and E complex injections: literature review and report of two cases.

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The term autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA) or Shoenfeld's syndrome refers to a wide group of immune-mediated diseases triggered by external agents. Several substances, such as vaccine adjuvants, squalene and silicone implants, are implied in the pathogenesis of ASIA syndrome. Treatment and prognosis of this complex condition are not completely known due to lack of good quality evidence. After a brief introductory literature review on ASIA, we report here two cases of patients that developed rapidly progressive systemic sclerosis clinical features after multiple intramuscular local injections of a substance recommended by a non-medical professional called ADE. ADE is an oily vitamin complex for veterinary use, and it was used in these cases for cosmetic muscular definition and enhancement purpose. To our knowledge, this is the first paper to describe the relation between injections of ADE and the development of ASIA with severe systemic sclerosis phenotype. Further investigation is needed to better understand the pathophysiology and to provide the basis for the treatment of this condition.

DOI: 10.1007/s12026-016-8851-5

PMID: 27515982 [Indexed for MEDLINE]

1112. J Eur Acad Dermatol Venereol. 2017 Mar;31(3):536-543. doi: 10.1111/jdv.13858. Epub 2016 Aug 12.

Recurrent lipoatrophic panniculitis of children.

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**BACKGROUND:** Recurrent panniculitis in children with lipoatrophy has been loosely described and reported under different names, but has never been systematically evaluated by immunohistochemical stains.

**OBJECTIVE:** To depict the profile of children with recurrent idiopathic panniculitis.

**METHODS:** Study of clinical, histopathological and immunohistochemical features in five cases with recurrent idiopathic panniculitis.

**RESULTS:** Five children with repeated attacks of painful subcutaneous nodules in association with fever, malaise and abdominal pain or arthralgia, with subsequent lipoatrophy were reviewed. In two patients, extensive involvement led to loss of the cutaneous fatty tissue. Laboratory abnormalities included increased acute phase reactants, leukocytosis with mild neutrophilia, microcytic anaemia and elevated liver enzymes. Histopathology showed lobar panniculitis without vasculitis and with a mixed infiltrate, composed of neutrophils, mononuclear cells, lymphocytes, macrophages and myeloid cells. Neutrophils and myeloid cells were more prominent in early lesions, whereas macrophages predominated in late stages, leading to lipophagia and lipoatrophy. Immunohistochemistry showed positive staining for myeloperoxidase around the necrotic adipocytes in early stages and CD68/PGM1 macrophages in late stages. Intense STAT1 staining was observed in the inflammatory infiltrate. All patients improved with methotrexate and corticosteroids.

**CONCLUSION:** We present five cases of lobar panniculitis and lipoatrophy in childhood. The clinico-pathologic presentation shares features with other autoinflammatory diseases.

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DOI: 10.1111/jdv.13858

PMID: 27515780 [Indexed for MEDLINE]

## Extending the Clinical Phenotype of Adenosine Deaminase 2 Deficiency.

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Adenosine deaminase 2 deficiency is an autoinflammatory disease, characterized by various forms of vasculitis. We describe 5 patients with adenosine deaminase 2 deficiency with various hematologic manifestations, including pure red cell aplasia, with no evidence for vasculitis.

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DOI: 10.1016/j.jpeds.2016.06.058

PMID: 27514238 [Indexed for MEDLINE]

1114. Turk J Med Sci. 2016 Jun 23;46(4):967-71. doi: 10.3906/sag-1505-131.

MEFV mutations in Iranian Azari Turkish patients with Henoch-Schönlein purpura.

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**BACKGROUND/AIM:** The aim of the current study was to screen the rate of MEFV mutations in Henoch-Schönlein purpura (HSP) and to investigate the association of these mutations plus clinical symptoms with HSP disease in the Iranian Azari Turkish ethnic group.

**MATERIALS AND METHODS:** The study groups included 40 unrelated HSP patients and 200 apparently healthy people without any kind of inflammatory diseases as a control group. Molecular screening was performed for eight main mutations, namely M694V, M694I, M680I, V726A, E148Q, R761H, P396S, and R408Q, using polymerase chain reaction (PCR), restriction fragment length polymorphism (RFLP), and sequencing.

**RESULTS:** Out of the 40 studied patients, 27 subjects (67.5%) did not show any mutation, whereas 10 patients (25%) were heterozygotes for one of the following mutations: M694V, M680I, V726A, E148Q. Moreover, three patients (7.5%) were compound heterozygotes for P369S and R408Q. The significant differences between the patient and control groups for M680I, V726A, E148Q, P396S, and R408Q were  $P = 0.0043$ ,  $P = 0.0324$ ,  $P = 0.0145$ ,  $P = 0.0043$ , and  $P = 0.0043$ , respectively.

Furthermore, no significant difference in clinical manifestations was observed between the two groups of patients with and without mutations.

**CONCLUSION:** Based on the results, MEFV mutations could be considered effective genetic factors for development of HSP in the Iranian Azari Turkish ethnic group.

DOI: 10.3906/sag-1505-131

PMID: 27513391 [Indexed for MEDLINE]

Recent insights into the molecular mechanisms of the NLRP3 inflammasome activation.

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Inflammasomes are high-molecular-weight protein complexes that are formed in the cytosolic compartment in response to danger- or pathogen-associated molecular patterns. These complexes enable activation of an inflammatory protease caspase-1, leading to a cell death process called pyroptosis and to proteolytic cleavage and release of pro-inflammatory cytokines interleukin (IL)-1 $\beta$  and IL-18. Along with caspase-1, inflammasome components include an adaptor protein, ASC, and a sensor protein, which triggers the inflammasome assembly in response to a danger signal. The inflammasome sensor proteins are pattern recognition receptors belonging either to the NOD-like receptor (NLR) or to the AIM2-like receptor family. While the molecular agonists that induce inflammasome formation by AIM2 and by several other NLRs have been identified, it is not well understood how the NLR family member NLRP3 is activated. Given that NLRP3 activation is relevant to a range of human pathological conditions, significant attempts are being made to elucidate the molecular mechanism of this process. In this review, we summarize the current knowledge on the molecular events that lead to activation of the NLRP3 inflammasome in response to a range of K (+) efflux-inducing danger signals. We also comment on the reported involvement of cytosolic Ca (2+) fluxes on NLRP3 activation. We outline the recent advances in research on the physiological and pharmacological mechanisms of regulation of NLRP3 responses, and we point to several open questions regarding the current model of NLRP3 activation.

DOI: 10.12688/f1000research.8614.1

PMCID: PMC4963208

PMID: 27508077

1116. Appl Clin Genet. 2016 Jul 20;9:101-10. doi: 10.2147/TACG.S93933. eCollection 2016.

Mevalonate kinase deficiency: current perspectives.

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Mevalonate kinase deficiency (MKD) is a recessively inherited autoinflammatory disorder with a spectrum of manifestations, including the well-defined clinical phenotypes of hyperimmunoglobulinemia D and periodic fever syndrome and mevalonic aciduria. Patients with MKD have recurrent attacks of hyperinflammation associated with fever, abdominal pain, arthralgias, and mucocutaneous lesions, and more severely affected patients also have dysmorphisms and central nervous system anomalies. MKD is caused by mutations in the gene encoding mevalonate kinase, with the degree of residual enzyme activity largely determining disease severity. Mevalonate kinase is essential for the biosynthesis of nonsterol isoprenoids, which mediate protein prenylation. Although the precise pathogenesis of MKD remains unclear, increasing evidence suggests that deficiency in protein prenylation leads to innate immune activation and systemic hyperinflammation. Given the emerging understanding of MKD as an autoinflammatory disorder, recent treatment approaches have largely focused on cytokine-directed biologic therapy. Herein, we review the current genetic and pathologic understanding of MKD, its various clinical phenotypes, and the evolving treatment approach for this multifaceted disorder.

DOI: 10.2147/TACG.S93933

PMCID: PMC4959763

PMID: 27499643

1117. Anatol J Cardiol. 2017 Feb;17(2):139. doi: 10.14744/AnatolJCardiol.2016.22571. Epub 2016 Jul 21.

Vascular risk in familial Mediterranean fever.

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DOI: 10.14744/AnatolJCardiol.2016.22571

PMCID: PMC5336752

PMID: 27488760

1118. Anatol J Cardiol. 2017 Feb;17(2):132-138. doi: 10.14744/AnatolJCardiol.2016.6985. Epub 2016 Jul 21.

Investigation of the arterial stiffness and associated factors in patients with familial Mediterranean fever.

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**OBJECTIVE:** Because of the ongoing and recurring inflammatory state in familial Mediterranean fever (FMF), patients may experience a high risk of cardiovascular events. Our aim was to investigate the arterial stiffness and associated factors in patients with FMF.

**METHODS:** Sixty-nine consecutive FMF patients (including 11 females) and 35 controls (including 5 females) were enrolled in the study. The demographical,

clinical, and laboratory data and genetic mutations of the patients were recorded. In the study, FMF patients according to the Tel-Hashomer criteria were included, whereas patients with other known inflammatory rheumatologic disease, atherosclerotic cardiovascular disease, hypertension, diabetes, those under the age of 18 years, or those refusing to participate in the study were excluded. Arterial stiffness measurements were performed using the TensioMed device (TensioMed Ltd, Budapest, Hungary).

**RESULTS:** The patient and control groups were similar in terms of the mean ages, BMIs, gender, systolic blood pressures, and smoking. FMF patients had a higher pulse wave velocity (PWV) ( $7.73 \pm 1.3$  and  $7.18 \pm 1.1$  m/s;  $p=0.03$ ) and lower brachial and aortic augmentation indexes ( $-64.6 \pm 14.6\%$  and  $-54.6 \pm 25.9\%$ ,  $p=0.041$  and  $4.9 \pm 7.4\%$  and  $14.0 \pm 11.5\%$ ,  $p=0.025$ , respectively) compared with the controls. Thirty-one (45%) patients were in the "during-attack" state and had higher PWV ( $8.17 \pm 1.6$  and  $7.38 \pm 0.9$  m/s;  $p=0.027$ ) compared with the asymptomatic patients. PWV was correlated to serum CRP, WBC, ESR, fibrinogen, and neutrophil/lymphocyte ratios ( $r=0.666$ ,  $0.429$ ,  $0.441$ ,  $0.388$ , and  $0.460$ , respectively). The genetic mutation and predominant attack type had no effect on arterial stiffness.

**CONCLUSION:** FMF patients have increased arterial stiffness during attacks compared with asymptomatic patients and controls. The impaired arterial stiffness is correlated to the severity of the inflammatory state rather than to the attack type or genetic mutations.

DOI: 10.14744/AnatolJCardiol.2016.6985

PMCID: PMC5336751

PMID: 27488756

1119. J Clin Immunol. 2016 Oct;36(7):649-55. doi: 10.1007/s10875-016-0314-1. Epub 2016 Aug 2.

Patterns of Primary Immunodeficiency Disorders Among a Highly Consanguineous Population: Cairo University Pediatric Hospital's 5-Year Experience.

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**INTRODUCTION:** Primary immunodeficiency disorders (PIDs) are heterogeneous disorders that mainly present with severe, persistent, unusual, or recurrent infections in childhood. Reports from different parts of the world indicate a difference between Western and Eastern populations.

**AIM:** The aim of this study was to report on the different patterns of PIDs and identify subgroup characteristics in a highly consanguineous population in Egypt.

**METHODS:** We performed a retrospective chart review for children below 18 years diagnosed with PID at Cairo University Pediatric Hospital from 2010 to 2014.

**RESULTS:** Four hundred seventy-six children were diagnosed with PID disorders. Major categories included combined immunodeficiency disorders, which constituted a large proportion (30 %) of cases, along with predominantly antibody disorders (18 %) followed by syndromic combined disorders (16.8 %), phagocytic disorders (13.2 %), immune dysregulation disorders (10.5 %), and autoinflammatory disorders (9 %).

**CONCLUSION:** PIDs have different patterns within inbred populations with high consanguinity.

DOI: 10.1007/s10875-016-0314-1

PMID: 27484503 [Indexed for MEDLINE]

1120. Proc Natl Acad Sci U S A. 2016 Aug 16;113(33):E4857-66. doi: 10.1073/pnas.1601700113. Epub 2016 Aug 1.

Site-specific phosphorylation and microtubule dynamics control Pyrin inflammasome activation.

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Pyrin, encoded by the MEFV gene, is best known for its gain-of-function mutations causing familial Mediterranean fever (FMF), an autoinflammatory disease. Pyrin forms a caspase-1-activating inflammasome in response to inactivating modifications of Rho GTPases by various bacterial toxins or effectors. Pyrin-mediated innate immunity is unique in that it senses bacterial virulence rather than microbial molecules, but its mechanism of activation is unknown. Here we show that Pyrin was phosphorylated in bone marrow-derived macrophages and dendritic cells. We identified Ser-205 and Ser-241 in mouse Pyrin whose phosphorylation resulted in inhibitory binding by cellular 14-3-3 proteins. The two serines underwent dephosphorylation upon toxin stimulation or bacterial infection, triggering 14-3-3 dissociation, which correlated with Pyrin inflammasome activation. We developed antibodies specific for phosphorylated Ser-205 and Ser-241, which confirmed the stimuli-induced dephosphorylation of endogenous Pyrin. Mutational analyses indicated that both phosphorylation and signal-induced dephosphorylation of Ser-205/241 are important for Pyrin activation. Moreover, microtubule drugs, including colchicine, commonly used to treat FMF, effectively blocked activation of the Pyrin inflammasome. These drugs did not affect Pyrin dephosphorylation and 14-3-3 dissociation but inhibited Pyrin-mediated apoptosis-associated Speck-like protein containing CARD (ASC) aggregation. Our study reveals that site-specific (de)phosphorylation and microtubule dynamics critically control Pyrin inflammasome activation, illustrating a fine and complex mechanism in cytosolic immunity.

DOI: 10.1073/pnas.1601700113

PMCID: PMC4995971

PMID: 27482109 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare no conflict of interest.

1121. Z Rheumatol. 2016 Oct;75(8):786-794.

[Mesenchymal stem/stroma cells : Therapeutic potential in the treatment of autoimmune diseases].

[Article in German]

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Mesenchymal stem and stromal cells (MSC) are propagated for the treatment of autoimmune and autoinflammatory processes. These cells can be relatively easily obtained from various tissues. The MSC feature anti-inflammatory and immunosuppressive properties in vitro as well as in animal models. Initial reports on the clinical application of MSC for various diseases are available, some with promising results and so far no reported toxicity; however, data from phase III studies are still lacking and crucial questions are still unanswered. The MSC preparations used are heterogeneous and also differ depending on the source and it is unclear whether autologous (own) or allogeneic (foreign) MSC are more suitable for therapeutic use. Long-term consequences, such as possible malignant transformation and possible endogenous tumor growth stimulation cannot be completely excluded. Ultimately, these questions can only be answered through randomized controlled trials for defined clinical indications with defined MSC.

DOI: 10.1007/s00393-016-0161-8

PMID: 27481118 [Indexed for MEDLINE]

1122. Cell Rep. 2016 Aug 9;16(6):1492-1501. doi: 10.1016/j.celrep.2016.07.002. Epub 2016 Jul 28.

Restriction by SAMHD1 Limits cGAS/STING-Dependent Innate and Adaptive Immune Responses to HIV-1.

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SAMHD1 is a restriction factor for HIV-1 infection. SAMHD1 mutations cause the autoinflammatory Aicardi-Goutières syndrome that is characterized by chronic type I interferon (IFN) secretion. We show that the spontaneous IFN response in SAMHD1-deficient cells and mice requires the cGAS/STING cytosolic DNA-sensing pathway. We provide genetic evidence that cell-autonomous control of lentivirus infection in myeloid cells by SAMHD1 limits virus-induced production of IFNs and the induction of co-stimulatory markers. This program of myeloid cell activation required reverse transcription, cGAS and STING, and signaling through the IFN receptor. Furthermore, SAMHD1 reduced the induction of virus-specific cytotoxic T cells in vivo. Therefore, virus restriction by SAMHD1 limits the magnitude of IFN and T cell responses. This demonstrates a competition between cell-autonomous virus control and subsequent innate and adaptive immune responses, a concept with important implications for the treatment of infection.

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DOI: 10.1016/j.celrep.2016.07.002

PMCID: PMC4978700

PMID: 27477283 [Indexed for MEDLINE]

1123. Biochem Genet. 2016 Dec;54(6):886-893. Epub 2016 Jul 30.

Is the IL-6 -174G/C Gene Polymorphism Related to the Disease Severity Score in Turkish Children with Familial Mediterranean Fever?

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Familial Mediterranean fever (FMF) is an autosomal recessively inherited disease characterized by recurrent self-limited attacks of fever accompanied by aseptic inflammation of serosal spaces, joints and skin, peritonitis, pleuritis, and arthritis. Clinical features differ according to genetics variants. The aim of this study was to identify relationship between IL-6 -174G/C gene polymorphisms and clinical features, disease severity score (DSS) and proteinuria in children diagnosed with FMF. In this study, 99 children who were followed-up in Gaziosmanpasa University Medical Faculty Department of Pediatrics and diagnosed with Familial Mediterranean fever according to Tel-Hashomer criteria were included. One hundred and fifty seven children who admitted to the hospital with any complain and found healthy included in control group. Genotyping was done for polymorphism in a promoter region of IL-6 gene (G/C at -174). The IL-6 -174G/C gene polymorphism and the clinical features of FMF, proteinuria, the DSS, and the healthy control group were investigated. Data for the clinical features were obtained retrospectively from the electronic records of patients. All of the genotyping of blood samples were done in Medical Genetic laboratory of Gaziosmanpasa University School of Medicine. The results revealed that the distribution of the genotypes and allele frequencies of the IL-6 -174G/C polymorphism were not significantly different between the FMF patients and the healthy controls. The IL-6 -174G/C polymorphisms did not affect proteinuria, the DSS, and the clinical features of FMF patients.

DOI: 10.1007/s10528-016-9764-7

PMID: 27476063 [Indexed for MEDLINE]

1124. Clin Rheumatol. 2017 Feb;36(2):445-449. doi: 10.1007/s10067-016-3367-x. Epub 2016 Jul 31.

Auditory involvement in Behcet's disease: relationship with demographic, clinical, and therapeutic characteristics.

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The study objective was to evaluate the occurrence of sensorineural hearing loss (SNHL) in patients with Behçet's disease (BD), looking at potential correlations with specific demographic, clinical, and therapeutic features. Forty-four consecutive patients (15 males, 29 females) fulfilling the International Study Group (ISG) and/or the International Criteria for Behçet's Disease (ICBD) were enrolled. The endpoints of the study consisted in identifying a deflection of at least 25 dB on pure-tone audiometry and performing statistical analysis to evaluate demographic, clinical, or therapeutic differences between patients with and without SNHL. Our patients showed a mean age  $\pm$  SD of  $45.43 \pm 14.05$  years; a mean age at disease onset  $\pm$  SD of  $31.54 \pm 15.53$  years; a disease duration  $\pm$  SD of  $13.89 \pm 9.15$  years. SNHL was highlighted in 28 (63 %) patients representing the fourth most frequent clinical manifestation in our group of patients. Otologic involvement was significantly more frequent among subjects fulfilling ISG criteria than in patients fulfilling ICBD criteria ( $p = 0.04$ ). Regarding correlations with BD manifestations, SNHL was significantly associated with cutaneous plus articular involvement ( $p = 0.013$ ). Conversely, detached analysis of articular and skin manifestations led to no significant differences ( $p = 0.085$  and  $p = 0.067$ ). No further significant correlations were found between SNHL and BD clinical features or previous or concomitant treatments. Hearing loss was the fourth most common clinical feature in our patients and probably represents an underrated aspect of BD. Hearing impairment was significantly associated with

cutaneous plus articular involvement, suggesting the importance of an otologic evaluation in such patients.

DOI: 10.1007/s10067-016-3367-x

PMID: 27475793 [Indexed for MEDLINE]

1125. Clin Immunol. 2016 Nov;172:83-89. doi: 10.1016/j.clim.2016.07.018. Epub 2016 Jul 27.

The proteasome - victim or culprit in autoimmunity.

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The ubiquitin proteasome system is closely connected to apoptosis, autophagy, signaling of inflammatory cytokines and generation of ligands for MHC class I antigen presentation. Proteasome function in the innate immune response becomes particularly evident in patients with proteasome-associated autoinflammatory syndromes (PRAAS), where disease causing mutations result in reduced proteasome activity. PRAAS can be classified as a novel type of interferonopathy, however the molecular mechanism and signaling pathways leading from impaired proteasome capacity, the accumulation of damaged proteins, and the induction of type I IFN-genes remain to be determined. In contrast, several studies have confirmed an up-regulation of inducible subunits of the proteasome in systemic autoimmune diseases. Since proteasome inhibition was shown to be efficacious in several in-vitro studies and animal models of autoimmune diseases, it is justified to investigate the application of proteasome inhibitors in human disease. In this context, a number of available proteasome inhibitors has been characterized as potent immune-suppressants. The mode of action of proteasome inhibition interferes with the quality control of the huge amounts of synthesized antibodies

causing an unfolded protein response. Further effects of proteasome inhibition includes inhibition of NFκB activation as well as direct activation of intrinsic and extrinsic pathways of apoptosis. The preliminary clinical work on proteasome inhibition in autoimmune diseases comprises only few studies in small cohorts with promising effects, which needs to be confirmed in controlled clinical trials.

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DOI: 10.1016/j.clim.2016.07.018

PMID: 27475228 [Indexed for MEDLINE]

1126. Ann Rheum Dis. 2017 Jan;76(1):303-309. doi: 10.1136/annrheumdis-2016-209335. Epub 2016 Jul 29.

Canakinumab reverses overexpression of inflammatory response genes in tumour necrosis factor receptor-associated periodic syndrome.

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**OBJECTIVE:** To explore whether gene expression profiling can identify a molecular mechanism for the clinical benefit of canakinumab treatment in patients with tumour necrosis factor receptor-associated periodic syndrome (TRAPS).

**METHODS:** Blood samples were collected from 20 patients with active TRAPS who received canakinumab 150 mg every 4 weeks for 4 months in an open-label proof-of-concept phase II study, and from 20 aged-matched healthy volunteers.



Gene expression levels were evaluated in whole blood samples by microarray analysis for arrays passing quality control checks.

**RESULTS:** Patients with TRAPS exhibited a gene expression signature in blood that differed from that in healthy volunteers. Upon treatment with canakinumab, many genes relevant to disease pathogenesis moved towards levels seen in the healthy volunteers. Canakinumab downregulated the TRAPS-causing gene (TNF super family receptor 1A (TNFRSF1A)), the drug-target gene (interleukin (IL)-1B) and other inflammation-related genes (eg, MAPK14). In addition, several inflammation-related pathways were evident among the differentially expressed genes. Canakinumab treatment reduced neutrophil counts, but the observed expression differences remained after correction for this.

**CONCLUSIONS:** These gene expression data support a model in which canakinumab produces clinical benefit in TRAPS by increasing neutrophil apoptosis and reducing pro-inflammatory signals resulting from the inhibition of IL-1 $\beta$ .

Notably, treatment normalised the overexpression of TNFRSF1A, suggesting that canakinumab has a direct impact on the main pathogenic mechanism in TRAPS.

TRIAL REGISTRATION NUMBER: NCT01242813.

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DOI: 10.1136/annrheumdis-2016-209335

PMCID: PMC5264306

PMID: 27474763 [Indexed for MEDLINE]

Conflict of interest statement: KA: employee of Novartis Pharmaceuticals. MC: received speaker fees and served as a consultant for Novartis and SOBI. MG: received speaker fees and served as a consultant for Novartis and SOBI, and has received unrestricted grants for the Eurofever Registry from Novartis and SOBI. NH: employee of Novartis Institutes for Biomedical Research. HL: received speaker fees and served as a consultant for Novartis and SOBI. ML: employee of Novartis Institutes for Biomedical Research. NN: employee of Novartis Institutes for Biomedical Research. LO: received speaker fees and served as a consultant for Novartis. SS-S: employee of Novartis Institutes for Biomedical Research. RT: employee of Novartis Institutes for Biomedical Research.

Familial Mediterranean fever is no longer a rare disease in Japan.

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**BACKGROUND:** The aim of this study was to evaluate the clinical manifestations and prevalence of familial Mediterranean fever (FMF) in Japanese patients with unexplained fever and rheumatic manifestations.

**METHODS:** We enrolled 601 patients with unexplained fever or suspected FMF throughout Japan between 2009 and 2015. Patients were divided into three groups according to Tel Hashomer criteria: sure FMF, probable FMF, and non-FMF patients, including definitive rheumatic diseases. Mutation detection in exons 1, 2, 3, and 10 of the FMF gene MEFV was performed by direct sequencing.

**RESULTS:** A total of 192 patients (31.9 %) were diagnosed with FMF according to FMF diagnostic criteria. These could be divided into sure FMF (56.3 %, n = 108) and probable FMF (43.7 %, n = 84) patients. Fever, abdominal symptoms, and thoracic symptoms were significantly more common in FMF than non-FMF patients. Among FMF patients, 26 (13.5 %) had concomitant rheumatic diseases. Most FMF patients (94.3 %, 181/192) carried at least one MEFV mutation. Allele frequencies of M694I (13.5 % vs 0 %) and E148Q (39.1 % vs 24.8 %) mutations were significantly higher in FMF compared with healthy subjects. Allele frequencies of common MEFV mutations in FMF patients were M694I (13.5 %), P369S (8.6 %), R408Q (8.1 %), G304R (2.9 %), R202Q (4.4 %), E148Q (39.1 %), L110P (11.7 %), and E84K (3.1 %). Patients with a sure FMF phenotype had a higher frequency of MEFV exon 10 mutation (M694I) and a lower frequency of MEFV exon 3 mutations (P369S, R408Q) compared with those with a probable FMF phenotype.

**CONCLUSION:** The high prevalence of FMF in Japanese patients with unexplained fever was confirmed in the present study. FMF should be suspected in cases of unexplained fever or non-specific rheumatic manifestations, and mutational analysis of MEFV could be useful to predict the clinical phenotypes of FMF in Japan.

DOI: 10.1186/s13075-016-1071-5

PMCID: PMC4967332

PMID: 27473114 [Indexed for MEDLINE]

1128. J Cardiovasc Med (Hagerstown). 2016 Sep;17(9):707-12. doi: 10.2459/JCM.0000000000000300.

## Recurrent pericarditis in children and adolescents: a multicentre cohort study.

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**OBJECTIVE:** Limited data are available about recurrent pericarditis in children. We sought to explore contemporary causes, characteristics, therapies and outcomes of recurrent pericarditis in paediatric patients.

**METHODS:** A multicentre (eight sites) cohort study of 110 consecutive cases of paediatric patients with at least two recurrences of pericarditis over an 11-year period (2000-2010) [median 13 years, interquartile range (IQR) 5, 69 boys].

**RESULTS:** Recurrences were idiopathic or viral in 89.1% of cases, followed by postpericardiotomy syndrome (9.1%) and familial Mediterranean fever (0.9%). Recurrent pericarditis was treated with nonsteroidal anti-inflammatory drugs (NSAIDs) in 80.9% of cases, corticosteroids in 64.8% and colchicine was added in 61.8%. Immunosuppressive therapies were administered in 15.5% of patients after subsequent recurrences. After a median follow-up of 60th months, 528 subsequent recurrences were recorded (median 3, range 2-25). Corticosteroid-treated patients experienced more recurrences (standardized risk of recurrence per 100 person-years was 93.2 for patients treated with corticosteroids and 45.2 for those without), side effects and disease-related hospitalizations (for all  $P < 0.05$ ). Adjuvant therapy with colchicine was associated with a decrease in the risk of recurrence from 3.74 per year before initiation of colchicine to 1.37 per year after ( $P < 0.05$ ). Anakinra therapy ( $n = 12$ ) was associated with a drop in

the number of recurrences from 4.29 per year before to 0.14 per year after ( $P < 0.05$ ). Transient constrictive pericarditis developed in 2.7% of patients. CONCLUSION: Recurrent pericarditis has an overall favourable prognosis in children, although it may require frequent readmissions and seriously affect the quality of life, especially in patients treated with corticosteroids. Colchicine or anakinra therapies were associated with significant decrease in the risk of recurrence.

DOI: 10.2459/JCM.0000000000000300

PMID: 27467459 [Indexed for MEDLINE]

1129. Eur Rev Med Pharmacol Sci. 2016 Jul;20(15):3255-61.

MEFV gene variation R202Q is associated with metabolic syndrome.

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OBJECTIVE: MEFV (Mediterranean fever) gene encoding pyrin regulates inflammatory responses. It has been shown that MEFV gene variations are associated with higher acute phase responses and altered course in the different inflammatory diseases.

MEFV gene variations may affect the course of metabolic syndrome components.

PATIENTS AND METHODS: This study included 50 patients with metabolic syndrome and 50 unrelated healthy controls. Genomic DNAs were isolated from patients and healthy controls with standard methods and analysis of exon 2 and 10 of MEFV gene was performed by using Sanger sequencing method.

RESULTS: The MEFV gene variations were detected in 21 patients with metabolic syndrome (42%) and 12 healthy controls (24%) ( $p = 0.55$ ). The frequency of MEFV gene variations with high penetrance (i.e. M694V, M680I, V726A) was similar between patients and healthy controls ( $p > 0.05$ ). We found that R202Q was more frequent in the patient group ( $n = 11$  [22%] vs.  $n = 3$  [6%]) and associated with metabolic syndrome ( $p = 0.021$ ; OR: 4.42; CI95%: 1.15-16.97). When patients with and without MEFV gene variations were compared, no significant difference was found in laboratory and clinical parameters.

CONCLUSIONS: To best of our knowledge, this is the first study indicating an

association between MeS and R202Q mutation of MEFV gene. Familial Mediterranean fever (FMF) related MEFV gene variations may contribute to the pathogenesis of metabolic syndrome.

PMID: 27467001 [Indexed for MEDLINE]

1130. Curr Opin Rheumatol. 2016 Sep;28(5):550-9. doi: 10.1097/BOR.0000000000000314.

Alarming consequences - autoinflammatory disease spectrum due to mutations in proline-serine-threonine phosphatase-interacting protein 1.

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**PURPOSE OF REVIEW:** To give an overview about the expanding spectrum of autoinflammatory diseases due to mutations in proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1) and new insights into their pathogenesis.

**RECENT FINDINGS:** In addition to classical pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome, PSTPIP1-associated myeloid-related proteinemia inflammatory (PAMI) syndrome has been described as a distinct clinical phenotype of PSTPIP1-associated inflammatory diseases (PAID) and other entities are emerging. In addition to dysregulation of IL-1 $\beta$  release from activated PAPA monocytes that requires NLR family, pyrin domain containing 3 (NLRP3), PSTPIP1 mutations have an general impact on cellular dynamics of cells of the innate immune system. In addition, overwhelming expression and release of the alarmins myeloid-related protein (MRP) 8 and 14 by activated phagocytes and keratinocytes, which promote innate immune mechanisms in a Toll like receptor (TLR) 4-dependent manner, are a characteristic feature of these diseases and form a positive feed-back mechanism with IL-1 $\beta$ .

**SUMMARY:** Autoinflammatory diseases due to PSTPIP1 mutations are not restricted to the classical PAPA phenotype but might present with other distinct clinical features. MRP8/14 serum levels are a hallmark of PAPA and PAMI and can be used as

screening tool to initiate targeted genetic testing in suspected cases. The feedback mechanism of IL-1 $\beta$  and MRP-alarmin release may offer novel targets for future therapeutic approaches.

DOI: 10.1097/BOR.0000000000000314

PMID: 27464597 [Indexed for MEDLINE]

1131. Eur J Immunol. 2016 Sep;46(9):2068-77. doi: 10.1002/eji.201546092.

Understanding inflammation in juvenile idiopathic arthritis: How immune biomarkers guide clinical strategies in the systemic onset subtype.

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The translation of basic insight in immunological mechanisms underlying inflammation into clinical practice of inflammatory diseases is still challenging. Here we describe how-through continuous dialogue between bench and bedside-immunological knowledge translates into tangible clinical use in a complex inflammatory disease, juvenile idiopathic arthritis (JIA). Systemic JIA (sJIA) is an autoinflammatory disease, leading to the very successful use of IL-1 antagonists. Further immunological studies identified new immune markers for diagnosis, prediction of complications, response to and successful withdrawal of therapy. Myeloid related protein (MRP)8, MRP14, S100A12, and Interleukin-18 are already used daily in clinic as markers for active sJIA. For non-sJIA subtypes, HLA-B27, antinuclear-antibodies, rheumatoid factor, erythrocyte sedimentation rate, and C-reactive protein are still used for classification, prognosis or active disease. MRP8, MRP14, and S100A12 are now under study for clinical practice. We believe that with biomarkers, algorithms can soon be designed for the individual risk of disease, complications, damage, prediction of response to, and successful withdrawal of therapy. In that way, less time will be lost and less pain will be suffered by the patients. In this review, we describe the current status of immunological biomarkers used in diagnosis and treatment of

JIA.

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DOI: 10.1002/eji.201546092

PMID: 27461267 [Indexed for MEDLINE]

1132. *Pediatr Allergy Immunol Pulmonol*. 2016 Jun 1;29(2):91-94.

Rituximab Desensitization in Pediatric Patients: Results of a Case Series.

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Rituximab is a monoclonal antibody (mAb) primarily used to treat oncologic and autoinflammatory conditions. Although hypersensitivity reactions (HSRs) and desensitization protocols to mAbs have been well described in adults, the experience in the pediatric population is very limited. We sought to determine the safety and efficacy of desensitization to rituximab in the pediatric population at our institution. We retrospectively reviewed the experience with HSRs and desensitization to rituximab during a 5-year period in our tertiary care pediatric center, including reaction evaluation, premedication regimens, and desensitization procedures and protocols. A total of 17 desensitizations to rituximab were performed in three patients. A 14-year-old patient underwent successful desensitization to rituximab using a published adult protocol without incident. Two younger patients (ages 7 years and 23 months) experienced significant reactions during initial desensitization attempts. Therefore, we designed a modified desensitization protocol to rituximab, with particular attention to the rate of infusion as mg/kg/h. This new patient weight-based protocol was successfully used in a total of 13 desensitizations in these two patients. Desensitization to rituximab was a safe and effective procedure in our pediatric population. We present a new patient weight-based desensitization protocol for pediatric patients who develop HSRs to rituximab, with particular usefulness for younger pediatric patients and potential utility in pediatric



patients with HSRs to other mAbs.

DOI: 10.1089/ped.2015.0615

PMCID: PMC4926203

PMID: 27458538

1133. Int J Rheum Dis. 2018 Oct;21(10):1857-1862. doi: 10.1111/1756-185X.12929. Epub 2016 Jul 26.

Familial Mediterranean fever patients homozygous for E148Q variant may have milder disease.

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AIM: Familial Mediterranean fever (FMF) results from MEFV gene mutations. E148Q is a variant of unknown significance in MEFV. We aimed to define characteristics of FMF patients homozygous for E148Q, check for other MEFV variants in a subgroup, and compare the characteristics with FMF patients carrying other mutations.

METHODS: Thirty FMF patients homozygous for E148Q were reviewed. MEFV variant analysis was performed with strip assay. All MEFV exons were screened by direct DNA sequencing in 14 randomly selected E148Q/E148Q patients. E148Q was also checked in 100 healthy adolescents. We compared the characteristics of FMF patients between three groups: E148Q/E148Q (n = 30), M694V/E148Q (n = 19) and exon 10/exon 10 MEFV mutations (n = 48).

RESULTS: Among 30 FMF patients (E148Q/E148Q), the median age at disease onset and diagnosis were 60 (12-168) and 94 (41-196) months, respectively. Fifteen (50%) patients had mild, 14 (46.7%) moderate and one (3.3%) had severe disease.

Twenty-two (73.3%) patients had complete, seven (23.3%) had incomplete response to colchicine, while only one was unresponsive. The detected MEFV variants in 14 E148Q/E148Q FMF patients were as follows: R314R (n = 9; 64.3%), E474E (n = 13;

92.9%), Q476Q (n = 13; 92.9%), D510D (n = 13; 92.9%), and P588P (n = 8; 57.1%).

The E148Q allele frequency was 6.5% in healthy adolescents. When compared to FMF patients with other MEFV mutations, disease onset was later, disease was less severe and the ratio of patients responding completely to colchicine was higher in E148Q/E148Q patients.

CONCLUSION: Patients homozygous for E148Q and negative for other pathogenic MEFV variants may display FMF phenotype and may experience moderate/severe disease activity, although the disease may be milder when compared to FMF patients with other mutations.

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DOI: 10.1111/1756-185X.12929

PMID: 27457448

1134. Diabetes Metab Res Rev. 2017 Feb;33(2). doi: 10.1002/dmrr.2839. Epub 2016 Oct 5.

Autoantibodies to post-translationally modified type I and II collagen in Charcot neuroarthropathy in subjects with type 2 diabetes mellitus.

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**AIMS:** Charcot neuroarthropathy (CN) is a disabling complication, culminating in bone destruction and involving joints and articular cartilage with high inflammatory environment. Its real pathogenesis is as yet unknown. In autoinflammatory diseases, such as rheumatoid arthritis, characterized by inflammation and joint involvement, autoantibodies against oxidative post-translationally modified (oxPTM) collagen type I (CI) and type II (CII) were detected. Therefore, the aim of our study was to assess the potential involvement of autoimmunity in charcot neuroarthropathy, investigating the presence of autoantibodies oxPTM-CI and oxPTM-CII, in participants with charcot neuroarthropathy.

**METHODS:** In this case-control study, we enrolled 124 participants with type 2 diabetes mellitus (47 with charcot neuroarthropathy, 37 with diabetic peripheral neuropathy without charcot neuroarthropathy, and 40 with uncomplicated diabetes), and 32 healthy controls. The CI and CII were modified with ribose and other oxidant species, and the modifications were evaluated with sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Binding of sera from the participants was analyzed with enzyme-linked immunosorbent assay.

**RESULTS:** Age, body mass index, waist and hip circumferences, and lipid profile were similar across the 4 groups, as well as glycated hemoglobin and duration of diabetes among people with diabetes. An increased binding to both native and all oxidation-modified forms of CII was found in participants with CN and diabetic neuropathy. Conversely, for CI, an aspecific increased reactivity was noted.

**CONCLUSIONS:** Our results detected the presence of autoantibodies against oxidative post-translational modified collagen, particularly type 2 collagen, in participants with charcot neuroarthropathy and diabetic neuropathy, suggesting the possible involvement of autoimmunity. Further studies are required to understand the role of autoimmunity in the pathogenesis of charcot neuroarthropathy.

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DOI: 10.1002/dmrr.2839

PMID: 27454862 [Indexed for MEDLINE]

1135. Tumour Biol. 2016 Oct;37(10):13121-13136. Epub 2016 Jul 24.

A novel colchicine-based microtubule inhibitor exhibits potent antitumor activity by inducing mitochondrial mediated apoptosis in MIA PaCa-2 pancreatic cancer cells.

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Colchicine, an antimitotic alkaloid isolated from *Colchicum autumnale*, is a classical drug for treatment of gout and familial Mediterranean fever. It causes antiproliferative effects through the inhibition of microtubule formation, which leads to mitotic arrest and cell death by apoptosis. Here, we report that a novel colchicine analog, 4o

(N-[(7S)-1,2,3-trimethoxy-9-oxo-10-[3-(trifluoromethyl)-4-chlorophenylamino]-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]acetamide), which exhibited potent anticancer activities both in vitro and in vivo. In this study, 4o with excellent pharmacokinetic profile and no P-gp induction liability displayed strong inhibition of proliferation against various human cancer cell lines. However,

pancreatic cancer cell line MIA PaCa-2 was found to be more sensitive towards 4o and showed strong inhibition in concentration and time-dependent manner. By increasing intracellular reactive oxygen species (ROS) levels, 4o induced endoplasmic reticular stress and mitochondrial dysfunction in MIA PaCa-2 cells. Blockage of ROS production reversed 4o-induced endoplasmic reticulum (ER) stress, calcium release, and cell death. More importantly, it revealed that increased ROS generation might be an effective strategy in treating human pancreatic cancer. Further 4o treatment induced mitotic arrest, altered the expression of cell cycle-associated proteins, and disrupted the microtubules in MIA PaCa-2 cells. 4o treatment caused loss of mitochondrial membrane potential, cytochrome c release, upregulation of Bax, downregulation of Bcl-2, and cleavage of caspase-3, thereby showing activation of mitochondrial mediated apoptosis. The in vivo anticancer activity of the compound was studied using sarcoma-180 (ascitic) and leukemia (P388 lymphocytic and L1210 lymphoid) models in mice and showed promising antitumor activity with the least toxicity unlike colchicine. Such studies have hitherto not been reported. Taken together, these findings highlighted that 4o, a potent derivative of colchicine, causes tumor regression with reduced toxicity and provides a novel anticancer candidate for the therapeutic use.

DOI: 10.1007/s13277-016-5160-5

PMID: 27449046 [Indexed for MEDLINE]

1136. Front Immunol. 2016 Jun 30;7:261. doi: 10.3389/fimmu.2016.00261. eCollection 2016.

Inhibitors of Serine Proteases in Regulating the Production and Function of Neutrophil Extracellular Traps.

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Neutrophil extracellular traps (NETs), DNA webs released into the extracellular environment by activated neutrophils, are thought to play a key role in the entrapment and eradication of microbes. However, NETs are highly cytotoxic and a

likely source of autoantigens, suggesting that NET release is tightly regulated. NET formation involves the activity of neutrophil elastase (NE), which cleaves histones, leading to chromatin decondensation. We and others have recently demonstrated that inhibitors of NE, such as secretory leukocyte protease inhibitor (SLPI) and SerpinB1, restrict NET production in vitro and in vivo. SLPI was also identified as a NET component in the lesional skin of patients suffering from the autoinflammatory skin disease psoriasis. SLPI-competent NET-like structures (a mixture of SLPI with neutrophil DNA and NE) stimulated the synthesis of interferon type I (IFN $\alpha$ ) in plasmacytoid dendritic cells (pDCs) in vitro. pDCs uniquely respond to viral or microbial DNA/RNA but also to nucleic acids of "self" origin with the production of IFN $\alpha$ . Although IFNs are critical in activating the antiviral/antimicrobial functions of many cells, IFNs also play a role in inducing autoimmunity. Thus, NETs decorated by SLPI may regulate skin immunity through enhancing IFN $\alpha$  production in pDCs. Here, we review key aspects of how SLPI and SerpinB1 can control NET production and immunogenic function.

DOI: 10.3389/fimmu.2016.00261

PMCID: PMC4928128

PMID: 27446090

1137. Drug Des Devel Ther. 2016 Jun 24;10:2069-80. doi: 10.2147/DDDT.S105263. eCollection 2016.

Secukinumab for rheumatology: development and its potential place in therapy.

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Rheumatic disease is not a single disorder, but a group of more than 100 diseases that affect joints, connective tissues, and/or internal organs. Although rheumatic diseases like rheumatoid arthritis (RA), psoriatic arthritis, and ankylosing spondylitis (AS) differ in their pathogenesis and clinical presentation, the treatment of these inflammatory disorders overlaps. Non-steroid anti-inflammatory drugs are used to reduce pain and inflammation. Additional

disease-modifying anti-rheumatic drugs are prescribed to slowdown disease progression, and is in RA more frequently and effectively applied than in AS. Biologicals are a relatively new class of treatments that specifically target cytokines or cells of the immune system, like tumor necrosis factor alpha inhibitors or B-cell blockers. A new kid on the block is the interleukin-17 (IL-17) inhibitor secukinumab, which has been recently approved by the US Food and Drug Administration for moderate-to-severe plaque psoriasis, psoriatic arthritis, and AS. IL-17 is a proinflammatory cytokine that has an important role in host defense, but its proinflammatory and destructive effects have also been linked to pathogenic processes in autoimmune diseases like RA and psoriasis. Animal models have greatly contributed to further insights in the potential of IL-17 blockade in autoimmune and autoinflammatory diseases, and have resulted in the development of various potential drugs targeting the IL-17 pathway. Secukinumab (AIN457) is a fully human monoclonal antibody that selectively binds to IL-17A and recently entered the market under the brand name Cosentyx<sup>®</sup>. By binding to IL-17A, secukinumab prevents it from binding to its receptor and inhibits its ability to trigger inflammatory responses that play a role in the development of various autoimmune diseases. With secukinumab being the first in class to receive Food and Drug Administration approval, this article will further focus on this new biologic agent and review the milestones in its development and marketing.

DOI: 10.2147/DDDT.S105263

PMCID: PMC4928657

PMID: 27445458 [Indexed for MEDLINE]

1138. Cornea. 2016 Dec;35(12):1656-1657. doi: 10.1097/ICO.0000000000000951.

Ocular Manifestations of Inherited Phospholipase-Cy2-Associated Antibody Deficiency and Immune Dysregulation.

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**PURPOSE:** To report the ocular manifestations of phospholipase-Cy2-associated antibody deficiency and immune dysregulation (PLAID).

**METHODS:** Case report and literature review.

**RESULTS:** A 21-year-old woman diagnosed with PLAID was referred for evaluation of repeated episodes of ocular inflammation resulting in bilateral peripheral corneal pannus with episcleritis and corneal scarring accompanied by systemic manifestations including epidermolysis bullosa and interstitial lung disease.

Systemic immunosuppression with corticosteroids and interleukin-1 (IL-1) receptor antagonist (anakinra) was supplemented with topical anakinra to avoid systemic side effects, which resulted in partial improvement of the ocular symptoms. Oral prednisone was restarted to treat active lesions during bouts of inflammation.

**CONCLUSIONS:** Ocular PLAID is a bilateral chronic or recurrent inflammatory disease of the ocular surface leading to severe and early cicatricial ocular surface and corneal involvement because of high IL-1 production. Management of PLAID may require both topical and systemic immunomodulatory treatments, potentially including targeted local anti-IL-1 therapy.

DOI: 10.1097/ICO.0000000000000951

PMCID: PMC5250612

PMID: 27442322 [Indexed for MEDLINE]

1139. Angiology. 2017 Apr;68(4):315-321. doi: 10.1177/0003319716659220. Epub 2016 Jul 20.

The Relationship Between Atherogenic Index and Carotid Artery Atherosclerosis in Familial Mediterranean Fever.

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Familial Mediterranean fever (FMF) is a disease characterized by chronic inflammation. Atherogenic index of plasma (AIP) is a logarithmic value of the triglyceride to high-density lipoprotein cholesterol ratio and it is a good marker for atherosclerotic heart disease and cardiac risk. In this study, we investigated subclinical atherosclerosis and cardiac risks in patients with FMF. Patients with FMF (78 men and 84 women) and healthy controls (74 men and 82 women) were included in this study. The AIP values of the patients were calculated and carotid intima-media thicknesses (cIMTs) were measured. The cIMT ( $P < .001$ ) and AIP ( $P < .001$ ) values of patients with FMF were higher than the values of the control group. There was a positive correlation between cIMT and AIP values ( $r = .304$ ,  $P < .001$ ). In regression analysis, we detected an independent relationship between cIMT and AIP ( $\beta = .248$ ,  $P = .001$ ). Atherogenic index of plasma may be highly correlated with the subclinical atherosclerosis. Particularly, male patients with FMF may have a high cardiac risk.

DOI: 10.1177/0003319716659220

PMID: 27436495 [Indexed for MEDLINE]

1140. *Pediatr Dermatol*. 2016 Sep;33(5):e311-4. doi: 10.1111/pde.12905. Epub 2016 Jul 19.

Muckle-Wells Syndrome: A Case Report with an NLRP3 T348M Mutation.

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Autoinflammatory syndromes are a recently described group of conditions caused by mutations in multiple genes that code for proteins of the innate immune system. Cryopyrin-associated periodic syndromes are autoinflammatory diseases comprising three clinically overlapping disorders: familial cold urticaria syndrome, Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease. MWS is characterized by a moderate phenotype with fever, rash, arthralgia, conjunctivitis, sensorineural deafness, and potentially life-threatening amyloidosis. We report a 5-year-old girl with MWS that manifested as a recurrent skin rash without fever episodes or intracranial hypertension with papilledema. Genetic analysis revealed a T348M mutation of the NLRP3 gene in the patient and her mother. She was successfully treated with the interleukin-1 $\beta$  antagonist receptor anakinra.

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DOI: 10.1111/pde.12905

PMID: 27435956 [Indexed for MEDLINE]

1141. Genome Med. 2016 Jul 19;8(1):76. doi: 10.1186/s13073-016-0329-5.

Targeted genomic analysis reveals widespread autoimmune disease association with regulatory variants in the TNF superfamily cytokine signalling network.

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**BACKGROUND:** Tumour necrosis factor (TNF) superfamily cytokines and their receptors regulate diverse immune system functions through a common set of signalling pathways. Genetic variants in and expression of individual TNF superfamily cytokines, receptors and signalling proteins have been associated with autoimmune and inflammatory diseases, but their interconnected biology has been largely unexplored.

**METHODS:** We took a hypothesis-driven approach using available genome-wide datasets to identify genetic variants regulating gene expression in the TNF superfamily cytokine signalling network and the association of these variants with autoimmune and autoinflammatory disease. Using paired gene expression and genetic data, we identified genetic variants associated with gene expression, expression quantitative trait loci (eQTLs), in four peripheral blood cell subsets. We then examined whether eQTLs were dependent on gene expression level or the presence of active enhancer chromatin marks. Using these eQTLs as genetic markers of the TNF superfamily signalling network, we performed targeted gene set association analysis in eight autoimmune and autoinflammatory disease genome-wide association studies.

**RESULTS:** Comparison of TNF superfamily network gene expression and regulatory variants across four leucocyte subsets revealed patterns that differed between cell types. eQTLs for genes in this network were not dependent on absolute gene expression levels and were not enriched for chromatin marks of active enhancers. By examining autoimmune disease risk variants among our eQTLs, we found that risk alleles can be associated with either increased or decreased expression of co-stimulatory TNF superfamily cytokines, receptors or downstream signalling

molecules. Gene set disease association analysis revealed that eQTLs for genes in the TNF superfamily pathway were associated with six of the eight autoimmune and autoinflammatory diseases examined, demonstrating associations beyond single genome-wide significant hits.

CONCLUSIONS: This systematic analysis of the influence of regulatory genetic variants in the TNF superfamily network reveals widespread and diverse roles for these cytokines in susceptibility to a number of immune-mediated diseases.

DOI: 10.1186/s13073-016-0329-5

PMCID: PMC4952362

PMID: 27435189 [Indexed for MEDLINE]

1142. Biomed Res Int. 2016;2016:8631061. doi: 10.1155/2016/8631061. Epub 2016 Jun 27.

Autoimmune/Inflammatory Arthritis Associated Lymphomas: Who Is at Risk?

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Specific autoimmune and inflammatory rheumatic diseases have been associated with an increased risk of malignant lymphomas. Conditions such as rheumatoid arthritis (RA), primary Sjögren's syndrome (pSS), systemic lupus erythematosus (SLE), dermatomyositis, and celiac disease have been consistently linked to malignant lymphomas. Isolated cases of lymphomas associated with spondyloarthropathies and autoinflammatory diseases have also been reported. Direct association between autoimmunity and lymphomagenesis has been reinforced by large epidemiological studies. It is still uncertain whether disease specific determinants or phenotypic or treatment related characteristics increase likelihood of lymphomagenesis in these patients. For example, recent literature has indicated a positive correlation between severity of inflammation and risk of lymphomas among RA and Sjögren's syndrome patients. It is also debated whether specific lymphoma variants are more commonly seen in accordance with certain chronic autoimmune arthritis. Previous studies have revealed a higher incidence of diffuse large B-cell lymphomas in RA and SLE patients, whereas pSS has been linked with

increased risk of mucosa-associated lymphoid tissue lymphoma. This review summarizes recent literature evaluating risk of lymphomas in arthritis patients and disease specific risk determinants. We also elaborate on the association of autoimmune arthritis with specific lymphoma variants along with genetic, environmental, and therapeutic risk factors.

DOI: 10.1155/2016/8631061

PMCID: PMC4939344

PMID: 27429984 [Indexed for MEDLINE]

1143. J Autoimmun. 2016 Sep;73:120-9. doi: 10.1016/j.jaut.2016.06.018. Epub 2016 Jul 12.

Avenues to autoimmune arthritis triggered by diverse remote inflammatory challenges.

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Environmental factors contribute to development of autoimmune diseases. For instance, human autoimmune arthritis can associate with intestinal inflammation, cigarette smoking, periodontal disease, and various infections. The cellular and molecular pathways whereby such remote challenges might precipitate arthritis or flares remain unclear. Here, we used a transfer model of self-reactive arthritis-inducing CD4(+) cells from KRNtg mice that, upon transfer, induce a very mild form of autoinflammatory arthritis in recipient animals. This model enabled us to identify external factors that greatly aggravated disease. We show that several distinct challenges precipitated full-blown arthritis, including intestinal inflammation through DSS-induced colitis, and bronchial stress through Influenza infection. Both triggers induced strong IL-17 expression primarily in self-reactive CD4(+) cells in lymph nodes draining the site of inflammation. Moreover, treatment of mice with IL-1 $\beta$  greatly exacerbated arthritis, while transfer of KRNtg CD4(+) cells lacking IL-1R significantly reduced disease and IL-17 expression. Thus, IL-1 $\beta$  enhances the autoaggressive potential of self-reactive CD4(+) cells, through increased Th17 differentiation, and this influences inflammatory events in the joints. We propose that diverse challenges that cause remote inflammation (lung infection or colitis, etc.) result in IL-1 $\beta$ -driven Th17 differentiation, and this precipitates arthritis in genetically susceptible individuals. Thus the etiology of autoimmune inflammatory arthritis likely relates to diverse triggers that converge to a common pathway involving IL-1 $\beta$  production and Th17 cell distribution.

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DOI: 10.1016/j.jaut.2016.06.018

PMID: 27427404 [Indexed for MEDLINE]

1144. Acta Paediatr. 2016 Oct;105(10):1140-51. doi: 10.1111/apa.13531. Epub 2016 Aug 19.

Review of autoinflammatory diseases, with a special focus on periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome.

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There have been remarkable developments in the field of autoinflammatory diseases over the last 20 years. Research has led to definitions of new conditions, increased understanding of disease mechanisms and specific treatment. The polygenic autoinflammatory condition of periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) is the most common autoinflammatory disorder among children in many parts of the world. The clinical features often include clockwork regularity of episodes, prompt responses to corticosteroids and therapeutic effects of tonsillectomy, but the disease mechanisms are largely unknown. CONCLUSION: This review discusses the emerging understanding of autoinflammatory diseases, with special emphasis on PFAPA.

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DOI: 10.1111/apa.13531

PMCID: PMC5095866

PMID: 27426283 [Indexed for MEDLINE]

1145. Ren Fail. 2016 Sep;38(8):1161-6. doi: 10.1080/0886022X.2016.1208465. Epub 2016 Jul 17.

The evaluation of renal hemodynamics changes in Familial Mediterranean fever with color Doppler sonography.

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**BACKGROUND:** Renal resistive index (RRI) scanned through renal Doppler is a practical marker employed in measuring blood flow in renal and intrarenal arteries and in noninvasive evaluation of renal vascular resistance. We aimed to investigate the renal hemodynamic variations in patients with Familial Mediterranean Fever (FMF).

**MATERIAL AND METHODS:** Seventy-nine FMF patients and 51 healthy subjects suitable for age and sex were included. Patients were divided into two groups according to their urinary albumin excretion. Fifty-two patients with 0-29 mg/day albuminuria were included in the normoalbuminuric group while 27 patients with 30-299 mg/day albuminuria were included in the microalbuminuric group.

**RESULTS:** RRI values were higher in patients with FMF compared to the healthy subjects ( $p < 0.0001$ ). Additionally, RRI values were found to be higher in the microalbuminuric patients group compared to the normoalbuminuric patients group, and RRI values were also higher in normoalbuminuric patients group compared to the control group ( $p = 0.002$ ,  $p < 0.0001$ ). The ROC curve analysis suggested that the optimum RRI cutoff value for microalbuminuria in patients was 0.63, sensitivity of 66%, specificity of 60%, and  $p = 0.013$ .

**CONCLUSION:** RRI may be a marker that may be used in assessing resistance to renal blood flow, early renal damage, and progression of renal damage in FMF patients.

DOI: 10.1080/0886022X.2016.1208465

PMID: 27425449 [Indexed for MEDLINE]



1146. Z Rheumatol. 2016 Aug;75(6):542-55. doi: 10.1007/s00393-016-0158-3.

[Autoinflammatory syndromes : Practical approach to diagnostics and therapy].

[Article in German]

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DOI: 10.1007/s00393-016-0158-3

PMID: 27412666 [Indexed for MEDLINE]

1147. Immunol Res. 2017 Feb;65(1):120-128. doi: 10.1007/s12026-016-8821-y.

Two hundreds cases of ASIA syndrome following silicone implants: a comparative  
study of 30 years and a review of current literature.

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In this study, we compared one hundred patients with autoimmune/inflammatory  
syndrome induced by adjuvants (ASIA) due to silicone implant incompatibility  
syndrome diagnosed in 2014 in Maastricht, the Netherlands, with one hundred

historical patients with adjuvant breast disease diagnosed in the Baylor College of Medicine, Houston, USA, between 1985 and 1992. Similarities and differences between these two cohorts were identified to determine whether the spectrum of silicone-related disease changed during the last 30 years. Patients with complaints possibly due to silicone-filled breast implants were prospectively examined in the Reinaert Clinic, Maastricht, the Netherlands between January 2014 and October 2014. All patients were evaluated for the fulfilment of ASIA criteria. Results were compared to results of the Baylor College cohort and 18 other reviewed historical cohorts. Clinical manifestations between the Maastricht and Baylor College cohorts were comparable. Fatigue was observed in 98 current patients and in 95 historical patients. Arthralgia was observed in 91 versus 81 historical patients. Myalgia was observed in 54 versus 91 patients. Cognitive impairment was observed in 78 versus 81 patients, pyrexia was observed in 64 versus 52 patients, sicca complaints in 73 versus 72 patients and severe neurological manifestations in 20 versus 32 patients. From the 54 patients who underwent removal of their silicone breast implant, 50 % (n = 27) of the patients experienced improvement of complaints after explantation of the implant. Also, in the 18 reviewed historical cohorts, similar clinical manifestations were described. Our findings suggest that no major changes were present in the observed clinical manifestations between the Maastricht and Baylor College cohorts. Also, despite changes in the principal constituents of the silicone implants during the past fifty years, silicone remained an adjuvant that may 'bleed' and subsequently may be a chronic stimulus to the immune system resulting in similar clinical manifestations as observed in the Maastricht cohort, the Baylor College cohort and 18 other large cohorts of patients. We therefore conclude that silicone-related disease has not changed during the last 30 years.

DOI: 10.1007/s12026-016-8821-y

PMCID: PMC5406475

PMID: 27406737 [Indexed for MEDLINE]

1148. Clin Nucl Med. 2016 Sep;41(9):730-1. doi: 10.1097/RLU.0000000000001293.

Chronic Nonbacterial Osteomyelitis With FDG Avid Rib Destruction and Extensive Lymphadenopathy.

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Chronic nonbacterial osteomyelitis is a rare entity of unknown etiology and most likely an autoinflammatory disease. A 45-year-old man complained of a growing painful mass of the right chest wall. FDG PET/CT demonstrated a large destructive rib lesion with intense uptake and extensive FDG avid lymphadenopathy, which mimicked a malignant or metastatic disease. Both CT guided core-needle and excisional biopsies showed reactive/regenerative/granulomatous changes coupled with focal neutrophils and marrow atrophy, consistent with chronic osteomyelitis. Stains and cultures of surgical and wound specimens and multiple blood cultures were all negative for any kind of microorganism.

DOI: 10.1097/RLU.0000000000001293

PMID: 27405029 [Indexed for MEDLINE]

1149. ScientificWorldJournal. 2016;2016:2597376. doi: 10.1155/2016/2597376. Epub 2016 Jun 15.

Nod2-Nodosome in a Cell-Free System: Implications in Pathogenesis and Drug Discovery for Blau Syndrome and Early-Onset Sarcoidosis.

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Nucleotide-binding oligomerization domain-containing protein (Nod) 2 is an intracellular pattern recognition receptor, which recognizes muramyl dipeptide (N-Acetylmuramyl-L-Alanyl-D-Isoglutamine: MDP), a bacterial peptidoglycan component, and makes a NF- $\kappa$ B-activating complex called nodosome with adaptor protein RICK (RIP2/RIPK2). Nod2 mutants are associated with the autoinflammatory diseases, Blau syndrome (BS)/early-onset sarcoidosis (EOS). For drug discovery of BS/EOS, we tried to develop Nod2-nodosome in a cell-free system. FLAG-tagged RICK, biotinylated-Nod2, and BS/EOS-associated Nod2 mutants were synthesized, and proximity signals between FLAG-tagged and biotinylated proteins were detected by amplified luminescent proximity homogeneous assay (ALPHA). Upon incubation with MDP, the ALPHA signal of interaction between Nod2-WT and RICK was increased in a dose-dependent manner. The ALPHA signal of interaction between RICK and the BS/EOS-associated Nod2 mutants was more significantly increased than Nod2-WT. Notably, the ALPHA signal between Nod2-WT and RICK was increased upon incubation with MDP, but not when incubated with the same concentrations, L-alanine, D-isoglutamic acid, or the MDP-D-isoform. Thus, we successfully developed Nod2-nodosome in a cell-free system reflecting its function in vivo, and it can be useful for screening Nod2-nodosome-targeted therapeutic molecules for BS/EOS and granulomatous inflammatory diseases.

DOI: 10.1155/2016/2597376

PMCID: PMC4926014

PMID: 27403452 [Indexed for MEDLINE]

1150. J Allergy Clin Immunol. 2017 Jan;139(1):202-211.e6. doi: 10.1016/j.jaci.2016.05.016. Epub 2016 Jul 7.

DNA demethylation of inflammasome-associated genes is enhanced in patients with cryopyrin-associated periodic syndromes.

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**BACKGROUND:** Inflammasomes are cytosolic multiprotein complexes in macrophages. They assemble after infection- or stress-associated stimuli, activating both caspase-1-mediated inflammatory cytokine secretion and pyroptosis. Increased inflammasome activity resulting from gene mutations is related to monogenic autoinflammatory syndromes. However, variable penetrance among patients with the same gene mutations suggests involvement of additional mechanisms associated with inflammasome gene regulation.

**OBJECTIVE:** We sought to investigate the role of DNA demethylation in activating inflammasome genes during macrophage differentiation and monocyte activation in healthy control subjects and patients with autoinflammatory syndrome.

**METHODS:** Inflammasome-related genes were tested for DNA methylation and mRNA levels by using bisulfite pyrosequencing and quantitative RT-PCR in monocytes in vitro differentiated to macrophages and exposed to inflammatory conditions.

The contribution of Tet methylcytosine dioxygenase 2 (TET2) and nuclear factor  $\kappa$ B to DNA demethylation was tested by using chromatin immunoprecipitation, small interfering RNA-mediated downregulation, and pharmacologic inhibition.

**RESULTS:** We observed that inflammasome-related genes are rapidly demethylated in both monocyte-to-macrophage differentiation and on monocyte activation.

Demethylation associates with increased gene expression, and both mechanisms are

impaired when TET2 and nuclear factor  $\kappa$ B are downregulated. We analyzed DNA methylation levels of inflammasome-related genes in patients with cryopyrin-associated periodic syndromes (CAPS) and familial Mediterranean fever, 2 archetypical monogenic autoinflammatory syndromes. Under the above conditions, monocytes from untreated patients with CAPS undergo more efficient DNA demethylation than those of healthy subjects. Interestingly, patients with CAPS treated with anti-IL-1 drugs display methylation levels similar to those of healthy control subjects.

**CONCLUSION:** Our study is the first to demonstrate the involvement of DNA methylation-associated alterations in patients with monogenic autoinflammatory disease and opens up possibilities for novel clinical markers.

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DOI: 10.1016/j.jaci.2016.05.016

PMID: 27394913 [Indexed for MEDLINE]

1151. Arch Rheumatol. 2016 Jul 11;31(4):377-380. doi: 10.5606/ArchRheumatol.2016.6000. eCollection 2016 Dec.

Different Therapeutic Paths (Colchicine vs. Anakinra) in Two Patients With Schnitzler's Syndrome.

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Schnitzler's syndrome is a rare autoinflammatory syndrome with unidentified mechanism of disease and etiology with unknown definitive treatment algorithm. The two obligatory criteria for the diagnosis of Schnitzler's syndrome include chronic urticarial rash and monoclonal gammopathy (immunoglobulin M or immunoglobulin G). In this article, we describe two patients with different courses of disease with different average lengths of time between initial

symptoms and the final diagnosis (6 months to 8 years). Exclusion of more common conditions is needed to ensure the correct diagnosis. Treatment strategy depends on the patient's constitutional symptoms (fever, malaise, generalized myalgia, and arthralgias) and laboratory tests of inflammation. Treatment includes usage of conventional drugs and cytokine blockade (interleukin-1 and interleukin-6). Further studies are needed to determine the precise mechanism of disease and the appropriate targeted therapy.

DOI: 10.5606/ArchRheumatol.2016.6000

PMCID: PMC6190980

PMID: 30375570

1152. Int J Cardiol. 2016 Oct 1;220:654-5. doi: 10.1016/j.ijcard.2016.06.257. Epub 2016 Jun 29.

Pericardial enhancement using multimodality imaging in a rare auto-inflammatory disorder.

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DOI: 10.1016/j.ijcard.2016.06.257

PMID: 27393844 [Indexed for MEDLINE]

1153. Autoimmun Rev. 2016 Sep;15(9):877-82. doi: 10.1016/j.autrev.2016.07.011. Epub 2016 Jul 6.

Autoimmunity and infection in common variable immunodeficiency (CVID).

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Common variable immunodeficiency (CVID) is a heterogeneous group of diseases, characterized by primary hypogammaglobulinemia. B and T cell abnormalities have been described in CVID. Typical clinical features of CVID are recurrent airway infections; lymphoproliferative, autoinflammatory, or neoplastic disorders; and autoimmune diseases among which autoimmune thrombocytopenia (ITP) is the most common. The coexistence of immunodeficiency and autoimmunity appears paradoxical, since one represents a hypoimmune state and the other a hyperimmune state. Considering both innate and adaptive immune response abnormalities in CVID, it is easier to understand the mechanisms that lead to a breakdown of self-tolerance. CD21(low) B cells derive from mature B cells that have undergone chronic immune stimulation; they are increased in CVID patients. The expansion of CD21(low) B cells is also observed in certain autoimmune diseases. We have studied CD21(low) B cells in patients with CVID, CVID, and ITP and with ITP only. We observed a statistically significant increase in the CD21(low) population in the three pathological groups. Moreover, we found statistical differences between the two groups of CVID patients: patients with ITP had a higher percentage of CD21(low) cells. Our data suggest that CD21(low) cells are related to autoimmunity and may represent a link between infection and autoimmunity.

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DOI: 10.1016/j.autrev.2016.07.011

PMID: 27392505 [Indexed for MEDLINE]

1154. Autoimmun Rev. 2016 Sep;15(9):931-4. doi: 10.1016/j.autrev.2016.07.004. Epub 2016 Jul 6.



Systemic-onset juvenile idiopathic arthritis.

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Systemic-onset juvenile idiopathic arthritis (SoJIA) is a systemic inflammatory disease which has up to now been classified as a category of juvenile idiopathic arthritis. However, in this context, systemic inflammation has been associated with dysregulation of the innate immune system, suggesting that it may rather be part of the spectrum of autoinflammatory disorders. The disease is in fact unique with regard to the other JIA categories, in terms of clinical manifestations, prognosis, and response to conventional immunosuppressant therapies. It is characterized clinically by fever, lymphadenopathy, arthritis, rash, and serositis. IL-1 and IL-6 play a major role in the pathogenesis of SoJIA, and treatment with IL-1 and IL-6 inhibitors has shown to be highly effective. However, complications of SoJIA, including macrophage activation syndrome, limitations in functional outcome by arthritis and long-term damage from chronic inflammation continue to be a major issue in patients' care. Recent advances on the pathogenesis and treatment have revolutionized the care and prognosis of this potentially life-threatening pediatric condition.

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DOI: 10.1016/j.autrev.2016.07.004

PMID: 27392503 [Indexed for MEDLINE]

1155. Proc Natl Acad Sci U S A. 2016 Jul 19;113(29):8284-9. doi: 10.1073/pnas.1605635113. Epub 2016 Jul 5.

Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis.

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Comment in

Nature. 2017 May 3;545(7652):20-22.

Nat Rev Rheumatol. 2016 Sep;12(9):500.

Rheumatoid arthritis (RA) is a heterogeneous, prevalent, chronic autoimmune disease characterized by painful swollen joints and significant disabilities. Symptomatic relief can be achieved in up to 50% of patients using biological agents that inhibit tumor necrosis factor (TNF) or other mechanisms of action, but there are no universally effective therapies. Recent advances in basic and preclinical science reveal that reflex neural circuits inhibit the production of cytokines and inflammation in animal models. One well-characterized cytokine-inhibiting mechanism, termed the "inflammatory reflex," is dependent upon vagus nerve signals that inhibit cytokine production and attenuate experimental arthritis severity in mice and rats. It previously was unknown whether directly stimulating the inflammatory reflex in humans inhibits TNF production. Here we show that an implantable vagus nerve-stimulating device in epilepsy patients inhibits peripheral blood production of TNF, IL-1 $\beta$ , and IL-6. Vagus nerve stimulation (up to four times daily) in RA patients significantly inhibited TNF production for up to 84 d. Moreover, RA disease severity, as measured by standardized clinical composite scores, improved significantly.

Together, these results establish that vagus nerve stimulation targeting the inflammatory reflex modulates TNF production and reduces inflammation in humans. These findings suggest that it is possible to use mechanism-based neuromodulating devices in the experimental therapy of RA and possibly other autoimmune and autoinflammatory diseases.

DOI: 10.1073/pnas.1605635113

PMCID: PMC4961187

PMID: 27382171 [Indexed for MEDLINE]

1156. Immunol Cell Biol. 2016 Nov;94(10):994-999. doi: 10.1038/icb.2016.58. Epub 2016 Jul 5.

Mevalonate kinase deficiency leads to decreased prenylation of Rab GTPases.

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Mevalonate kinase deficiency (MKD) is caused by mutations in a key enzyme of the mevalonate-cholesterol biosynthesis pathway, leading to recurrent autoinflammatory disease characterised by enhanced release of interleukin-1 $\beta$  (IL-1 $\beta$ ). It is currently believed that the inflammatory phenotype of MKD is triggered by temperature-sensitive loss of mevalonate kinase activity and reduced

biosynthesis of isoprenoid lipids required for the prenylation of small GTPase proteins. However, previous studies have not clearly shown any change in protein prenylation in patient cells under normal conditions. With lymphoblast cell lines from two compound heterozygous MKD patients, we used a highly sensitive in vitro prenylation assay, together with quantitative mass spectrometry, to reveal a subtle accumulation of unprenylated Rab GTPases in cells cultured for 3 days or more at 40 °C compared with 37 °C. This included a 200% increase in unprenylated Rab7A, Rab14 and Rab1A. Inhibition of sterol regulatory element-binding protein (SREBP) activation by fatostatin led to more pronounced accumulation of unprenylated Rab proteins in MKD cells but not parent cells, suggesting that cultured MKD cells may partially overcome the loss of isoprenoid lipids by SREBP-mediated upregulation of enzymes required for isoprenoid biosynthesis. Furthermore, while inhibition of Rho/Rac/Rap prenylation promoted the release of IL-1 $\beta$ , specific inhibition of Rab prenylation by NE10790 had no effect in human peripheral blood mononuclear cells or human THP-1 monocytic cells. These studies demonstrate for the first time that mutations in mevalonate kinase can lead to a mild, temperature-induced defect in the prenylation of small GTPases, but that loss of prenylated Rab GTPases is not the cause of enhanced IL-1 $\beta$  release in MKD.

DOI: 10.1038/icb.2016.58

PMCID: PMC5122740

PMID: 27377765 [Indexed for MEDLINE]

1157. Reumatol Clin. 2017 Mar - Apr;13(2):120-121. doi: 10.1016/j.reuma.2016.06.001. Epub 2016 Jul 1.

Familial mediterranean fever treated with anakinra: A case report.

[Article in English, Spanish]

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DOI: 10.1016/j.reuma.2016.06.001  
PMID: 27377451 [Indexed for MEDLINE]

1158. J Allergy Clin Immunol. 2016 Jul;138(1):3-14. doi: 10.1016/j.jaci.2016.05.001.  
Epub 2016 May 17.

The role of the inflammasome in patients with autoinflammatory diseases.

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Autoinflammatory diseases are disorders of the innate immune system, characterized by systemic inflammation often driven by inflammasomes, and independent of infection and autoreactive antibodies or antigen-specific T cells. These diseases are increasingly recognized as disorders of immune dysregulation, presenting with a constellation of fevers, rashes, and mucosal symptoms in many cases, which suggests that the allergist/immunologist is the appropriate specialist for these patients. However, many practicing physicians are unaware of these disorders in their pediatric and adult patient populations, leading to substantial delays in diagnosis. Recognizing autoinflammatory disease symptom patterns, performing appropriate diagnostic tests, and instituting early effective therapy are essential to reduce morbidity and mortality in these patients. This review will focus on understanding the molecular basis of inflammasomes, recognizing the distinguishing features of the classic autoinflammatory disorders, and appreciating the treatment modalities available.

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DOI: 10.1016/j.jaci.2016.05.001  
PMID: 27373321 [Indexed for MEDLINE]

1159. Int J Pediatr Otorhinolaryngol. 2016 Aug;87:139-42. doi: 10.1016/j.ijporl.2016.06.015. Epub 2016 Jun 14.

Evaluation of cochlear functions in children with Familial Mediterranean Fever.

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**OBJECTIVES:** To evaluate cochlear functions in patients with Familial Mediterranean Fever in relation to the disease severity score and treatment duration.

**METHODS:** 50 patients (4-18 years) who had been followed-up with the diagnosis of FMF and regularly receiving appropriate colchicine treatment and 39 healthy controls were included in the study. All the patients and controls were evaluated by audiologic evaluation, including high-frequency pure-tone audiometry and distortion product otoacoustic emission tests (DPOAE). The disease severity was determined by scoring system developed by Pras et al.

**RESULTS:** Fifty patients (52% female, 48% male; mean age  $12.2 \pm 4.1$  years) and 39 controls (58.9% female, 41.1% male, mean age  $11.1 \pm 3.4$  years) were enrolled the study. The pure tone average of FMF patients was significantly higher than that of the control group at 500, 4000, and 8000 Hz frequencies. The patients' DPOAE signal values at 6 kHz, 8 kHz frequencies and SNR values at 8 kHz were

significantly higher than control group. The patients' audiometry and DPOAE results were compared with the disease severity scores. Pure tone average was significantly higher in severe and moderate patient groups compared to the mild patient group at 2000 Hz frequency. DPOAE signal values showed statistically significant differences between the patient severity scores at 1.4 and 2.8 kHz frequencies. The mean colchicine treatment duration was found to be  $5.1 \pm 3.7$  years. There were significant differences at 250 and 500 Hz frequencies when patients' audiometry results were compared with the treatment periods.

CONCLUSIONS: FMF affects cochlear functions particularly at high frequencies.

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DOI: 10.1016/j.ijporl.2016.06.015

PMID: 27368461 [Indexed for MEDLINE]

1160. Haematologica. 2016 Oct;101(10):e392-e396. Epub 2016 Jun 30.

Specific antibody deficiency and autoinflammatory disease extend the clinical and immunological spectrum of heterozygous NFKB1 loss-of-function mutations in humans.

Schipp C(1), Nabhani S(1), Bienemann K(1), Simanovsky N(2), Kfir-Erenfeld S(3), Assayag-Asherie N(3), Oommen PT(1), Revel-Vilk S(4), Hönscheid A(1), Gombert M(1), Ginzl S(5), Schäfer D(1), Laws HJ(1), Yefenof E(3), Fleckenstein B(6), Borkhardt A(1), Stepensky P(4), Fischer U(7).

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DOI: 10.3324/haematol.2016.145136

PMCID: PMC5046658

PMID: 27365489 [Indexed for MEDLINE]

1161. *Pediatr Rheumatol Online J.* 2016 Jul 1;14(1):39. doi: 10.1186/s12969-016-0097-1.

Distribution of MEFV gene mutations and R202Q polymorphism in the Serbian population and their influence on oxidative stress and clinical manifestations of inflammation.

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**BACKGROUND:** The Mediterranean fever (MEFV) gene codes for protein pyrin, one of



the regulators of inflammasome activity in innate immune cells. Mutations in this gene are considered the primary cause of Familial Mediterranean fever, but are also found in other monogenic and multifactorial autoinflammatory diseases. The aim of the study was to determine if healthy carriers of MEFV gene mutations and R202Q polymorphism have clinical manifestations of inflammation and impaired oxidative stress parameters.

**METHODS:** One hundred DNA samples from healthy volunteers ( $13.3 \pm 8.87$  years of age (mean  $\pm$  SD); range 2-35) were sequenced by ABI PRISM 310 automated sequencer (PE Applied Biosystems, Norwalk, USA). The Eurofever questionnaire was used to collect retrospectively medical history data. Oxidative stress was determined by measuring spectrophotometrically thiobarbituric acid reactive substances (TBARS) in plasma and erythrocytes, as well as advanced oxidation protein products in plasma. Superoxide dismutase (SOD) activity was determined by McCord and Fridovich method in plasma and erythrocytes, while the catalase erythrocyte activity was assessed using a catalase ELISA kit.

**RESULTS:** We found heterozygous carriers of K695R/N mutations in 5 %, E148Q/N mutations in 6 %, R202Q homozygous polymorphism in 10 % and heterozygous R202Q alterations in 45 % of healthy volunteers. The MEFV mutation carriers and R202Q polymorphism homozygotes reported significantly more often recurrent febrile episodes ( $p = 0.009$ ), diffuse abdominal pain ( $p = 0.025$ ), and malaise ( $p = 0.012$ ) compared to non-carriers. Erythrocyte TBARS levels and plasma SOD activity were higher in persons with MEFV mutations and R202Q/R202Q ( $p = 0.03$  and  $p = 0.049$ , respectively).

**CONCLUSIONS:** Healthy individuals may bear E148Q and K695R MEFV gene mutations, as well as R202Q polymorphism in homozygous state. The determined gene alterations contribute to a subtle oxidative stress and may be associated with more frequent episodes of fever and unspecific inflammatory manifestations. An incomplete penetrance or variable expressivity of R202Q in populations of different ethnicity could influence the expression of autoinflammatory diseases phenotype.

DOI: 10.1186/s12969-016-0097-1

PMCID: PMC4929733

PMID: 27364639 [Indexed for MEDLINE]

1162. Annu Rev Genomics Hum Genet. 2016 Aug 31;17:245-72. doi: 10.1146/annurev-genom-090413-025334. Epub 2016 Jun 2.

Old Dogs, New Tricks: Monogenic Autoinflammatory Disease Unleashed.

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Autoinflammatory diseases are inborn disorders of the innate immune system characterized by episodes of systemic inflammation that are mediated largely by myeloid cells. The field of autoinflammatory diseases has been established since 1999, following the identification of the first genes underlying periodic fever syndromes. This review focuses on developments that have transformed the field in the last two years. We discuss three newly described monogenic autoinflammatory diseases [deficiency of adenosine deaminase 2 (DADA2), a subtype of macrophage activation syndrome (MAS), and stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI)], discuss the possibilities of somatic mosaicism and digenic inheritance, and give an update on new concepts in pathways involved in familial Mediterranean fever (FMF). Finally, the new monogenic autoinflammatory disease haploinsufficiency of A20 (HA20) underscores the placement of monogenic diseases in the firmament of common autoinflammatory phenotypes. The advances in the last two years have shed light on the pathophysiology of several autoinflammatory diseases and have elucidated new pathways that play a role in innate immunity.

DOI: 10.1146/annurev-genom-090413-025334

PMID: 27362340 [Indexed for MEDLINE]

1163. J Cutan Med Surg. 2016 Nov;20(6):575-578. Epub 2016 Jun 29.

Schnitzler Syndrome Without a Monoclonal Gammopathy: A Case Report.

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**BACKGROUND:** Schnitzler syndrome (SS) is a rare autoinflammatory disorder characterized by a recurrent urticarial rash and a monoclonal immunoglobulin M gammopathy, as well as 2 of the following minor criteria: recurrent fever (>38°C), objective signs of abnormal bone remodeling, elevated C-reactive protein level or leukocytosis, and a neutrophilic infiltrate on skin biopsy.

Alternatively, a monoclonal immunoglobulin G gammopathy may be present along with 3 minor criteria for diagnosis.

**OBJECTIVE:** To report a rare case of SS without monoclonal gammopathy and inform physicians of this possible clinical presentation so that treatment is not delayed.

**METHODS:** We report a case of a 62-year-old white man with a clinical diagnosis of SS without monoclonal gammopathy. He presented with chronic urticaria unresponsive to conventional therapy.

**RESULTS AND CONCLUSIONS:** To our knowledge, there have only been 3 case reports of SS in the absence of monoclonal gammopathy documented in the literature. SS should be considered based on clinical presentation, even in the absence of monoclonal gammopathy, to facilitate appropriate management.

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DOI: 10.1177/1203475416657999

PMID: 27358310 [Indexed for MEDLINE]

1164. J Innate Immun. 2016;8(5):493-506. doi: 10.1159/000446615. Epub 2016 Jun 29.

Induction of Myeloid-Derived Suppressor Cells in Cryopyrin-Associated Periodic Syndromes.

Ballbach M(1), Hall T, Brand A, Neri D, Singh A, Schaefer I, Herrmann E, Hansmann S, Handgretinger R, Kuemmerle-Deschner J, Hartl D, Rieber N.

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Cryopyrin-associated periodic syndromes (CAPS) are caused by mutations in the NLRP3 gene leading to overproduction of IL-1 $\beta$  and other NLRP3 inflammasome products. Myeloid-derived suppressor cells (MDSCs) represent a novel innate immune cell subset capable of suppressing T-cell responses. As inflammasome products were previously found to induce MDSCs, we hypothesized that NLRP3 inflammasome-dependent factors induce the generation of MDSCs in CAPS. We studied neutrophilic MDSCs, their clinical relevance, and MDSC-inducing factors in a unique cohort of CAPS patients under anti-IL-1 therapy. Despite anti-IL-1 therapy and low clinical disease activity, CAPS patients showed significantly elevated MDSCs compared to healthy controls. MDSCs were functionally competent, as they suppressed polyclonal T-cell proliferation, as well as Th1 and Th17 responses. In addition, MDSCs decreased monocytic IL-1 $\beta$  secretion. Multiplex assays revealed a distinct pattern of MDSC-inducing cytokines, chemokines, and growth factors. Experimental analyses demonstrated that IL-1 cytokine family members and autoinflammation-associated alarmins differentially induced human MDSCs. Increased MDSCs might represent a novel autologous anti-inflammatory mechanism in autoinflammatory conditions and may serve as a future therapeutic target.

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DOI: 10.1159/000446615

PMID: 27351923 [Indexed for MEDLINE]

1165. Cell Mol Immunol. 2017 Jan;14(1):65-79. doi: 10.1038/cmi.2016.29. Epub 2016 Jun 27.

Post-translational regulation of inflammasomes.

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Inflammasomes play essential roles in immune protection against microbial infections. However, excessive inflammation is implicated in various human diseases, including autoinflammatory syndromes, diabetes, multiple sclerosis, cardiovascular disorders and neurodegenerative diseases. Therefore, precise regulation of inflammasome activities is critical for adequate immune protection while limiting collateral tissue damage. In this review, we focus on the emerging roles of post-translational modifications (PTMs) that regulate activation of the NLRP3, NLRP1, NLRC4, AIM2 and IFI16 inflammasomes. We anticipate that these types of PTMs will be identified in other types of and less well-characterized inflammasomes. Because these highly diverse and versatile PTMs shape distinct inflammatory responses in response to infections and tissue damage, targeting the enzymes involved in these PTMs will undoubtedly offer opportunities for precise modulation of inflammasome activities under various pathophysiological conditions.

DOI: 10.1038/cmi.2016.29

PMCID: PMC5214939

PMID: 27345727 [Indexed for MEDLINE]

1166. Antioxid Redox Signal. 2016 Dec 1;25(16):870-885. Epub 2016 Nov 14.

TCF11/Nrf1-Mediated Induction of Proteasome Expression Prevents Cytotoxicity by Rotenone.

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AIMS: Precise regulation of cellular protein degradation is essential for maintaining protein and redox homeostasis. The ubiquitin proteasome system (UPS) represents one of the major degradation machineries, and UPS disturbances are strongly associated with neurodegeneration. We have previously shown that the transcription factor TCF11/Nrf1 induces antioxidant response element-mediated

upregulation of UPS components in response to proteotoxic stress. Knockout of TCF11/Nrf1 is embryonically lethal, and therefore, the present investigation describes the role of oxidative stress in regulating TCF11/Nrf1-dependent proteasome expression in a model system relevant to Parkinson's disease. RESULTS: Using the human dopaminergic neuroblastoma cell line SH-SY5Y and mouse nigrostriatal organotypic slice cultures, gene and protein expression analysis and functional assays revealed oxidative stress is induced by the proteasome inhibitor epoxomicin or the mitochondrial complex I inhibitor rotenone and promotes the upregulation of proteasome expression and function mediated by TCF11/Nrf1 activation. In addition, we show that these stress conditions induce the unfolded protein response. TCF11/Nrf1, thus, has a cytoprotective function in response to oxidative and proteotoxic stress. Innovation and Conclusion: We here demonstrate that adaption of the proteasome system in response to oxidative stress is dependent on TCF11/Nrf1 in this model system. We conclude that TCF11/Nrf1, therefore, plays a vital role in maintaining redox and protein homeostasis. This work provides a vital insight into the molecular mechanisms of neurodegeneration due to oxidative stress by rotenone, and further studies investigating the role of TCF11/Nrf1 in the human condition would be of considerable interest. Antioxid. Redox Signal. 25, 870-885.

DOI: 10.1089/ars.2015.6539

PMID: 27345029 [Indexed for MEDLINE]

1167. Arch Rheumatol. 2016 Jun 28;31(3):287-289. doi: 10.5606/ArchRheumatol.2016.5802. eCollection 2016 Sep.

Early Onset of Periodic Fever Syndrome in a Patient Carrying Both Tumor Necrosis Factor Receptor Superfamily 1A and Mediterranean Fever Mutations.

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In this article, we report a nine-month-old male patient with a history of three unexplained, prolonged attacks of high fever, including one in the neonatal period, accompanied by an erythematous, migratory rash. There was no family

history that might have suggested a hereditary periodic fever syndrome, but the overall clinical picture was in accordance with tumor necrosis factor receptor-associated disease. Genetic analysis revealed two heterozygous mutations: C30Y in the tumor necrosis factor receptor superfamily 1A gene and K695R in the Mediterranean fever gene. This case shows that diagnosis of an autoinflammatory syndrome should be considered even in the youngest infants with incomplete presentation and no family history of recurrent fever.

DOI: 10.5606/ArchRheumatol.2016.5802

PMCID: PMC5827856

PMID: 29900987

Conflict of interest statement: Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

1168. Int J Dermatol. 2017 Feb;56(2):218-220. doi: 10.1111/ijd.13337. Epub 2016 Jun 23.

Long-term efficacy and safety of anakinra in a patient with Behçet's disease and concomitant tuberculosis infection.

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DOI: 10.1111/ijd.13337

PMID: 27336860 [Indexed for MEDLINE]

Correlation of Secretory Activity of Neutrophils With Genotype in Patients With Familial Mediterranean Fever.

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**OBJECTIVE:** Familial Mediterranean fever (FMF) is an autoinflammatory disorder caused by pyrin-encoding MEFV mutations. Patients present with recurrent but self-limiting episodes of acute inflammation and often have persistent subclinical inflammation. The pathophysiology is only partially understood, but neutrophil overactivation is a hallmark of the disease. S100A12 is a neutrophil-derived proinflammatory danger signal that is strongly elevated in active FMF. This study was undertaken to characterize the secretory activity of neutrophils in vitro and investigate the association of S100A12 with disease activity and genotype in patients with FMF.

**METHODS:** Neutrophils from FMF patients carrying the p.M694V mutation (1 compound heterozygous and 5 homozygous) and neutrophils from 4 healthy control subjects were purified and stimulated in vitro. Neutrophil secretion of S100A12, interleukin-18 (IL-18), IL-1 $\beta$ , and caspase 1 was determined. Based on these in vitro analyses, serum concentrations of S100A12, IL-18, and IL-1 $\beta$  were also analyzed in 128 clinically and genetically characterized patients with FMF.

**RESULTS:** In vitro, unstimulated neutrophils from p.M694V-positive patients



spontaneously secreted more S100A12, IL-18, and caspase 1 compared to neutrophils from healthy controls. Serum concentrations of S100A12 correlated with disease activity and genotype, with the levels being highest in homozygous patients and with compound heterozygotes displaying higher levels than heterozygotes. Compared to individuals negative for the p.M694V mutation, heterozygous, compound heterozygous, or homozygous p.M694V-positive patients had higher serum levels of S100A12 and IL-18 during inactive and subclinical disease.

**CONCLUSION:** The FMF phenotype is known to be more severe in patients carrying the p.M694V mutation. This report describes 2 molecules secreted by unconventional secretory pathways, S100A12 and IL-18, whose concentrations correlated with clinical disease activity and genotype in patients with FMF. In this clinically and genetically heterogeneous disease, management of these surrogate markers might help to improve patient care and outcomes.

© 2016, American College of Rheumatology.

DOI: 10.1002/art.39784

PMID: 27333294 [Indexed for MEDLINE]

1170. Mod Rheumatol. 2017 Mar;27(2):350-355. doi: 10.1080/14397595.2016.1194510. Epub 2016 Jun 22.

Anti-interleukin-1 treatment in 26 patients with refractory familial mediterranean fever.

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**OBJECTIVE:** To investigate the effect of anti-interleukin-1 (anti-IL-1) treatment on the frequency and severity of attacks and other disease-related clinical

parameters and to evaluate the adverse effects associated with anti-IL-1 treatment in 26 patients with refractory familial mediterranean fever (FMF). METHODS: The study included 26 FMF patients followed up in our centre using colchicine for 4 months to 30 years. The treatment was switched to anti-IL-1 treatment for various reasons; 20 cases were resistant to colchicine, 8 were intolerant to colchicine, and 3 had prolonged arthritis under colchicine. Clinical response was monitored through the number of attacks, and laboratory inflammation was monitored through erythrocyte sedimentation rate, C-reactive protein, and serum amyloid A concentrations. Colchicine resistance was defined as at least two attacks/month together with C-reactive protein and serum amyloid A levels above the normal range between attacks. The colchicine dose was increased to 2 mg/day before they were considered colchicine-resistant.

RESULTS: 24 patients used anakinra (100 mg/day), and 2 used canakinumab (150 mg/month), for -36 months. Sixteen patients with colchicine resistance had no attacks under anti-IL-1 treatment, and 4 had decreased frequency and duration of attacks. Seven of 8 patients intolerant to colchicine used anakinra, and 6 were attack-free under treatment, while 1 using canakinumab had attacks under treatment. One patient with prolonged arthritis used canakinumab but arthritis showed progression and the treatment was changed to IL-6 inhibitor. Three patients had injection site erythema and one had fatigue with anti-IL-1 treatment. Topical steroids with systemic antihistaminics were sufficient for symptom control in two cases, but canakinumab treatment was given due to severe injection site erythema in one case.

CONCLUSION: Anti-IL-1 agents are rational treatment modalities in patients resistant or intolerant to colchicine. Anti-IL-1 agents can control FMF attacks quite effectively and they have a promising role in the treatment of FMF.

DOI: 10.1080/14397595.2016.1194510

PMID: 27328763 [Indexed for MEDLINE]

1171. Nat Commun. 2016 Jun 21;7:11932. doi: 10.1038/ncomms11932.

Activation of STING requires palmitoylation at the Golgi.

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Stimulator of interferon genes (STING) is essential for the type I interferon response against DNA pathogens. In response to the presence of DNA and/or cyclic dinucleotides, STING translocates from the endoplasmic reticulum to perinuclear compartments. However, the role of this subcellular translocation remains poorly defined. Here we show that palmitoylation of STING at the Golgi is essential for activation of STING. Treatment with palmitoylation inhibitor 2-bromopalmitate (2-BP) suppresses palmitoylation of STING and abolishes the type I interferon response. Mutation of two membrane-proximal Cys residues (Cys88/91) suppresses palmitoylation, and this STING mutant cannot induce STING-dependent host defense genes. STING variants that constitutively induce the type I interferon response were found in patients with autoimmune diseases. The response elicited by these STING variants is effectively inhibited by 2-BP or an introduction of Cys88/91Ser mutation. Our results may lead to new treatments for cytosolic DNA-triggered autoinflammatory diseases.

DOI: 10.1038/ncomms11932

PMCID: PMC4919521

PMID: 27324217 [Indexed for MEDLINE]

1172. J AAPOS. 2016 Aug;20(4):365-8. doi: 10.1016/j.jaapos.2016.03.015. Epub 2016 Jun 16.

Autoinflammatory retinopathy in chronic infantile neurological cutaneous and articular (CINCA) syndrome.

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Chronic infantile neurological cutaneous and articular (CINCA) syndrome is a rare autosomal dominant autoinflammatory disease. We report the cases of monozygotic twins with CINCA syndrome whose predominant ocular manifestation was inflammatory rod-cone retinal dystrophy. Atypically, there were significant differences between twins in phenotype severity, suggestive of epigenetic differences and/or involvement of environmental factors.

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DOI: 10.1016/j.jaapos.2016.03.015

PMID: 27320017 [Indexed for MEDLINE]

1173. J Oral Maxillofac Surg. 2016 Dec;74(12):2393-2402. doi: 10.1016/j.joms.2016.05.021. Epub 2016 May 26.

Pediatric Chronic Nonbacterial Osteomyelitis of the Jaw: Clinical, Radiographic, and Histopathologic Features.

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**PURPOSE:** Chronic nonbacterial osteomyelitis (CNO) is a focal sterile inflammatory osteitis in children that most commonly develops in the long bones, but can occur in any bone. The disease course is variable, ranging from acute and self-resolving isolated lesions to chronic recurrent multifocal osteomyelitis (CRMO), which is frequently associated with extraosseous inflammatory disease. The purpose of this study was to present our clinical experience with CNO of the mandible in children. The specific aims were to 1) document the clinical characteristics, radiographic findings, and histologic features of CNO and 2) determine the percentage of our sample with multifocal disease (CRMO).

**MATERIALS AND METHODS:** This is a retrospective case series of patients with mandibular CNO. To be included, patients had to have a mandibular lesion radiographically consistent with osteomyelitis without infection, onset before aged 18 years, and complete records. Medical records were reviewed for history, clinical features, imaging, and pathology. Descriptive data were summarized.

**RESULTS:** The sample included 22 patients (13 female and 9 male patients) with disease onset at a mean age of  $9.05 \pm 2.4$  years. On presentation, all patients reported mandibular pain and swelling, and 45% had trismus. All had clinical and/or radiographic findings of multifocal intraosseous disease and/or extraosseous inflammatory lesions. Of the patients, 12 (54%) had a documented family history of autoimmune or autoinflammatory disease and 15 (68%) had elevated erythrocyte sedimentation rates during a flare. Computed tomography scans typically showed expansion of the affected mandible with sclerosis of the medullary space, small foci of poorly defined lytic destruction with a lamellated periosteal reaction, and swollen muscles of mastication. Four distinct histologic features were noted including parallel and interconnected osteoid seams, atypical osteoid, areas of woven bone and hypocellular fibroblastic stroma resembling fibrous dysplasia, and patchy nodular fibrosis.

**CONCLUSION:** Pediatric CNO of the mandible has characteristic radiographic and pathologic features and is usually found as one of multiple disease foci in CRMO rather than as an isolated lesion.

DOI: 10.1016/j.joms.2016.05.021  
PMID: 27318191 [Indexed for MEDLINE]

1174. PLoS One. 2016 Jun 17;11(6):e0156981. doi: 10.1371/journal.pone.0156981.  
eCollection 2016.

Identification of a Novel NLRP12 Nonsense Mutation (Trp408X) in the Extremely  
Rare Disease FCAS by Exome Sequencing.

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Familial cold autoinflammatory syndrome (FCAS) is an extremely rare autosomal  
dominant inherited disease. Although there are four genes that have been linked  
with FCAS, its molecular diagnosis has been challenging in a relatively large  
proportion of cases. In this study, we aimed to investigate the genetic defect of  
a recruited FCAS family using exome sequencing followed by in-depth  
bioinformatics analysis. As a result, a novel heterozygous stop-gain mutation  
(Trp408X) in NLRP12 was identified in autosomal dominant inherited FCAS with  
clinical features of recurrent fever and skin urticaria due to cold conditions.  
When combined with previous studies, all of the reported mutations were found to  
have occurred in a highly conserved region in the NACHT domain coding sequence in  
NLRP12 exon 3, suggesting that a screening strategy for FCAS should focus on this  
area of the gene. In conclusion, this study demonstrates the importance of exome  
sequencing for clinical diagnosis of genetic disorders and provides molecular  
insight into FCAS treatment and diagnosis.

DOI: 10.1371/journal.pone.0156981  
PMCID: PMC4912109  
PMID: 27314497 [Indexed for MEDLINE]

1175. Rheumatology (Oxford). 2016 Sep;55(9):1705-6. doi: 10.1093/rheumatology/kew239. Epub 2016 Jun 15.

The response to the inactivated Hepatitis A vaccine in children with autoinflammatory diseases: a prospective observational controlled study.

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DOI: 10.1093/rheumatology/kew239

PMID: 27313277 [Indexed for MEDLINE]

1176. Science. 2016 Jun 17;352(6292):aad1210. doi: 10.1126/science.aad1210.

T helper 1 immunity requires complement-driven NLRP3 inflammasome activity in CD4<sup>+</sup> T cells.

Arbore G(#)(1), West EE(#)(2), Spolski R(2), Robertson AAB(3), Klos A(4), Rheinheimer C(4), Dutow P(4), Woodruff TM(3), Yu ZX(5), O'Neill LA(6), Coll RC(3), Sher A(7), Leonard WJ(2), Köhl J(8)(9), Monk P(10), Cooper MA(3), Arno M(11), Afzali B(1)(12), Lachmann HJ(13), Cope AP(14), Mayer-Barber KD(15), Kemper C(1)(2).

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Comment in

Transplantation. 2016 Sep;100(9):1789-1790.

The NLRP3 inflammasome controls interleukin-1 $\beta$  maturation in antigen-presenting cells, but a direct role for NLRP3 in human adaptive immune cells has not been described. We found that the NLRP3 inflammasome assembles in human CD4(+) T cells and initiates caspase-1-dependent interleukin-1 $\beta$  secretion, thereby promoting interferon- $\gamma$  production and T helper 1 (T(H)1) differentiation in an autocrine fashion. NLRP3 assembly requires intracellular C5 activation and stimulation of C5a receptor 1 (C5aR1), which is negatively regulated by surface-expressed C5aR2. Aberrant NLRP3 activity in T cells affects inflammatory responses in human autoinflammatory disease and in mouse models of inflammation and infection. Our results demonstrate that NLRP3 inflammasome activity is not confined to "innate



immune cells" but is an integral component of normal adaptive T(H)1 responses.

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DOI: 10.1126/science.aad1210

PMCID: PMC5015487

PMID: 27313051 [Indexed for MEDLINE]

1177. *Mod Rheumatol*. 2017 Mar;27(2):378-379. doi: 10.1080/14397595.2016.1193111. Epub 2016 Jun 16.

A Japanese familial Mediterranean fever patient with a rare G632S MEFV mutation in exon 10.

Umeda M(1)(2), Migita K(3), Ueki Y(1), Nonaka F(4), Aramaki T(1), Terada K(1), Koga T(1), Ichinose K(1), Eguchi K(1), Kawakami A(2).

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DOI: 10.1080/14397595.2016.1193111

PMID: 27310525

1178. *Mod Rheumatol*. 2016 Sep;26(5):805. doi: 10.1080/14397595.2016.1193107. Epub 2016 Jun 16.

Biologic therapy in familial Mediterranean fever: Comment on the study by Koga et al.

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Comment on

Mod Rheumatol. 2016 Sep;26(5):637-41.

DOI: 10.1080/14397595.2016.1193107

PMID: 27310397

1179. Int J Rheum Dis. 2018 Mar;21(3):755-760. doi: 10.1111/1756-185X.12906. Epub 2016 Jun 16.

Diagnosis of familial Mediterranean fever following the initial presentation of monoarthritis.

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**AIMS:** To determine if familial Mediterranean fever (FMF) genetic testing should be advised in children with initial presentation of monoarthritis and to identify clinical parameters associated with FMF-induced arthritis that warrant genetic investigation.

**METHODS:** A prospective study of 71 otherwise healthy children admitted to our pediatric department between 2010-2013 with a first episode of idiopathic monoarthritis. Demographic, clinical and laboratory data were documented and genetic assay of the five common mutations in our population of the MEFV gene that cause FMF syndrome were analyzed in the entire study population. Statistical analysis compared two groups according to FMF status (FMF arthritis and idiopathic arthritis).

**RESULTS:** Among the cohort seven (10%) children harbored two pathogenic mutations in the MEFV gene, thus confirming diagnosis of FMF. This FMF-induced arthritis

group had a statistically significant female predominance compared with the idiopathic arthritis group (six [86%] vs. 19 [30%], respectively) ( $P = 0.006$ , odds ratio [OR] = 14.2). In addition, associated abdominal pain during the attack (two [28%] vs. two [3%], respectively) ( $P = 0.04$ , OR = 12.4) and a family history of FMF (two [29%] vs. five [8%], respectively) ( $P = 0.1$ , OR 4.7,) were more common in the FMF-induced arthritis group.

**CONCLUSIONS:** In Mediterranean populations where FMF is relatively common we recommend for every child with a first episode of arthritis, without an identifying cause to strongly consider MEFV genetic testing of the common mutations in the relevant population.

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DOI: 10.1111/1756-185X.12906

PMID: 27310037 [Indexed for MEDLINE]

1180. Acta Derm Venereol. 2017 Jan 4;97(1):126-127. doi: 10.2340/00015555-2485.

Diagnosis and Treatment of Blau Syndrome/Early-onset Sarcoidosis, an Autoinflammatory Granulomatous Disease, in an Infant.

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DOI: 10.2340/00015555-2485

PMID: 27304707 [Indexed for MEDLINE]

1181. Hum Mutat. 2016 Sep;37(9):847-64. doi: 10.1002/humu.23026. Epub 2016 Jul 7.

Mutation Update for Kabuki Syndrome Genes KMT2D and KDM6A and Further Delineation of X-Linked Kabuki Syndrome Subtype 2.

Bögershausen N(1), Gatinois V(2)(3)(4), Riehmer V(5), Kayserili H(6), Becker J(5), Thoenes M(5), Simsek-Kiper PÖ(7), Barat-Houari M(2)(4), Elcioglu NH(8), Wieczorek D(9), Tinschert S(10)(11), Sarabay G(2)(3)(4), Strom TM(12)(13), Fabre A(2), Baynam G(14)(15)(16)(17), Sanchez E(4), Nürnberg G(18), Altunoglu U(19), Capri Y(20), Isidor B(21), Lacombe D(22), Corsini C(3)(4)(23), Cormier-Daire V(24)(25), Sanlaville D(26), Giuliano F(27), Le Quan Sang KH(24), Kayirangwa H(24), Nürnberg P(18), Meitinger T(12)(13), Boduroglu K(7), Zoll B(1), Lyonnet S(24)(25), Tzschach A(10), Verloes A(20), Di Donato N(10), Touitou I(2)(3)(4), Netzer C(5), Li Y(1), Geneviève D(3)(4)(23), Yigit G(1), Wollnik B(1).

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Kabuki syndrome (KS) is a rare but recognizable condition that consists of a characteristic face, short stature, various organ malformations, and a variable degree of intellectual disability. Mutations in KMT2D have been identified as the main cause for KS, whereas mutations in KDM6A are a much less frequent cause. Here, we report a mutation screening in a case series of 347 unpublished patients, in which we identified 12 novel KDM6A mutations (KS type 2) and 208 mutations in KMT2D (KS type 1), 132 of them novel. Two of the KDM6A mutations were maternally inherited and nine were shown to be de novo. We give an up-to-date overview of all published mutations for the two KS genes and point out possible mutation hot spots and strategies for molecular genetic testing. We also report the clinical details for 11 patients with KS type 2, summarize the published clinical information, specifically with a focus on the less well-defined X-linked KS type 2, and comment on phenotype-genotype correlations as well as sex-specific phenotypic differences. Finally, we also discuss a possible role of KDM6A in Kabuki-like Turner syndrome and report a mutation screening of KDM6C (UTY) in male KS patients.

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DOI: 10.1002/humu.23026

PMID: 27302555 [Indexed for MEDLINE]

# Serum Amyloid A Type 1 Gene Polymorphism in Egyptian Children with Familial Mediterranean Fever.

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**BACKGROUND:** Since spontaneous inflammation is an important contributor to familial Mediterranean fever (FMF), genetic variants mediating inflammation are of interest. We investigated gene variants in the acute-phase serum amyloid A type 1 (SAA1), a sensitive marker of inflammatory activity, and their association with susceptibility and severity of FMF.

**METHODS:** The genotypes of 2 single-nucleotide polymorphisms within exon 3 of SAA1 (2995C/T and 3010C/T) were determined in 105 Egyptian children with FMF and in 125 controls by polymerase chain reaction-restriction fragment length polymorphism. Genotyping of the causative MEFV mutations was performed by reverse hybridization.

**RESULTS:** The M694I mutation was the most frequent allele (42.8%), followed by V726A (18.6%), M680I (17.1%), E148Q (11.9%) and M694V (9.0%). The frequency of the SAA1  $\alpha$ ,  $\beta$  and  $\alpha$ 3B3; alleles was not significantly different between FMF patients and controls. The genotype frequency of SAA1  $\alpha/\alpha$  was higher in patients than in healthy subjects (21.0 vs. 14.4%) although it did not reach statistical significance. The clinical manifestations including age at disease onset, number of FMF attacks, colchicine dose and severity score were not related to genotypes of SAA1. However, M694V mutation and female gender were significantly associated with severity.

**CONCLUSION:** The genetic polymorphism of SAA1 is not associated with susceptibility and severity of FMF in Egyptian children.

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DOI: 10.1159/000444933

PMID: 27300189 [Indexed for MEDLINE]

1183. Reumatol Clin. 2017 Jul - Aug;13(4):221-223. doi: 10.1016/j.reuma.2016.05.001. Epub 2016 Jun 11.

Coexistence of sarcoidosis and Familial Mediterranean Fever.

[Article in English, Spanish]

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Sarcoidosis is a chronic inflammatory disease with unknown cause characterized by non-caseating granuloma formations. It may present with bilateral hilar lymphadenopathy, skin lesions, the involvement of eye and symptoms on the locomotor system. FMF (Familial Mediterranean Fever) is an autosomal recessive autoinflammatory disease, characterized by recurrent episodes of fever and polyserositis. Simultaneous occurrence of these diseases is rare. In this paper, we reported the coexistence of sarcoidosis with FMF.

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DOI: 10.1016/j.reuma.2016.05.001

PMID: 27297261 [Indexed for MEDLINE]

1184. Ter Arkh. 2016;88(6):58-64. doi: 10.17116/terarkh201688658-64.

[Serum calgranulin C is a highly sensitive autoinflammation activity indicator in patients with familial periodic fevers].

[Article in Russian; Abstract available in Russian from the publisher]

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**AIM:** To determine the possibility of using the serum proinflammatory calcium-binding protein, or calgranulin C (S100A12), to assess activity and therapeutic efficiency in patients with periodic disease (PD) and other familial periodic fevers (FPFs).

**SUBJECTS AND METHODS:** Thirty-five patients with PD and other FPDs, which were verified by molecular genetic study, were examined. In accordance with the disease activity, the patients were divided into 2 groups. The investigators determined the concentration of S100A12 by solid-phase enzyme immunoassay and that of other acute-phase inflammatory markers (erythrocyte sedimentation rate (ERT), neutrophil counts, and fibrinogen and C-reactive protein (CRP) concentrations).

**RESULTS:** The serum concentration of S100A12 in the stage of disease activity was 466.7 (265.22--851.7) ng/ml, which was significantly higher than in remission (244.29 (118.93--409.85) ng/ml ( $p=0.000002$ ). The highest S100A12 concentrations were noted in the patients with PD; these were 758.95 (434.80--1035.95) ng/ml; the S100A12 level in the majority of PD patients even during remission remained moderately higher. An investigation of the relationship of A100A12 to genetic variants found no differences between the patients homozygous for M694V and those with other genotypes ( $p=0.37$ ). Estimation of the time course of therapy-induced changes in the serum S100A12 concentration revealed its considerable reduction ( $p=0.0018$ ). However, normalization of S100A12 levels was not achieved in PD. The remaining increased S100A12 concentration in these patients may be suggestive of the activity of PD despite the absence of its clinical manifestations. S100A12 as a highly sensitive marker allows more exact evaluation of the anti-inflammatory effect of therapy. The S100A12 identification of the subclinical activity of autoinflammatory diseases made all the more important since traditional inflammatory markers, such as ERT, CRP, fibrinogen, and leukocyte counts, are less sensitive for these purposes. In our study, these markers were within the reference range in remission. No differences were found in the S100A12 levels between the groups with and without amyloidosis ( $p=0.62$ ).

**CONCLUSION:** S100A12 is a highly sensitive marker for the activity of autoinflammatory diseases and the efficiency of their therapy. The serum level of S100A12 in PD may be used to diagnose the subclinical activity of inflammation, which is of importance in monitoring the risk of amyloidosis.

Publisher: Цель исследования. Определение возможности использования сывороточного



провоспалительного белка, связывающего кальций, или кальгранулина С (S100A12), для оценки активности и эффективности лечения пациентов с периодической болезнью (ПБ) и другими семейными периодическими лихорадками (СПЛ). Материалы и методы. Обследовали 35 больных ПБ и другими СПЛ, подтвержденными молекулярно-генетическим методом. В зависимости от активности заболевания больных разделили на 2 группы. Определяли концентрацию белка S100A12 (методом твердофазового иммуноферментного анализа) и других острофазовых маркеров воспаления (скорость оседания эритроцитов - СОЭ, количество нейтрофилов, концентрация фибриногена и С-реактивного белка - СРБ). Результаты. Концентрация S100A12 в сыворотке крови в стадию активности заболевания составила 466,7 (265,22; 851,7) нг/мл, что достоверно выше, чем в ремиссию, - 244,29 (118,93; 409,85) нг/мл ( $p=0,000002$ ). Самые высокие концентрации S100A12 отмечены нами у больных ПБ - 758,95 (434,80; 1035,95) нг/мл, даже во время ремиссии уровень S100A12 у большинства больных ПБ сохранялся умеренно повышенным. При исследовании зависимости концентрации S100A12 от генетического варианта различий между гомозиготами M694V и больными с другими генотипами не выявлено ( $p=0,37$ ). При оценке динамики концентрации S100A12 в сыворотке в результате лечения выявлено значительное снижение его уровня ( $p=0,0018$ ). Однако при ПБ нормализации уровня S100A12 не достигнуто. Сохраняющаяся повышенная концентрация S100A12 у этих больных может свидетельствовать об остаточной активности ПБ, несмотря на отсутствие ее клинических проявлений. S100A12, являясь высокочувствительным маркером, позволяет более точно оценивать противовоспалительный эффект терапии. Выявление субклинической активности аутовоспалительных заболеваний с помощью S100A12 тем более важно, что традиционные показатели воспаления (СОЭ, СРБ, фибриноген, уровень лейкоцитов) менее чувствительны для этих целей. В нашем исследовании в период ремиссии болезни эти показатели не выходили за референтные значения. Различий по уровню S100A12 между группами больных амилоидозом и без него не выявлено ( $p=0,62$ ). Заключение. S100A12 является высокочувствительным маркером активности и эффективности терапии аутовоспалительных заболеваний. При ПБ уровень S100A12 в сыворотке может быть использован для диагностики субклинической активности воспаления, что важно для мониторингирования риска развития амилоидоза. DOI: 10.17116/terarkh201688658-64 PMID: 27296263 [Indexed for MEDLINE]

[Autoinflammatory diseases].

[Article in Spanish]

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The monogenic autoinflammatory diseases are rare, genetic disorders resulting in constitutive innate immune defects leading to excessive response to danger signals, spontaneous activation of inflammatory mediators or loss of inhibitory regulators. During the past 15 years, a growing number of monogenic inflammatory diseases have been described and their respective responsible genes identified. The proteins encoded by these genes are involved in the regulatory pathways of inflammation and are mostly expressed in cells of the innate immune system. Although a group of patients exhibit episodic systemic inflammation (periodic fevers), these disorders are mediated by continuous overproduction and release of pro-inflammatory mediators, notably IL-1 $\beta$ , and are best considered as autoinflammatory diseases rather than periodic fevers. The most common autoinflammatory diseases are familial Mediterranean fever (FMF), TNF receptor-associated periodic syndrome (TRAPS), mevalonate kinase deficiency/hyperimmunoglobulin D syndrome (MKD/HIDS) and the cryopyrin-associated periodic syndromes (CAPS). Clinical features often include fever, cutaneous rash, serosal involvement and acute phase reactants. Autoantibodies are usually absent but may accompany certain syndromes. Diagnosis remains clinical and is based on the different phenotypic features. Genetic diagnosis is of utmost importance, but must be performed judiciously and interpreted cautiously. Treatment with biologic agents that block proinflammatory cytokines, particularly IL-1, has proved to be dramatically effective in many patients. Still, in many cases of autoinflammation no genetic abnormalities are detected and treatment remains suboptimal, raising the question of novel pathogenic mutations in unexplored genes and pathways.

PMID: 27295706 [Indexed for MEDLINE]

1186. Br J Haematol. 2016 Jul;174(2):175-87. doi: 10.1111/bjh.14144. Epub 2016 Jun 12.

Understanding the spectrum of haemophagocytic lymphohistiocytosis: update on diagnostic challenges and therapeutic options.

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The cytokine storm syndrome 'haemophagocytic lymphohistiocytosis' (HLH) is an under-recognized hyperinflammatory disorder, causing high morbidity and mortality risk in children and adults. It can be subdivided into a primary, genetic form and a secondary, acquired form that complicates diverse infections, malignancies and autoimmune or autoinflammatory disorders. Both subtypes present with the same spectrum of non-specific symptoms, making accurate diagnosis and rapid treatment initiation challenging. In the last decade, increased awareness and international collaborative efforts fuelled a marked progress in diagnostic protocols and novel treatment strategies for HLH and new diagnostic guidelines are being tailored to specific secondary HLH subtypes. Therapy is gradually shifting its focus from overall immunosuppression towards targeting specific cytokines, cell types or signalling pathways underlying pathophysiology. Nevertheless, continued research efforts remain indispensable to customize therapy to individual patient needs.

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DOI: 10.1111/bjh.14144

PMID: 27292929 [Indexed for MEDLINE]

1187. Curr Opin Rheumatol. 2016 Sep;28(5):523-9. doi: 10.1097/BOR.0000000000000315.

Familial Mediterranean fever.

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**PURPOSE OF REVIEW:** Familial Mediterranean fever (FMF) is the oldest and most common of the hereditary autoinflammatory diseases (AIDs). A large body of information has been accumulated over recent years on the pathophysiology, diagnosis and treatment of these diseases. The purpose of this review is to bring an up-to-date summary of the clinic manifestations, diagnostic criteria and treatment of FMF.

**RECENT FINDINGS:** An overview of the pathophysiologic basis of FMF as part of the AID is discussed. Over the last year, attempts to establish new criteria for childhood FMF, new guidelines for treatment and follow-up of disease and novel treatment for FMF were made. A comparison of the different disease severity scores for research purposes suggests that a new score is needed. New evidence for antiinterleukin-1 blockade as a new treatment modality is described.

**SUMMARY:** New diagnostic criteria, disease severity score, treatment and follow-up guidelines have been proposed, and need validation in the next several years.

DOI: 10.1097/BOR.0000000000000315

PMID: 27286236 [Indexed for MEDLINE]

1188. J Back Musculoskelet Rehabil. 2016 Jun 3. [Epub ahead of print]

Protracted febrile myalgia in a patient with Familial Mediterranean Fever and Ankylosing Spondylitis.

Ekşioğlu E, Kesikburun B, Çakçı A.

**BACKGROUND:** Protracted Febrile Myalgia is a rare form of vasculitis that is diagnosed in patients with Familial Mediterranean Fever.

**OBJECTIVE:** To present a case with Familial Mediterranean and Anklosing Spondylitis on anti-TNF therapy for three years, who developed protracted febrile myalgia syndrome.

**METHODS:** Case report.

**RESULTS:** A 35-year-old woman with known Familial Mediterranean Fever and Anklosing Spondylitis for 3 years presented with fever, diarrhea, intermittent

abdominal pain and severe diffuse muscular pain lasting for two weeks. The patient was investigated for any infection focus. The patient was diagnosed as having Protracted Febrile Myalgia four weeks after the onset of the symptoms. Prednisolone 1 mg/kg per day was applied. Her fever and muscle pain resolved within 48 hours.

CONCLUSION: The coexisting Ankylosing Spondylitis disease and the use of anti-TNF treatment in patients with Familial Mediterranean Fever could be a confounding factor for the investigation of fever. Steroid therapy has a dramatic response.

DOI: 10.3233/BMR-160719

PMID: 27284852

1189. Clin Exp Optom. 2016 Jul;99(4):385-7. doi: 10.1111/cxo.12401. Epub 2016 Jun 9.

Acute posterior multifocal placoid pigment epitheliopathy in a patient with familial Mediterranean fever.

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DOI: 10.1111/cxo.12401

PMID: 27277194 [Indexed for MEDLINE]

1190. Clin Proteomics. 2016 Jun 5;13:12. doi: 10.1186/s12014-016-9113-1. eCollection 2016.

Synovial fluid proteome in rheumatoid arthritis.

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**BACKGROUND:** Rheumatoid arthritis (RA) is a chronic autoinflammatory disorder that affects small joints. Despite intense efforts, there are currently no definitive markers for early diagnosis of RA and for monitoring the progression of this disease, though some of the markers like anti CCP antibodies and anti vimentin antibodies are promising. We sought to catalogue the proteins present in the synovial fluid of patients with RA. It was done with the aim of identifying newer biomarkers, if any, that might prove promising in future.

**METHODS:** To enrich the low abundance proteins, we undertook two approaches-multiple affinity removal system (MARS14) to deplete some of the most abundant proteins and lectin affinity chromatography for enrichment of glycoproteins. The peptides were analyzed by LC-MS/MS on a high resolution Fourier transform mass spectrometer.

**RESULTS:** This effort was the first total profiling of the synovial fluid proteome in RA that led to identification of 956 proteins. From the list, we identified a number of functionally significant proteins including vascular cell adhesion molecule-1, S100 proteins, AXL receptor protein tyrosine kinase, macrophage colony stimulating factor (M-CSF), programmed cell death ligand 2 (PDCD1LG2), TNF receptor 2, (TNFRSF1B) and many novel proteins including hyaluronan-binding protein 2, semaphorin 4A (SEMA4D) and osteoclast stimulating factor 1. Overall,

our findings illustrate the complex and dynamic nature of RA in which multiple pathways seems to be participating actively.

CONCLUSIONS: The use of high resolution mass spectrometry thus, enabled identification of proteins which might be critical to the progression of RA.

DOI: 10.1186/s12014-016-9113-1

PMCID: PMC4893419

PMID: 27274716

1191. Nat Immunol. 2016 Aug;17(8):914-21. doi: 10.1038/ni.3457. Epub 2016 Jun 6.

Pyrin inflammasome activation and RhoA signaling in the autoinflammatory diseases FMF and HIDS.

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Comment in

Nat Immunol. 2016 Jul 19;17 (8):900-2.

Mutations in the genes encoding pyrin and mevalonate kinase (MVK) cause distinct interleukin-1 $\beta$  (IL-1 $\beta$ )-mediated autoinflammatory diseases: familial Mediterranean fever (FMF) and hyperimmunoglobulinemia D syndrome (HIDS). Pyrin forms an inflammasome when mutant or in response to bacterial modification of the GTPase RhoA. We found that RhoA activated the serine-threonine kinases PKN1 and PKN2 that bind and phosphorylate pyrin. Phosphorylated pyrin bound to 14-3-3 proteins, regulatory proteins that in turn blocked the pyrin inflammasome. The binding of 14-3-3 and PKN proteins to FMF-associated mutant pyrin was substantially decreased, and the constitutive IL-1 $\beta$  release from peripheral blood mononuclear cells of patients with FMF or HIDS was attenuated by activation of PKN1 and PKN2. Defects in prenylation, seen in HIDS, led to RhoA inactivation and consequent pyrin inflammasome activation. These data suggest a previously unsuspected fundamental molecular connection between two seemingly distinct autoinflammatory disorders.

DOI: 10.1038/nl.3457

PMCID: PMC4955684

PMID: 27270401 [Indexed for MEDLINE]

1192. Nat Immunol. 2016 Aug;17(8):922-9. doi: 10.1038/nl.3487. Epub 2016 Jun 6.

Control of the innate immune response by the mevalonate pathway.

Akula MK(1)(2)(3), Shi M(1)(2), Jiang Z(4), Foster CE(4), Miao D(1)(2), Li AS(4), Zhang X(4), Gavin RM(4), Forde SD(4), Germain G(4), Carpenter S(4), Rosadini CV(5), Gritsman K(6)(7), Chae JJ(8), Hampton R(9), Silverman N(4), Gravallesse EM(10), Kagan JC(5), Fitzgerald KA(4), Kastner DL(8), Golenbock DT(4), Bergo MO(3), Wang D(1)(2)(4).

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Comment in

Nat Immunol. 2016 Jul 19;17 (8):900-2.

Deficiency in mevalonate kinase (MVK) causes systemic inflammation. However, the molecular mechanisms linking the mevalonate pathway to inflammation remain obscure. Geranylgeranyl pyrophosphate, a non-sterol intermediate of the mevalonate pathway, is the substrate for protein geranylgeranylation, a protein post-translational modification that is catalyzed by protein geranylgeranyl transferase I (GGTase I). Pyrin is an innate immune sensor that forms an active inflammasome in response to bacterial toxins. Mutations in MEFV (encoding human PYRIN) result in autoinflammatory familial Mediterranean fever syndrome. We found that protein geranylgeranylation enabled Toll-like receptor (TLR)-induced activation of phosphatidylinositol-3-OH kinase (PI(3)K) by promoting the interaction between the small GTPase Kras and the PI(3)K catalytic subunit p110 $\delta$ . Macrophages that were deficient in GGTase I or p110 $\delta$  exhibited constitutive release of interleukin 1 $\beta$  that was dependent on MEFV but independent of the NLRP3, AIM2 and NLRC4 inflammasomes. In the absence of protein geranylgeranylation, compromised PI(3)K activity allows an unchecked TLR-induced inflammatory responses and constitutive activation of the Pyrin inflammasome.

DOI: 10.1038/ni.3487

PMCID: PMC4955724

PMID: 27270400 [Indexed for MEDLINE]

1193. Ann Rheum Dis. 2017 Jan;76(1):173-178. doi: 10.1136/annrheumdis-2015-209031. Epub 2016 Jun 7.

Canakinumab treatment for patients with active recurrent or chronic TNF receptor-associated periodic syndrome (TRAPS): an open-label, phase II study.

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**OBJECTIVE:** To evaluate the efficacy of canakinumab, a high-affinity human monoclonal anti-interleukin-1 $\beta$  antibody, in inducing complete or almost complete responses in patients with active tumour necrosis factor receptor-associated periodic syndrome (TRAPS).

**METHODS:** Twenty patients (aged 7-78 years) with active recurrent or chronic TRAPS were treated with canakinumab 150 mg every 4 weeks for 4 months (2 mg/kg for those  $\leq 40$  kg) in this open-label, proof-of-concept, phase II study. Canakinumab was then withdrawn for up to 5 months, with reintroduction on relapse, and 4 weekly administration (subsequently increased to every 8 weeks) for 24 months. The primary efficacy variable was the proportion of patients achieving complete or almost complete response at day 15, defined as clinical remission (Physician's Global Assessment score  $\leq 1$ ) and full or partial serological remission.

**RESULTS:** Nineteen patients (19/20, 95%; 95% CI 75.1% to 99.9%) achieved the primary efficacy variable. Responses to canakinumab occurred rapidly; median time to clinical remission 4 days (95% CI 3 to 8 days). All patients relapsed after canakinumab was withdrawn; median time to relapse 91.5 days (95% CI 65 to 117 days). On reintroduction of canakinumab, clinical and serological responses were similar to those seen during the first phase, and were sustained throughout treatment. Canakinumab was well tolerated and clinical responses were accompanied by rapid and sustained improvement in health-related quality of life. Weight normalised pharmacokinetics of canakinumab, although limited, appeared to be consistent with historical canakinumab data.

**CONCLUSIONS:** Canakinumab induces rapid disease control in patients with active TRAPS, and clinical benefits are sustained during long-term treatment.

**TRIAL REGISTRATION NUMBER:** NCT01242813; Results.

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DOI: 10.1136/annrheumdis-2015-209031

PMCID: PMC5264215

PMID: 27269295 [Indexed for MEDLINE]

Conflict of interest statement: KA: employee of Novartis Pharmaceuticals Corporation. SB: employee of Novartis Pharmaceuticals Corporation. MC: received speaker fees and served as a consultant for Novartis and SOBI. ND: employee of Novartis Pharmaceuticals Corporation. MG: received speaker fees and served as a consultant for Novartis and SOBI, and has received unrestricted grants for the Eurofever Registry from Novartis and SOBI. HL: received speaker fees and served as a consultant for Novartis and SOBI. AM: received speaker fees and served as a consultant for Novartis. LO: received speaker fees and served as a consultant for Novartis. AS: employee of Novartis Pharma AG.

1194. Trends Mol Med. 2016 Jul;22(7):545-564. doi: 10.1016/j.molmed.2016.05.003. Epub 2016 Jun 3.

Autoinflammatory Skin Disorders: The Inflammasome in Focus.

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Autoinflammatory skin disorders are a group of heterogeneous diseases that include diseases such as cryopyrin-associated periodic syndrome (CAPS) and familial Mediterranean fever (FMF). Therapeutic strategies targeting IL-1 cytokines have proved helpful in ameliorating some of these diseases. While inflammasomes are the major regulators of IL-1 cytokines, inflammasome-independent complexes can also process IL-1 cytokines. Herein, we focus on recent advances in our understanding of how IL-1 cytokines, stemming from inflammasome-dependent and -independent pathways are involved in the regulation of skin conditions. Importantly, we discuss several mouse models of skin inflammation generated to help elucidate the basic cellular and molecular effects and modulation of IL-1 in the skin. Such models offer perspectives on how

these signaling pathways could be targeted to improve therapeutic approaches in the treatment of these rare and debilitating inflammatory skin disorders.

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DOI: 10.1016/j.molmed.2016.05.003

PMCID: PMC4925313

PMID: 27267764 [Indexed for MEDLINE]

1195. Rev Bras Reumatol Engl Ed. 2016 Jan-Feb;56(1):52-7. doi: 10.1016/j.rbre.2015.09.004. Epub 2015 Oct 20.

Guidelines for the management and treatment of periodic fever syndromes: periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome.

[Article in English, Portuguese]

Terreri MT(1), Bernardo WM(2), Len CA(3), da Silva CA(4), de Magalhães CM(5), Sacchetti SB(6), Ferriani VP(7), Piotto DG(3), Cavalcanti Ade S(8), de Moraes AJ(9), Sztajn bok FR(10), de Oliveira SK(11), Campos LM(4), Bandeira M(12), Santos FP(13), Magalhães CS(14).

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**OBJECTIVE:** To establish guidelines based on scientific evidence for the management of periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome.

**DESCRIPTION OF THE EVIDENCE COLLECTION METHOD:** The Guideline was prepared from 5 clinical questions that were structured through PICO (Patient, Intervention or indicator, Comparison and Outcome), to search in key primary scientific information databases. After defining the potential studies to support the recommendations, these were graduated considering their strength of evidence and grade of recommendation.

**RESULTS:** 806 articles were retrieved and evaluated by title and abstract; from these, 32 articles were selected to support the recommendations.

**RECOMMENDATIONS:** 1. PFAPA is a diagnosis of exclusion established on clinical grounds, and one must suspect of this problem in children with recurrent and periodic febrile episodes of unknown origin, or with recurrent tonsillitis interspersed with asymptomatic periods, especially in children in good general condition and with preservation of weight and height development. 2. Laboratory findings are nonspecific. Additional tests do not reveal pathognomonic changes. 3. The evidence supporting an indication for surgical treatment (tonsillectomy with or without adenoidectomy), is based on two non-blinded randomized clinical trials with small numbers of patients. 4. The use of prednisone at the onset of fever in patients with PFAPA proved to be an effective strategy. There is still need for more qualified evidence to support its use in patients with PFAPA. 5. Despite promising results obtained in studies with IL-1 $\beta$  inhibitors, such studies are limited to a few case reports.

DOI: 10.1016/j.rbre.2015.09.004

PMID: 27267334 [Indexed for MEDLINE]

1196. Rev Bras Reumatol Engl Ed. 2016 Jan-Feb;56(1):44-51. doi: 10.1016/j.rbre.2015.08.020. Epub 2015 Oct 20.

Guidelines for the management and treatment of periodic fever syndromes: Cryopyrin-associated periodic syndromes (cryopyrinopathies - CAPS).

[Article in English, Portuguese]

Terreri MT(1), Bernardo WM(2), Len CA(3), da Silva CA(4), de Magalhães CM(5), Sacchetti SB(6), Ferriani VP(7), Piotto DG(3), Cavalcanti Ade S(8), de Moraes AJ(9), Sztajn bok FR(10), de Oliveira SK(11), Campos LM(4), Bandeira M(12), Santos FP(13), Magalhães CS(14).

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**OBJECTIVE:** To establish guidelines based on scientific evidences for the management of cryopyrin associated periodic syndromes.

**DESCRIPTION OF THE EVIDENCE COLLECTION METHOD:** The Guideline was prepared from 4 clinical questions that were structured through PICO (Patient, Intervention or indicator, Comparison and Outcome), to search in key primary scientific information databases. After defining the potential studies to support the recommendations, these were graduated considering their strength of evidence and grade of recommendation.

**RESULTS:** 1215 articles were retrieved and evaluated by title and abstract; from these, 42 articles were selected to support the recommendations.

**RECOMMENDATIONS:** 1. The diagnosis of CAPS is based on clinical history and clinical manifestations, and later confirmed by genetic study. CAPS may manifest itself in three phenotypes: FCAS (mild form), MWS (intermediate form) and CINCA (severe form). Neurological, ophthalmic, otorhinolaryngological and radiological assessments may be highly valuable in distinguishing between syndromes; 2. The genetic diagnosis with NLRP3 gene analysis must be conducted in suspected cases of CAPS, i.e., individuals presenting before 20 years of age, recurrent episodes of inflammation expressed by a mild fever and urticaria; 3. Laboratory abnormalities include leukocytosis and elevated serum levels of inflammatory proteins; and 4. Targeted therapies directed against interleukin-1 lead to rapid remission of symptoms in most patients. However, there are important limitations on the long-term safety. None of the three anti-IL-1 $\beta$  inhibitors prevents progression of bone lesions.

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DOI: 10.1016/j.rbre.2015.08.020

PMID: 27267333 [Indexed for MEDLINE]

## Guidelines for the management and treatment of periodic fever syndromes familial Mediterranean fever.

[Article in English, Portuguese]

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**OBJECTIVE:** To establish guidelines based on scientific evidence for the management of familial Mediterranean fever.

**DESCRIPTION OF THE EVIDENCE COLLECTION METHOD:** The Guideline was prepared from 5 clinical questions that were structured through PICO (Patient, Intervention or indicator, Comparison and Outcome), to search key primary scientific information databases. After defining the potential studies to support the recommendations, these were graduated considering their strength of evidence and grade of recommendation.

**RESULTS:** 10,341 articles were retrieved and evaluated by title and abstract; from these, 46 articles were selected to support the recommendations.

**RECOMMENDATIONS:** 1. The diagnosis of FMF is based on clinical manifestations, characterized by recurrent febrile episodes associated with abdominal pain, chest or arthritis of large joints. 2. FMF is a genetic disease presenting an autosomal recessive trait, caused by mutation in the MEFV gene. 3. Laboratory tests are not specific, demonstrating high serum levels of inflammatory proteins in the acute phase of the disease, but also often showing high levels even between attacks. SAA serum levels may be especially useful in monitoring the effectiveness of treatment. 4. The therapy of choice is colchicine; this drug has proven its effectiveness in preventing acute inflammatory episodes and progression toward amyloidosis in adults. 5. Based on the available information, the use of biological drugs appears to be an alternative for patients with FMF who do not respond or are intolerant to therapy with colchicine.

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DOI: 10.1016/j.rbre.2015.08.019

PMID: 27267332 [Indexed for MEDLINE]

1198. Rev Bras Reumatol Engl Ed. 2016 Jan-Feb;56(1):1. doi: 10.1016/j.rbre.2015.10.002. Epub 2016 Feb 23.

Autoinflammatory syndromes: rare diseases with important implications in quality of life.

[Article in English, Portuguese]

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DOI: 10.1016/j.rbre.2015.10.002

PMID: 27267326 [Indexed for MEDLINE]

1199. Br J Haematol. 2016 Jul;174(2):203-17. doi: 10.1111/bjh.14147. Epub 2016 Jun 5.

Advances in the pathogenesis of primary and secondary haemophagocytic lymphohistiocytosis: differences and similarities.

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Haemophagocytic lymphohistiocytosis (HLH) comprises a heterogeneous spectrum of hyperinflammatory conditions that are inherited (primary HLH) or acquired in a context of infections, malignancies or autoimmune/autoinflammatory disorders (secondary HLH). Genetic defects in the cytotoxic machinery of natural killer and CD8(+) T cells underlie primary HLH, with residual cytotoxicity determining disease severity. Improved sequencing techniques have expanded the range of causal mutations and have redefined many cases of secondary HLH as primary HLH and vice versa, blurring the distinction between both subtypes. These insights allow HLH to be conceptualized as a threshold disease, in which interplay between various genetic and environmental factors causes progressive inflammation into a critical point, beyond which uncontrolled activation of immune cells and excessive cytokine production give rise to the cardinal symptoms of HLH. Various pathogenic pathways may thus converge to a common end stage of fulminant HLH.

DOI: 10.1111/bjh.14147

PMID: 27264204 [Indexed for MEDLINE]

1200. *Pediatr Rheumatol Online J*. 2016 Jun 4;14(1):35. doi: 10.1186/s12969-016-0094-4.

Type I interferonopathies in pediatric rheumatology.

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Defective regulation of type I interferon response is associated with severe inflammatory phenotypes and autoimmunity. Type I interferonopathies are a clinically heterogenic group of Mendelian diseases with a constitutive activation of this pathway that might present as atypical, severe, early onset rheumatic diseases. Skin vasculopathy with chilblains and livedo reticularis, interstitial lung disease, and panniculitis are common. Recent studies have implicated abnormal responses to nucleic acid stimuli or defective regulation of downstream effector molecules in disease pathogenesis. As observed for IL1- $\beta$  and autoinflammatory diseases, knowledge of the defects responsible for type I interferonopathies will likely promote the development of targeted therapy.

DOI: 10.1186/s12969-016-0094-4

PMCID: PMC4893274

PMID: 27260006 [Indexed for MEDLINE]

1201. *RMD Open*. 2016 May 16;2(1):e000236. doi: 10.1136/rmdopen-2015-000236.

eCollection

2016.

ADA2 deficiency: case report of a new phenotype and novel mutation in two sisters.

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The objective of this paper is to: describe the phenotype compound heterozygote for mutations in CECR1 in two children. We describe the clinical and immunological phenotype, including the assessment of ADA2 activity, cytokine

expression, interferon-stimulated and neutrophil-stimulated gene signatures, and the results of CECR1 sequencing. The first patient presented with intermittent fever, cutaneous vasculitis, myalgia and muscle inflammation on MRI leading to a provisional diagnosis of periarteritis nodosa. Subsequently, two cerebral lacunar lesions were identified following a brain stroke. Clinical features improved on anti-tumour necrosis factor therapy. The first patient's sister demonstrated early-onset, long-lasting anaemia with mild biological inflammation; at the ages of 3 and 5 years, she had presented 2 acute, transient neurological events with lacunar lesions on MRI. CECR1 sequencing identified both sisters to be compound heterozygous for a p.Tyr453Cys mutation and a previously undescribed deletion of exon 7. ADA2 activity was reduced by 50%. Neutrophil-stimulated genes were not overexpressed, but interferon-stimulated genes were. The expression of a panel of other cytokine transcripts was not significantly altered. In conclusion, searching for CECR1 mutation or assessing ADA2 activity should be considered in patients with an atypical presentation of inflammatory disease.

DOI: 10.1136/rmdopen-2015-000236

PMCID: PMC4879337

PMID: 27252897

1202. Front Microbiol. 2016 May 24;7:776. doi: 10.3389/fmicb.2016.00776. eCollection 2016.

Systemic Concentrations of Short Chain Fatty Acids Are Elevated in Salmonellosis and Exacerbation of Familial Mediterranean Fever.

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Gut microbiota-produced short chain fatty acids (SCFAs) play an important role in

the normal human metabolism and physiology. Although the gradients of SCFAs from the large intestine, where they are largely produced, to the peripheral blood as well as the main routes of SCFA metabolism by different organs are known well for the healthy state, there is a paucity of information regarding how these are affected in disease. In particular, how the inflammation caused by infection or autoinflammatory disease affect the concentration of SCFAs in the peripheral venous blood. In this work, we revealed that diseases caused either by infectious agents (two *Salmonella enterica* serovars, *S. Enteritidis*, and *S. Typhimurium*) or by the exacerbation of an autoinflammatory disease, familial Mediterranean fever (FMF), both result in a significantly elevated systemic concentration of SCFAs. In the case of salmonellosis the concentration of SCFAs in peripheral blood was significantly and consistently higher, from 5- to 20-fold, compared to control. In the case of FMF, however, a significant increase of SCFAs in the peripheral venous blood was detected only in the acute phase of the disease, with a lesser impact in remission. It seems counterintuitive that the dysbiotic conditions, with a reduced number of gut microorganisms, produce such an effect. This phenomenon, however, must be appraised within the context of how the inflammatory diseases affect the normal physiology. We discuss a number of factors that may contribute to the "leak" and persistence of gut-produced SCFAs into the systemic circulation in infectious and autoinflammatory diseases.

DOI: 10.3389/fmicb.2016.00776

PMCID: PMC4877380

PMID: 27252692

1203. Clin Rheumatol. 2017 Feb;36(2):463-468. doi: 10.1007/s10067-016-3317-7. Epub 2016 Jun 1.

A comprehensive comparison between pediatric and adult patients with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenopathy (PFAPA) syndrome.

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Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenopathy (PFAPA) syndrome is a mysterious disorder characterized by periodically recurrent fevers, oropharyngeal inflammation, and adenitis, which mainly affects children, though in very recent times, it has been also recognized in adulthood. We enrolled 115 unrelated pediatric and adult patients with history of periodic fevers who fulfilled the current diagnostic criteria for PFAPA syndrome in three Italian referral centers and highlighted differences between children and adults. Eighty-five children and 30 adults were evaluated: the frequency of flares was significantly higher in pediatric cases, while febrile attack duration was significantly longer in adults. Clockwork periodicity of fever and recurrent pharyngitis were more frequently observed in childhood, but no differences were identified for aphthosis and cervical adenopathy. Conversely, joint symptoms, myalgia, headache, fatigue, ocular signs, and rashes were more common in adults. The simultaneous occurrence of two or three cardinal PFAPA signs did not show any statistical difference between the groups, while the occurrence of only one cardinal manifestation was more frequent in adults. Corticosteroids were effective in 98.82 % of children and 88.2 % of adults. Tonsillectomy was rarely performed, resulting effective in only two patients. Our data illustrate the clinical overlap between pediatric and adult cases of PFAPA syndrome. Adults are characterized by a wider repertoire of inflammatory signs, suggesting that onset in adulthood might leave the disease misdiagnosed. Clinicians, not only pediatricians, should take into account this clinical entity in every patient of whatever age suffering from recurrent fevers of unknown origin.

DOI: 10.1007/s10067-016-3317-7

PMID: 27251674 [Indexed for MEDLINE]

1204. Mod Rheumatol. 2017 Jan;27(1):182-183. doi: 10.3109/14397595.2016.1173000. Epub 2016 Jun 2.

Familial Mediterranean fever complicated with refractory asthma: Successful treatment with colchicine.

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DOI: 10.3109/14397595.2016.1173000

PMID: 27250826

1205. Immunol Invest. 2016 Jul;45(5):450-70. doi: 10.3109/08820139.2016.1168831. Epub 2016 May 31.

Anti-Inflammatory Effects of Modified Adenoviral Vectors for Gene Therapy: A View through Animal Models Tested.

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The central dogma of gene therapy relies on the application of novel therapeutic genes to treat or prevent diseases. The main types of vectors used for gene transfer are adenovirus, retrovirus, lentivirus, liposome, and adeno-associated virus vectors. Gene therapy has emerged as a promising alternative for the treatment of inflammatory diseases. The main targets are cytokines, co-stimulatory molecules, and different types of cells from hematological and mesenchymal sources. In this review, we focus on molecules with anti-inflammatory effects used for in vivo gene therapy mediated by adenoviral gene transfer in the treatment of immune-mediated inflammatory diseases, with particular emphasis on autoinflammatory and autoimmune diseases.

DOI: 10.3109/08820139.2016.1168831

PMID: 27245510 [Indexed for MEDLINE]

1206. Clin Exp Dermatol. 2016 Jul;41(5):461-7. doi: 10.1111/ced.12828. Epub 2016 May 30.

Clinical characterization and long-term follow-up of Schnitzler syndrome.

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**BACKGROUND:** Schnitzler syndrome (SchS) is an acquired autoinflammatory disease characterized by chronic urticarial rash in association with monoclonal gammopathy. Patients may progress to lymphoproliferative disorders, but the associated factors and exact risk of progression are still not well defined.

**AIM:** To characterize the clinical findings, laboratory abnormalities and histopathology of patients with SchS and their respective outcomes.

**METHODS:** We retrospectively reviewed the clinical files and the histological specimens of patients with SchS diagnosed from 1988 to 2015.

**RESULTS:** Nine patients (two women, seven men) were diagnosed with SchS. Mean age at diagnosis was 61.1 years (range 29-80), with a mean time to diagnosis of 3.7 years and a mean follow-up period of 10.1 years (range 3-25). Four patients

displayed an association of fever and arthralgia, and all nine patients consistently showed laboratory markers of inflammation. Serum values of the monoclonal component, IgM $\kappa$  in eight patients and IgG $\lambda$  in one patient, progressively increased over time. During follow-up, carried out in association with the haematology department five patients progressed to lymphoproliferative disease, namely, lymphoplasmacytic lymphoma/Waldenström's macroglobulinaemia (n = 4) and diffuse large B-cell lymphoma (n = 1).

**CONCLUSIONS:** SchS is a rare chronic inflammatory disease with a substantial impact on quality of life. Our study highlights the importance of lifelong follow-up for individuals with SchS, owing to the risk of progression to a lymphoproliferative disorder.

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DOI: 10.1111/ced.12828

PMID: 27238847 [Indexed for MEDLINE]

1207. Joint Bone Spine. 2017 Mar;84(2):159-162. doi: 10.1016/j.jbspin.2016.02.021. Epub 2016 May 26.

Association of hidradenitis suppurativa and familial Mediterranean fever: A case series of 6 patients.

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**OBJECTIVES:** Familial mediterranean fever (FMF) is the most common monogenic autoinflammatory disease. Hidradenitis suppurativa (HS) is an inflammatory cutaneous disease. Those diseases can occur simultaneously among the same individual. Our objective was to describe the features of patients displaying both FMF and HS.

**METHODS:** We screened the French adult FMF reference center for FMF patients with HS.

**RESULTS:** Six patients out of 151 (4%) with a median age of 36 years old were concerned. Among them, FMF was symptomatic at a median age of 11.5years old and colchicine was introduced at a median age of 20.5years old. HS was diagnosed at a median age of 31.5years old. An elderly patient displayed AA amyloidosis in the outcome of FMF, with a late diagnosis of HS, with response to anakinra. There was no temporal relation between FMF and HS attacks. Some patients had a persistent

inflammatory syndrome under treatment.

CONCLUSION: FMF and HS are both inflammatory diseases involving young patients, with HS possibly being an autoinflammatory disease. Although their association seems to be fortuitous, both can induce an important inflammation state that could lead to AA amyloidosis and require a close monitoring of clinical signs and acute-phase reactants. Anakinra was successful in treating the only patient with both HS, FMF and amyloidosis.

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DOI: 10.1016/j.jbspin.2016.02.021

PMID: 27238193 [Indexed for MEDLINE]

1208. Clin Calcium. 2016 Jun;26(6):918-26. doi: CliCa1606918926.

[Molecular and Cellular Pathogenesis of Cherubism].

[Article in Japanese]

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Study of rare genetic disorder often provides fundamental insights into the pathology of common diseases. Cherubism is a rare craniofacial disorder in children characterized by the destruction of maxillary and mandibular bones due to expansile fibrous inflammatory lesions. Genetic study of cherubism families discovered that gain-of-function mutations in the signaling adaptor protein SH3BP2 are responsible for cherubism. Analysis of the mouse model revealed that cherubism is an autoinflammatory disorder that is caused by dysregulated signaling pathway mediated by toll-like receptors and spleen tyrosine kinase. Recent study of the SH3BP2-deficient mice showed that SH3BP2 plays important roles in bone resorption in mouse models of inflammatory arthritis. These results establish SH3BP2 as a key player in the osteoimmune system beyond its role in a rare inherited disorder and suggest that the signaling pathway mediated by SH3BP2

is involved in the pathogenesis of common inflammatory bone diseases such as rheumatoid arthritis.

DOI: ClCa1606918926

PMID: 27230848 [Indexed for MEDLINE]

1209. Isr Med Assoc J. 2016 Mar-Apr;18(3-4):221-4.

Update on Auto-Inflammatory Diseases and Familial Mediterranean Fever.

Berkun Y, Eisenstein EM.

PMID: 27228648 [Indexed for MEDLINE]

1210. Inflamm Regen. 2016 May 28;36:13. doi: 10.1186/s41232-016-0011-8. eCollection 2016.

Dysfunctional immunoproteasomes in autoinflammatory diseases.

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Recent progress in DNA sequencing technology has made it possible to identify specific genetic mutations in familial disorders. For example, autoinflammatory syndromes are caused by mutations in gene coding for immunoproteasomes. These diseases include Japanese autoinflammatory syndrome with lipodystrophy, Nakajo-Nishimura syndrome, joint contractures, muscular atrophy, microcytic anemia, panniculitis-associated lipodystrophy syndrome, and chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome. Causal mutations of these syndromes are present in gene coding for subunits of the immunoproteasome. Importantly, a genetically modified mouse that lacks the catalytic subunit of immunoproteasomes does not always develop an autoinflammatory syndrome. Analysis of causal gene mutations, assessment of

patients' phenotypic changes, and appropriate animal models will be indispensable for clarifying the underlying mechanisms responsible for the development of autoinflammatory syndromes and establishing curative approaches.

DOI: 10.1186/s41232-016-0011-8

PMCID: PMC5721717

PMID: 29259686

1211. Iran J Kidney Dis. 2016 May;10(3):107-12.

Mutational Spectrum of the MEFV Gene in AA Amyloidosis Associated With Familial Mediterranean Fever.

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**INTRODUCTION:** Familial Mediterranean fever (FMF) is a recessively inherited disease which is characterized by recurrent episodic fever, abdominal pain, and polyserositis. It is caused by mutations in the MEFV gene, encoding the pyrin protein. The most important complication of FMF is secondary (AA) amyloidosis that leads to kidney failure. This study aimed to identify the frequency and distribution of MEFV mutations in Turkish patients with FMF-associated AA amyloidosis.

**MATERIALS AND METHODS:** A total of 57 patients with FMF-associated AA amyloidosis and 60 healthy controls were included in this study. We analyzed the MEFV gene for E148Q, M694V, M680I, and V726A mutations and R202Q variant by polymerase chain reaction and restriction fragment length polymorphism methods. **Results.** The male-female ratio was 0.72. The mean age of the patients was  $29.8 \pm 12.8$  years. Among the patients, the rate of the MEFV mutations was found to be 77.2%. The most frequently observed genotype was homozygous M694V mutation, which was present in 17 patients (29.8%,  $P < .001$ ), followed by compound heterozygous M680I/M694V (14.3%,  $P = .01$ ). The R202Q allele frequencies were significantly different between patients and control group ( $P = .02$ ; odds ratio, 0.53; 95% confidence interval, 0.30 to 0.94).

**CONCLUSIONS:** In this study, mutation analysis of MEFV gene confirmed that the

most frequent mutation was homozygous M694V genotype. R202Q may be important in patients with FMF-associated AA amyloidosis. Thus, it is suggested that investigation of R202Q should be considered as a genetic test for Turkish FMF patients.

PMID: 27225717 [Indexed for MEDLINE]

1212. Methods Mol Biol. 2016;1417:247-54. doi: 10.1007/978-1-4939-3566-6\_18.

NLR in Human Diseases: Role and Laboratory Findings.

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Autoinflammatory diseases are a group of inherited and multifactorial disorders characterized by an overactivation of innate immune response. In most cases, the clinical manifestations are due to increased activity of the NLRP3 inflammasome resulting in increased IL-1 $\beta$  secretion. Investigating inflammatory cells from subjects affected by autoinflammatory diseases presents a number of technical difficulties related to the rarity of the diseases, to the young age of most patients, and to the difficult modulation of gene expression in primary cells. However, since cell stress is involved in the pathophysiology of these diseases, the study of freshly drawn blood monocytes from patients affected by IL-1-mediated diseases strongly increases the chances that the observed phenomena is indeed pertinent to the pathogenesis of the disease and not influenced by the long-term cell culture conditions (e.g., the high O<sub>2</sub> tension) or gene transfection in continuous cell lines that may lead to artifacts.

DOI: 10.1007/978-1-4939-3566-6\_18

PMID: 27221496 [Indexed for MEDLINE]

1213. Orthopade. 2016 Jun;45(6):484-90. doi: 10.1007/s00132-016-3271-8.

[Chronic recurrent multifocal osteomyelitis of the spine : Children and adolescent].

[Article in German]

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Chronic non-bacterial osteomyelitis (CNO) in childhood and adolescence is a non-infectious autoinflammatory disease of the bone with partial involvement of adjacent joints and soft tissue. The etiology is unknown. The disease can occur singular or recurrent. Individual bones can be affected and multiple lesions can occur. Chronic recurrent multifocal osteomyelitis (CRMO) shows the whole picture of CNO. Accompanying but temporally independent of the bouts of osteomyelitis, some patients show manifestations in the skin, eyes, lungs and the gastrointestinal tract. The article gives an overview of the clinical manifestations, diagnostic procedures, and treatment options for CRMO involvement of the spine based on the current literature and our own cases.

DOI: 10.1007/s00132-016-3271-8

PMID: 27221306 [Indexed for MEDLINE]

1214. Intern Emerg Med. 2016 Sep;11(6):781-91. doi: 10.1007/s11739-016-1466-y. Epub 2016 May 25.

Systemic and organ involvement in monogenic autoinflammatory disorders: a global



review filtered through internists' lens.

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Monogenic autoinflammatory disorders (AIDs) are rare diseases driven by cytokine-mediated extraordinary sterile inflammation that results from the activation of innate immune pathways. The clinical hallmark of these diseases is the recurrence of stereotyped episodes of systemic- and organ-specific inflammation; the most common systems involved being the skin, musculoskeletal system, gastrointestinal tract, and central nervous system. The autoinflammatory disorders may have a profound impact on the quality of life of the affected patients, and a delayed diagnosis may lead to severe complications, the most dreadful of which is AA-Amyloidosis. This review gives an overview on the four main AIDs, namely familial Mediterranean fever, tumor necrosis factor receptor-associated periodic syndrome, cryopyrinopathies, and mevalonate kinase deficiency, focusing on their clinical phenotype in adults and differential diagnosis, suggesting a diagnostic algorithm, and reviewing the available treatments.

DOI: 10.1007/s11739-016-1466-y

PMID: 27221072 [Indexed for MEDLINE]

1215. Immunol Invest. 2016 Jul;45(5):383-95. doi: 10.3109/08820139.2016.1153651. Epub 2016 May 24.

Cytokine Profile in Gout: Inflammation Driven by IL-6 and IL-18?

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**INTRODUCTION:** Gout is considered to be an autoinflammatory disease and the presence of monosodium urate (MSU) crystals stimulates activation of NLR3 inflammasome and subsequently caspase-1, generating production of active IL-1 $\beta$  and IL-18. However, the association between serum cytokines levels and clinical manifestations of the disease is not yet well understood. We evaluated the serum profile of proinflammatory cytokines (IL-1 $\beta$ , IL-6, IL-8, IL-17A, IL-18, IL-22, and IL-23) and described their relationship with clinical and laboratory data.

**METHODOLOGY:** Thirty-nine male patients with gout (GG) were assessed for clinical and laboratory variables and cytokine levels were measured by ELISA. For the purposes of comparison, 34 males with no previous history of arthritis were also included in the study (CG).

**RESULTS:** Seventeen participants (43%) exhibited active arthritis on evaluation. Levels of IL-18 were significantly higher in patients in relation to the CG ( $p = 0.0013$ ). No statistically significant differences were found between the GG and CG for the other measured cytokines. There was a moderate correlation between IL-18 and ESR ( $R = 0.43$ ,  $p = 0.0073$ ), CRP ( $R = 0.47$ ,  $p = 0.0025$ ), and serum levels of IL-6 ( $R = 0.36$ ,  $p = 0.023$ ). An association was observed between serum levels of IL-6 and the presence of tophi ( $p = 0.005$ ) and deformities ( $p = 0.0008$ ), as well as a correlation between this cytokine and ESR ( $R = 0.41$ ,  $p = 0.011$ ) and CRP ( $R = 0.48$ ,  $p = 0.02$ ).

**CONCLUSIONS:** IL-18 is associated with inflammatory activity in gout, as well as with IL-6 levels, while IL-6 is associated with clinical and laboratory activity, the presence of tophi and articular deformities, and may be a prognostic marker of this pathology.

DOI: 10.3109/08820139.2016.1153651

PMID: 27219123 [Indexed for MEDLINE]

1216. Nihon Rinsho Meneki Gakkai Kaishi. 2016;39(2):130-9. doi: 10.2177/jsci.39.130.

Fever of unknown origin in the outpatient setting: A retrospective analysis of 30 cases of familial Mediterranean fever.

[Article in Japanese]

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**BACKGROUND:** In Japan, familial Mediterranean fever (FMF) is a rare cause of fever of unknown origin (FUO). However, we experienced an extraordinary number of FMF cases over 3 years. This suggests that many patients with FMF remain misdiagnosed in Japan. This study examines the clinical picture of FMF to assist Japanese clinicians in daily practice dealing with FUO.

**PATIENTS AND METHODS:** Three years of medical records were reviewed, and 38 patients with FMF or suspected FMF were collected from our patient database. We applied the Tel-Hashomer criteria to those patients.

**RESULTS:** Of the 38 patients, 30 were classified as having FMF in this investigation. The mean patient age was 27.8 years. MEFV gene mutations were detected in 14 patients. Three cases were colchicine-resistant.

**CONCLUSION:** Clinicians should recognize the pattern of short, spontaneously resolving attacks of fever with fever-free intervals, especially when they see patients with recurrent FUO in the outpatient setting.

DOI: 10.2177/jsci.39.130

PMID: 27212599 [Indexed for MEDLINE]

1217. Clin Rheumatol. 2016 Jul;35(7):1683-9. doi: 10.1007/s10067-016-3308-8. Epub 2016 May 20.

Adult-onset Still's disease: an Italian multicentre retrospective observational study of manifestations and treatments in 245 patients.

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Adult-onset Still's disease (AOSD) is a systemic inflammatory condition of unknown aetiology characterized by typical episodes of spiking fever, evanescent rash, arthralgia, leukocytosis and hyperferritinemia. Given the lack of data in Italian series, we promote a multicentric data collection to characterize the clinical phenotype of Italian patients with AOSD. Data from 245 subjects diagnosed with AOSD were collected by 15 centres between March and May 2013. The diagnosis was made following Yamaguchi's criteria. Data regarding clinical manifestations, laboratory features, disease course and treatments were reported and compared with those presented in other published series of different ethnicity. The most frequent features were the following: arthritis (93 %), pyrexia (92.6 %), leukocytosis (89 %), negative ANA (90.4 %) and neutrophilia (82 %). As compared to other North American, North European, Middle Eastern and Far Eastern cohorts, Italian data show differences in clinical and laboratory findings. Regarding the treatments, in 21.9 % of cases, corticosteroids and traditional DMARDs have not been able to control the disease while biologics have been shown to be effective in 48 to 58 patients. This retrospective work summarizes the largest Italian multicentre series of AOSD patients and presents clinical and laboratory features that appear to be influenced by the ethnicity of the affected subjects.

DOI: 10.1007/s10067-016-3308-8

PMID: 27207567 [Indexed for MEDLINE]

1218. Br J Dermatol. 2017 Jan;176(1):244-248. doi: 10.1111/bjd.14757. Epub 2016 Dec 8.

Erythematous nodes, urticarial rash and arthralgias in a large pedigree with NLRC4-related autoinflammatory disease, expansion of the phenotype.

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DOI: 10.1111/bjd.14757

PMID: 27203668 [Indexed for MEDLINE]

1219. Methods Mol Biol. 2016;1413:403-21. doi: 10.1007/978-1-4939-3542-0\_25.

Anti-Microtubule Drugs.

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Small molecule drugs that target microtubules (MTs), many of them natural products, have long been important tools in the MT field. Indeed, tubulin (Tb) was discovered, in part, as the protein binding partner of colchicine. Several anti-MT drug classes also have important medical uses, notably colchicine, which is used to treat gout, familial Mediterranean fever (FMF), and pericarditis, and the vinca alkaloids and taxanes, which are used to treat cancer. Anti-MT drugs have in common that they bind specifically to Tb in the dimer, MT or some other form. However, their effects on polymerization dynamics and on the human body differ markedly. Here we briefly review the most-studied molecules, and comment on their uses in basic research and medicine. Our focus is on practical applications of different anti-MT drugs in the laboratory, and key points that users should be aware of when designing experiments. We also touch on interesting unsolved problems, particularly in the area of medical applications. In our opinion, the mechanism by which any MT drug cures or treats any disease is still unsolved, despite decades of research. Solving this problem for particular drug-disease combinations might open new uses for old drugs, or provide insights into novel routes for treatment.

DOI: 10.1007/978-1-4939-3542-0\_25

PMID: 27193863 [Indexed for MEDLINE]

1220. BMJ Case Rep. 2016 May 17;2016. pii: bcr2016214941. doi: 10.1136/bcr-2016-214941.

Hyperimmunoglobulinaemia D syndrome: a rare cause of prolonged fever and treatment with anti-interleukin 1 agent.

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Hyperimmunoglobulinaemia D syndrome (HIDS) is an autosomal recessive, autoinflammatory disease that is characterised with intermittent febrile episodes, cervical lymphadenopathy, rashes, arthritis and gastrointestinal symptoms associated with synovial or serosal inflammation. HIDS is caused by

mutations in the gene encoding mevalonate kinase enzyme. The febrile attacks usually start in early childhood and triggered by stress or vaccinations. We report a case of 16-month-old boy who had episodes of recurrent fever accompanied by maculopapular rash and lymphadenopathy. He was diagnosed as HIDS and he had heterozygote mutation of mevalonate kinase gene.

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DOI: 10.1136/bcr-2016-214941

PMCID: PMC4885411

PMID: 27190114 [Indexed for MEDLINE]

1221. Int J Mol Sci. 2016 May 13;17(5). pii: E725. doi: 10.3390/ijms17050725.

The Relationship between NALP3 and Autoinflammatory Syndromes.

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The nucleotide-binding domain, leucine-rich repeat/pyrin domain-containing-3 (NALP3) inflammasome, which is required for synthesis of interleukin-1 $\beta$ , has been implicated in the pathogenesis of several autoinflammatory syndromes. This review of the literature summarizes the interconnectedness of NALP3 inflammasome with some of these disorders. Familial Mediterranean fever results from a mutation in the Mediterranean fever (MEFV) gene, which encodes the pyrin protein. Previous study results suggest that pyrin suppresses caspase-1 activation, perhaps by competing for the adaptor protein, termed, pyrin domain of apoptosis/speck-like



protein containing a caspase-recruitment domain (ACS) which therefore interferes with NALP3 inflammasome activation. The nucleotide-binding domain, leucine-rich repeat/pyrin domain-containing-3 (NALP3) inflammasome is constitutively activated in cryopyrin-associated periodic syndromes due to gain-of-function mutations resulting from point mutations within the neuronal apoptosis inhibitor protein/class 2 transcription factor/heterokaryon incompatibility/telomerase-associated protein-1 (NACHT) domain of the NALP3 protein. Pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome is caused by mutations in the genes encoding proline-serine-threonine phosphatase interacting protein 1 (PSTPIP1). These PSTPIP1 mutants are thought to bind to pyrin causing an increase in the pyrin domain of apoptosis/speck-like protein containing a caspase-recruitment domain (ASC) pyroptosome assembly leading to procaspase-1 recruitment and therefore its activation. Hyperimmunoglobulinemia D syndrome is caused by mevalonate kinase (MVK) deficiency, which may be affected by protein accumulation that leads to NALP3 inflammasome activation. Tumor necrosis factor receptor-associated periodic syndrome is associated with mutations in the tumor necrosis factor receptor superfamily, member 1A (TNFRSF1A) gene which decreases the level of soluble tumor necrosis factor receptor-1 (TNFR1) leading to neutralization of tumor necrosis factor (TNF)- $\alpha$ . In general, these autoinflammatory disorders have shown a clinical response to interleukin-1 (IL-1) antagonists, suggesting that the NALP3 inflammasome serves a critical role in their pathogenesis.

DOI: 10.3390/ijms17050725

PMCID: PMC4881547

PMID: 27187378 [Indexed for MEDLINE]

1222. Kaohsiung J Med Sci. 2016 Apr;32(4):216-20. doi: 10.1016/j.kjms.2016.03.009. Epub 2016 Apr 24.

Red cell distribution width is associated with albuminuria in adults with familial Mediterranean fever.

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Systematic inflammation, enhanced oxidative stress, and endothelial dysfunction are important for evolution and progression of renal damage, and they cause an increase in red cell distribution width (RDW). Familial Mediterranean fever (FMF) patients who are in the attack-free period and its relation with albuminuria and performance on assessment of microalbuminuria. One hundred and seventy-seven patients who had been diagnosed in accordance with Tel-hoshmer criteria and were in the attack-free period, and 143 age- and sex-matched healthy individuals were enrolled in our study. RDW values of FMF patients were higher compared with those of the controls ( $13.85 \pm 1.07$  and  $13.15 \pm 0.91$ , respectively;  $p < 0.0001$ ). RDW values of FMF patients with microalbuminuria were higher compared with those of FMF patients with normoalbuminuria and the control group ( $p = 0.002$  and  $p < 0.0001$ , respectively). RDW values of FMF patients with normoalbuminuria were higher compared with those of the control group ( $p < 0.0001$ ). We have showed RDW levels are positively correlated with albuminuria ( $r = 0.185$ ,  $p = 0.014$ ). When assessing microalbuminuria with RDW in the patients, a cutoff value of 13.85 with sensitivity of 60%, specificity of 62%, and  $p = 0.002$  (area under curve: 0.651, 95% confidence interval 0.563-0.738), was observed according to receiver-operating characteristic curve analysis. Among the various variables associated with albuminuria in multivariate logistic regression analyses, RDW remained an independent predictor of albuminuria (95% confidence interval 0.479-0.942,  $p = 0.021$ ). RDW may be associated with albuminuria in FMF patients and it can be a predictor of microalbuminuria.

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DOI: 10.1016/j.kjms.2016.03.009

PMID: 27185605 [Indexed for MEDLINE]

1223. Intern Med. 2016;55(10):1345-9. doi: 10.2169/internalmedicine.55.5997. Epub 2016 May 15.

# Recurrence of Psoriasis Vulgaris Accompanied by Treatment with C-C Chemokine Receptor Type 4 (CCR4) Antibody (Mogamulizumab) Therapies in a Patient with Adult T cell Leukemia/ Lymphoma: Insight into Autoinflammatory Diseases.

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Adult T cell leukemia / lymphoma (ATL) is one of the most aggressive hematological malignancies caused by human T-lymphotropic virus type-I (HTLV-1). Mogamulizumab is a new defucosylated humanized monoclonal antibody agent which targets C-C chemokine receptor type 4 (CCR4) expressed occasionally on the surface of ATL cells. However, adverse events such as drug eruptions have also been highlighted, at least in part, via the dysfunction of regulatory T cells (Tregs). We herein report a pronounced recurrence of systemic psoriasis vulgaris accompanied by the treatment of mogamulizumab in a patient with ATL. Pathological examinations may suggest a mechanistic link between the recurrence of autoinflammatory diseases and anti-CCR4 antibody therapies.

DOI: 10.2169/internalmedicine.55.5997

PMID: 27181545 [Indexed for MEDLINE]

1224. Nihon Rinsho Meneki Gakkai Kaishi. 2016;39(1):72-7. doi: 10.2177/jsci.39.72.

A case of familial Mediterranean fever who complained of periodic fever and abdominal pain diagnosed by MEFV gene analysis.

[Article in Japanese]

Ogita C(1), Matsui K, Kisida D, Kakudou M, Yazaki M, Nakamura A, Azuma K, Tsuboi K, Abe T, Yokoyama Y, Furukawa T, Maruoka M, Tamura M, Yoshikawa T, Saito A, Nishioka A, Sekiguchi M, Azuma N, Kitano M, Tsunoda S, Hashimoto-Tamaoki T, Sano H.

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Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease caused by Mediterranean Fever gene (MEFV) mutations on Chromosome 16, and characterized by periodic fever and serositis. FMF is the result of gain-of-function mutations in pyrin that lead to interleukin-1 $\beta$  activation. FMF can be classified as "typical" and "atypical" types based on clinical finding and genetic screening. Although MEFV genotyping has enabled FMF to be confirmed in some cases, the diagnosis remains predominantly clinical since genotyping has shown that the disease is characterized by variable manifestations in Japanese. In 1976, the first report performed on the case of Japanese FMF with periodic fever and serositis. Since 2002, genetic analyses are performed on Japanese FMF patients by K. Shiozaki et al. and N. Tomiyama et al. In our case, she was a 25-year-old Japanese woman with periodic fever and abdominal pain. MEFV gene analysis demonstrated a heterozygous mutation of variant M694I, leading to a diagnosis of FMF. After the increase dose (up to 3 mg/day) of colchicine, periodic fever and abdominal pain disappeared. It is the important candidate of FMF for differential diagnosis with unexplained periodic fever and serositis, such as our case.

DOI: 10.2177/jsci.39.72

PMID: 27181238 [Indexed for MEDLINE]

1225. J Mol Biol. 2016 Aug 28;428(17):3495-513. doi: 10.1016/j.jmb.2016.04.032. Epub 2016 May 12.

Interferon-Inducible GTPases in Host Resistance, Inflammation and Disease.

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Cell-autonomous immunity is essential for host organisms to defend themselves against invasive microbes. In vertebrates, both the adaptive and the innate branches of the immune system operate cell-autonomous defenses as key effector mechanisms that are induced by pro-inflammatory interferons (IFNs). IFNs can activate cell-intrinsic host defenses in virtually any cell type ranging from professional phagocytes to mucosal epithelial cells. Much of this IFN-induced host resistance program is dependent on four families of IFN-inducible GTPases: the myxovirus resistance proteins, the immunity-related GTPases, the guanylate-binding proteins (GBPs), and the very large IFN-inducible GTPases. These GTPase families provide host resistance to a variety of viral, bacterial, and protozoan pathogens through the sequestration of microbial proteins, manipulation of vesicle trafficking, regulation of antimicrobial autophagy (xenophagy), execution of intracellular membranolytic pathways, and the activation of inflammasomes. This review discusses our current knowledge of the molecular function of IFN-inducible GTPases in providing host resistance, as well as their role in the pathogenesis of autoinflammatory Crohn's disease. While substantial advances were made in the recent past, few of the known functions of IFN-inducible GTPases have been explored in any depth, and new functions await discovery. This review will therefore highlight key areas of future exploration that promise to advance our understanding of the role of IFN-inducible GTPases in human diseases.

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DOI: 10.1016/j.jmb.2016.04.032

PMCID: PMC5010443

PMID: 27181197 [Indexed for MEDLINE]

Novel treatments for rare rheumatologic disorders: analysis of the impact of 30 years of the US orphan drug act.

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**BACKGROUND:** Rare rheumatologic diseases are a heterogeneous group of conditions associated with high morbidity. As a whole group, rare rheumatologic diseases afflict millions of people demanding for effective therapies. Therefore, we analyzed the impact of the US Orphan Drug Act on the development of anti-rheumatic orphan drugs.

**METHODS:** Analysis of the FDA database for orphan drug designations.

**RESULTS:** In the last three decades, out of 77 orphan drug designations, 14 orphan drug approvals were granted by the FDA for the treatment of rare rheumatologic disorders, i.e. juvenile idiopathic arthritis (N = 5), cryopyrin-associated periodic syndromes (N = 3), uveitis (N = 3), familial Mediterranean fever (N = 1), anti-neutrophil cytoplasmic antibody-associated vasculitis (N = 1), and xerostomia and keratoconjunctivitis sicca in Sjögren's syndrome (N = 1). Mean time (standard deviation) from designation to approval was 3.9 (2.81) [range 1 ... 12] years. Number of FDA-approved small molecules (N = 6, 43 %) and biologics (N = 8, 57 %) was comparable. Almost every fifth (19 %) orphan drug designation was withdrawn. Despite the rarity of conditions, 13/14 pivotal studies were

randomized controlled trials.

CONCLUSIONS: Orphan drug development is challenging: thirty years of US orphan drug act supported the development and FDA approval of 14 orphan drug programs with anti-rheumatic compounds for six rheumatologic diseases.

DOI: 10.1186/s13023-016-0443-x

PMCID: PMC4866287

PMID: 27176041 [Indexed for MEDLINE]

1227. J Atheroscler Thromb. 2016 Jul 1;23(7):884-90. doi: 10.5551/jat.34827. Epub 2016 May 10.

A Rare Coincidence of Sitosterolemia and Familial Mediterranean Fever Identified by Whole Exome Sequencing.

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Whole exome sequencing (WES) technologies have accelerated genetic studies of Mendelian disorders, yielding approximately 30% diagnostic success. We encountered a 13-year-old Japanese female initially diagnosed with familial hypercholesterolemia on the basis of clinical manifestations of severe hypercholesterolemia (initial LDL cholesterol=609 mg/dl at the age of one) and systemic intertriginous xanthomas with histories of recurrent self-limiting episodes of fever and arthritis. Both her phenotypes seemed to co-segregate in a recessive manner. We performed WES on this patient, who was considered a proband. Among 206,430 variants found in this individual, we found 18,220 nonsense, missense, or splice site variants, of which 3,087 were rare (minor allele frequency  $\leq 0.01$  or not reported) in 1000 Genome (Asian population). Filtering by assuming a recessive pattern of inheritance with the use of an in silico annotation prediction tool, we successfully narrowed down the candidates to the compound heterozygous mutations in the ABCG5 gene (c.1256G>A or p.Arg419His/c.1763-1G>A [splice acceptor site]) and to the double-compound

heterozygous mutations in the MEFV gene (c.329T>C/C or p.Leu110Pro/c.442G>C/C or p.Glu148Val). The patient was genetically diagnosed with sitosterolemia and familial Mediterranean fever using WES for the first time. Such a comprehensive approach is useful for identifying causative mutations for multiple unrelated inheritable diseases.

DOI: 10.5551/jat.34827

PMID: 27170062 [Indexed for MEDLINE]

1228. J Med Liban. 2016 Jan-Mar;64(1):13-7.

## HENOCH-SCHONLEIN PURPURA IN CHILDHOOD A FIFTEEN-YEAR EXPERIENCE AT A TERTIARY HOSPITAL.

Albaramki J.

**OBJECTIVE:** To examine the epidemiological and clinical characteristics of children diagnosed with Henoch Schönlein purpura (HSP) and to compare them with other areas in the world.

**METHODS:** The medical records of children with HSP were retrospectively reviewed at the Jordan University Hospital between the years 1998 and 2012. The clinical and demographical features, laboratory tests, management and outcome were assessed.

**RESULTS:** There were 55 children with HSP, with a mean age of 7 years (60% were males); 85.4% of patients were less than 10 years; 72.7% of cases presented during the winter and autumn. There was a history of antecedent upper respiratory tract infection in 49.1% of cases; 32.7% of children had more than one hospitalization. Purpuric skin rash was seen in 100%, abdominal pain in 74.5%, arthritis in 58.2%, renal involvement in 30.9% of patients. In four patients HSP was the presenting feature of familial Mediterranean fever (FMF).

**CONCLUSION:** HSP is a benign and self-limiting disease with an excellent prognosis. There are no significant differences in the epidemiological and clinical profile than reported elsewhere.

PMID: 27169160 [Indexed for MEDLINE]



1229. Expert Opin Investig Drugs. 2016 Jul;25(7):827-40. doi: 10.1080/13543784.2016.1181751. Epub 2016 May 10.

New therapeutic solutions for Behçet's syndrome.

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**INTRODUCTION:** Behçet's syndrome (BS) is a systemic inflammatory disorder characterized by a wide range of potential clinical manifestations with no gold-standard therapy. However, the recent classification of BS at a crossroads between autoimmune and autoinflammatory syndromes has paved the way to new further therapeutic opportunities in addition to anti-tumor necrosis factor agents.

**AREAS COVERED:** This review provides a digest of all current experience and evidence about pharmacological agents recently described as having a role in the treatment of BS, including interleukin (IL)-1 inhibitors, tocilizumab, rituximab, alemtuzumab, ustekinumab, interferon-alpha-2a, and apremilast.

**EXPERT OPINION:** IL-1 inhibitors currently represent the most studied agents among the latest treatment options for BS, proving to be effective, safe and with an acceptable retention on treatment. However, since BS is a peculiar disorder with clinical features responding to certain treatments that in turn can worsen other manifestations, identifying new treatment options for patients unresponsive to the current drug armamentarium is of great relevance. A number of agents have been studied in the last decade showing changing fortunes in some cases and promising results in others. The latter will potentially provide their

contribution for better clinical management of BS, improving patients' quality of life and long-term outcome.

DOI: 10.1080/13543784.2016.1181751

PMID: 27163156 [Indexed for MEDLINE]

1230. Intern Med. 2016;55(9):1239. doi: 10.2169/internalmedicine.55.6365. Epub 2016 May 1.

Jejunoileitis Associated with Adult-onset Familial Mediterranean Fever.

Kitade T(1), Horiki N, Katsurahara M, Harada T, Tano S, Yamada R, Hamada Y, Inoue H, Gabazza EC, Hayashi H, Tanaka M, Takei Y.

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DOI: 10.2169/internalmedicine.55.6365

PMID: 27150889

1231. Intern Med. 2016;55(9):1237. doi: 10.2169/internalmedicine.55.6105. Epub 2016 May 1.

Jejunoileitis in Adult-onset Familial Mediterranean Fever in Japan.

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DOI: 10.2169/internalmedicine.55.6105

PMID: 27150888

1232. Rheumatology (Oxford). 2017 Feb;56(2):209-213. doi: 10.1093/rheumatology/kew058. Epub 2016 May 5.

Autosomal dominant familial Mediterranean fever in Northern European Caucasians associated with deletion of p.M694 residue-a case series and genetic exploration.

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Comment in

Rheumatology (Oxford). 2017 Feb;56(2):173-175.

**OBJECTIVE:** This study was undertaken to characterize the phenotype and response to treatment in patients with autosomal dominant FMF caused by MEFV p.M694del mutation and to use haplotype reconstruction to investigate the possibility of common ancestry.

**METHODS:** MEFV gene was analysed in 3500 subjects with suspected FMF referred to a single UK centre between 2002 and 2014. Patients with p.M694del underwent additional screening of the SAA1 gene as well as haplotype reconstruction of the MEFV locus.

**RESULTS:** The p.M694del variant was identified in 21 patients, sharing an identical disease haplotype that appears to have arisen about 550 years ago. The SAA1.1 allele was found in four patients, including two with AA amyloidosis. The clinical features comprised typical FMF symptoms with median age at onset of 18 years; three patients presented with AA amyloidosis, of whom two had had symptoms of FMF in retrospect. Fifteen patients had received colchicine treatment, all with excellent responses.

**CONCLUSION:** The p.M694del variant is associated with autosomal dominantly inherited FMF in Northern European Caucasians. Symptoms may develop later in life than in classical recessive FMF but are otherwise similar, as is the response to colchicine treatment. The 14% incidence of AA amyloidosis may reflect delay in diagnosis associated with extreme rarity of FMF in this population. The common haplotype suggests a single founder living in about 1460.

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DOI: 10.1093/rheumatology/kew058

PMID: 27150194 [Indexed for MEDLINE]

1233. Rheumatology (Oxford). 2017 Feb;56(2):173-175. doi: 10.1093/rheumatology/kew203. Epub 2016 May 5.

Dominant familial Mediterranean fever.

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Comment on

Rheumatology (Oxford). 2017 Feb;56(2):209-213.

DOI: 10.1093/rheumatology/kew203

PMID: 27150192 [Indexed for MEDLINE]

1234. Gut Microbes. 2016 Jul 3;7(4):334-341. Epub 2016 May 5.

Microbiota and caspase-1/caspase-8 regulate IL-1 $\beta$ -mediated bone disease.

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A leucine-to-proline missense mutation at residue 98 in the proline-serine-threonine phosphatase interacting protein 2 (Pstpip2) gene leads to autoinflammatory disease that is characterized by splenomegaly, necrosis, and spontaneous development of osteomyelitis in mice (Pstpip2cmo). Disease progression in these mice resembles that of chronic recurrent multifocal osteomyelitis in humans. Our group and others have shown that disease progression in Pstpip2cmo mice is mediated by the cytokine IL-1 $\beta$ , independently of inflammasomes or IL-1 $\alpha$ . Our recent publication highlighted herein establishes that diet-induced changes in intestinal microbiota provide protection against the development of osteomyelitis in Pstpip2cmo mice. Moreover, the proteases caspase-1 and caspase-8 have redundant roles in cleaving IL-1 $\beta$  and promoting disease. This addendum reviews the current literature on the Pstpip2cmo murine disease model and the clinical significance of the role of PSTPIP2 in regulating autoinflammatory osteomyelitis, which is mediated by innate components of immune cells.

DOI: 10.1080/19490976.2016.1182289

PMCID: PMC4988461

PMID: 27148834 [Indexed for MEDLINE]

1235. J Clin Immunol. 2016 Jul;36(5):517-27. doi: 10.1007/s10875-016-0290-5. Epub 2016 May 5.

Testing the Activity of Complement Convertases in Serum/Plasma for Diagnosis of C4NeF-Mediated C3 Glomerulonephritis.

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Autoantibodies termed C3-nephritic factor (C3NeF), which stabilize convertases of the alternative complement pathway, often stimulate autoinflammatory diseases. However, knowledge about analogous autoantibodies acting on the classical pathway (C4NeF) is limited to a few reports, which indicate association with kidney dysfunction, systemic lupus erythematosus, and infections. C4NeF may appear independently from C3NeF, but the lack of a routine diagnostic method predisposes C4NeF for being an underestimated player in autoinflammatory episodes. We tested the activity of classical convertases directly in serum/plasma to screen samples from 13 patients with C3 glomerulopathies and identified one patient showing significantly prolonged half-life of these enzymes. Observed effect was reproduced by immunoglobulins purified from patient's plasma and additionally confirmed on classical convertase built from purified components. Isolated immunoglobulins protected classical convertases from both spontaneous and inhibitor-driven decay but not from C4b proteolysis. The patient had a decreased serum level of C3, elevated sC5b-9, and normal concentrations of factor B and C4. Neither C3NeF nor other autoantibodies directed against alternative pathway proteins (factor H, factor B, factor I, C3, and properdin) were found. Genetic analysis showed no mutations in C3, CFB, CFH, CFI, MCP, THBD, and DGKE genes. Renal biopsy revealed a membranoproliferative pattern with intense C3 deposits. Our results underline the importance of C4NeF as an independent pathogenic factor and a need for the implementation of routine examination of classical convertase activity. Proposed method may enable robust inspection of such atypical cases.

DOI: 10.1007/s10875-016-0290-5

PMCID: PMC4896984

PMID: 27146825 [Indexed for MEDLINE]

1236. Case Rep Med. 2016;2016:5134546. doi: 10.1155/2016/5134546. Epub 2016 Apr 7.

Sacroiliitis and Polyarteritis Nodosa in a Patient with Familial Mediterranean Fever.

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Familial Mediterranean fever (FMF) is an autoinflammatory disorder with autosomal recessive inheritance, characterized by recurrent fever and episodes of serositis. The condition is known to be caused by mutations in the MEFV (Mediterranean FeVer) gene, located in the short arm of chromosome 16. While more than 310 sequence variants in the MEFV gene have been described to date, the diagnosis is still established clinically. FMF may be accompanied by sacroiliitis and various forms of vasculitis. The most common forms of associated vasculitis are Henoch-Schonlein purpura and polyarteritis nodosa (PAN). We have presented here a fairly rare case of FMF, accompanied by both sacroiliitis and PAN.

DOI: 10.1155/2016/5134546

PMCID: PMC4838801

PMID: 27143975

1237. Rheumatology (Oxford). 2016 Aug;55(8):1499-506. doi: 10.1093/rheumatology/kew208. Epub 2016 May 3.

Long-term safety profile of anakinra in patients with severe cryopyrin-associated periodic syndromes.

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**OBJECTIVE:** Anakinra is approved for the treatment of RA and cryopyrin-associated periodic syndromes (CAPS). While the anakinra safety profile is well established in RA, the long-term safety profile in severe CAPS is less well documented and will therefore be discussed in this report.

**METHODS:** A prospective, open-label, single centre, clinical cohort study was conducted at the National Institutes of Health in the USA, from 2003 to 2010, investigating the efficacy and safety of anakinra treatment for up to 5 years in 43 patients with CAPS. Safety was evaluated using adverse event (AE) reports, laboratory assessments, vital signs and diary reports.

**RESULTS:** In total, 1233 AEs were reported during the study, with a yearly rate of 7.7 AEs per patient. The event rate decreased over time, and dose escalation during the study did not affect AE frequency. Anakinra had similar safety profiles in adults and children. The most frequently reported AEs were typical CAPS disease symptoms such as headache and arthralgia. Injection site reactions occurred mainly during the first month of anakinra treatment. In total, 14 patients experienced 24 serious AEs (SAEs), all of which resolved during the study period. The most common types of SAEs were infections such as pneumonia and gastroenteritis. There were no permanent discontinuations of treatment due to AEs.

**CONCLUSION:** In this study anakinra treatment of patients with severe CAPS for up to 5 years was safe and well tolerated both in paediatric and adult patients, with most AEs emerging during the first months after treatment initiation.

**TRIAL REGISTRATION:** ClinicalTrials.gov, [clinicaltrials.gov](http://clinicaltrials.gov), NCT00069329.

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DOI: 10.1093/rheumatology/kew208

PMCID: PMC4957676

PMID: 27143789 [Indexed for MEDLINE]



## Natural history of mevalonate kinase deficiency: a literature review.

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Mevalonate kinase deficiency (MKD), a very rare autosomal recessive autoinflammatory disease with multiple organ involvement, presents clinically as hyperimmunoglobulinemia D syndrome (HIDS), a less severe phenotype and more common form, and mevalonic aciduria (MVA), a more severe phenotype and rare form. MKD is characterized by recurrent febrile attacks that are frequently accompanied by lymphadenopathy, gastrointestinal symptoms, arthralgia, myalgia, skin rash, and aphthous ulcers. Patients with MVA also have intrauterine growth retardation, congenital defects (cataracts, shortened limbs, and dysmorphic craniofacial features), neurological disease, and failure to thrive. Mean age at onset of symptoms is within the first year of life. There is a delay by several years between symptom onset and diagnosis, which is in part attributable to the initial misdiagnosis due to the rarity and nonspecific clinical manifestations of disease. The frequency of recurrent febrile attacks is highest in childhood and gradually decreases after adolescence. MKD is associated with rare long-term complications such as type AA amyloidosis, joint contractures, abdominal adhesions, renal angiomyolipoma, and severe pneumococcal infections. Frequent febrile attacks significantly impair several aspects of patients' and caregivers' quality of life, with an adverse impact on patients' daily activities, education, and employment. Lifespan is generally normal for HIDS whereas MVA can be fatal in early childhood.

DOI: 10.1186/s12969-016-0091-7

PMCID: PMC4855321

PMID: 27142780 [Indexed for MEDLINE]

1239. J Rheumatol. 2016 Jun;43(6):1101-6. doi: 10.3899/jrheum.150681. Epub 2016 May 1.

NLRP3 A439V Mutation in a Large Family with Cryopyrin-associated Periodic Syndrome: Description of Ophthalmologic Symptoms in Correlation with Other Organ

## Symptoms.

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### Erratum in

J Rheumatol. 2016 Jul;43(7):1451.

**OBJECTIVE:** Cryopyrin-associated periodic syndrome (CAPS) is a group of inherited autoinflammatory disorders caused by mutations in the NLRP3 gene resulting in the overproduction of interleukin 1 $\beta$ . NLRP3 mutations cause a broad clinical phenotype of CAPS. The aims of the study were to evaluate clinical, laboratory, and genetic features of a 5-generation family with CAPS focusing in detail on ocular symptoms.

**METHODS:** In a retrospective observational cohort study, consecutive family

members were screened for the presence of the NLRP3 mutation. Patients underwent standardized clinical, laboratory, and ophthalmological assessments. The genotype-specific risk of ophthalmological findings and other organ symptoms was determined.

**RESULTS:** Twenty-nine patients were clinically affected. The A439V mutation encoded by exon 3 of the NLRP3 gene was found in 15 of 37 family members (41%). The most common clinical features were musculoskeletal symptoms, headaches, and ophthalmological symptoms. The mutation-positive patients were characterized by more frequent skin rashes, ocular symptoms, arthralgia, arthritis, and severe Muckle-Wells syndrome (MWS) Disease Activity Score. Rosacea was diagnosed in 8 patients.

**CONCLUSION:** The NLRP3 mutation A439V is associated with a heterogeneous clinical spectrum of familial cold autoinflammatory syndrome/MWS-overlap syndrome. Skin rash and eye diseases, such as conjunctivitis and uveitis, were positively correlated with this mutation.

DOI: 10.3899/jrheum.150681

PMID: 27134254 [Indexed for MEDLINE]

1240. Cell Host Microbe. 2016 May 11;19(5):664-74. doi: 10.1016/j.chom.2016.04.004. Epub 2016 Apr 28.

A Burkholderia Type VI Effector Deamidates Rho GTPases to Activate the Pyrin Inflammasome and Trigger Inflammation.

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*Burkholderia cenocepacia* is an opportunistic pathogen of the cystic fibrosis lung that elicits a strong inflammatory response. *B. cenocepacia* employs a type VI secretion system (T6SS) to survive in macrophages by disarming Rho-type GTPases, causing actin cytoskeletal defects. Here, we identified TecA, a non-VgrG T6SS effector responsible for actin disruption. TecA and other bacterial homologs bear a cysteine protease-like catalytic triad, which inactivates Rho GTPases by deamidating a conserved asparagine in the GTPase switch-I region. RhoA deamidation induces caspase-1 inflammasome activation, which is mediated by the familial Mediterranean fever disease protein Pyrin. In mouse infection, the deamidase activity of TecA is necessary and sufficient for *B. cenocepacia*-triggered lung inflammation and also protects mice from lethal *B. cenocepacia* infection. Therefore, *Burkholderia* TecA is a T6SS effector that modifies a eukaryotic target through an asparagine deamidase activity, which in turn elicits host cell death and inflammation through activation of the Pyrin inflammasome.

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DOI: 10.1016/j.chom.2016.04.004

PMID: 27133449 [Indexed for MEDLINE]

1241. Eur Arch Otorhinolaryngol. 2016 Dec;273(12):4119-4126. doi: 10.1007/s00405-016-4067-5. Epub 2016 Apr 29.

The evaluation of cochlear functions in Familial Mediterranean Fever.

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Familial Mediterranean Fever (FMF) is a progressive disease characterized by chronic inflammation, which also has negative effects on cochlear functions and hearing levels. We investigated whether the cochlear functions and hearing levels of FMF patients were different than healthy controls and also evaluated the relationship of hearing levels with the age at diagnosis, duration without treatment, and inflammation and lipid parameters in this study. A total of 60 patients diagnosed with FMF and 48 age, gender and body mass index (BMI)-matched healthy controls were included in the study. The hemogram, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and lipid parameters of the subjects were studied and they all underwent pure tone audiometry and Transient evoked otoacoustic emission tests after an otologic examination. The hearing levels of the FMF group were significantly higher than those of the control group. The TEOAE signal/noise (S/N) ratios were similar in both groups. A positive relationship was present between the audiometric test results and the age, BMI, low-density lipoprotein and triglyceride levels and a negative relationship with the high-density lipoprotein levels. A negative relationship was present between the TEOAE S/N ratios and the age of the patients, duration without treatment, lipid parameters, inflammation markers and the creatinine level. FMF patients are exposed to chronic inflammation and this can influence their hearing levels. The age at diagnosis, duration without treatment, chronic inflammation, unfavorable lipid parameters, and obesity can affect hearing tests negatively.

DOI: 10.1007/s00405-016-4067-5

PMID: 27130205 [Indexed for MEDLINE]

1242. Int J Rheum Dis. 2018 Jan;21(1):338-346. doi: 10.1111/1756-185X.12872. Epub 2016 Apr 29.

A variant allele of the Mediterranean-fever gene increases the severity of gout.

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**BACKGROUND:** Gout is a clinical syndrome that occurs as an inflammatory response to increased concentration of uric acid and monosodium urate crystals. Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease with autosomal recessive inheritance. The Mediterranean fever (MEFV) gene is responsible for FMF and encodes pyrin that suppresses the inflammatory response. Most of the FMF-related mutations have been identified in exon 2 (e.g., E148Q and R202Q) and exon 10 (M680I, M694V, M694I and V726A) of the MEFV gene, and each missense mutation is known to increase production of interleukin-1, a proinflammatory cytokine. Our aim was to investigate effects of MEFV variant alleles on the manifestations of gout.

**METHODS:** Seventy-one patients diagnosed with gout (age:  $61.73 \pm 11.73$  years, F/M: 14/57) and 50 healthy subjects (age:  $61.48 \pm 11.97$ , F/M: 10/40) as controls were included in this study.

**RESULTS:** MEFV variant alleles were found in 24 (33.8%) of the gout patients and in 13 (26%) of the control subjects; the difference was not statistically significant. In the gout patients with a MEFV variant allele, the interval between the first two attacks was shorter ( $P = 0.014$ ), and the platelet count was higher ( $P = 0.026$ ), compared to the patients without a variant allele. In addition, the patients with a MEFV variant allele showed the higher incidence of tophus (8.5% vs. 1.4%) ( $P = 0.005$ ) and the higher number of attacks per year ( $P = 0.001$ ).

**CONCLUSION:** We propose that a variant allele of the MEFV gene may be responsible

for the severity of gout.

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DOI: 10.1111/1756-185X.12872

PMID: 27125729 [Indexed for MEDLINE]

1243. Rheumatology (Oxford). 2016 Aug;55(8):1489-98. doi: 10.1093/rheumatology/kew192. Epub 2016 Apr 27.

Neutrophils from patients with SAPHO syndrome show no signs of aberrant NADPH oxidase-dependent production of intracellular reactive oxygen species.

Wekell P(1), Björnsdottir H(2), Björkman L(2), Sundqvist M(2), Christenson K(2), Osla V(2), Berg S(3), Fasth A(3), Welin A(2), Bylund J(4), Karlsson A(5).

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**OBJECTIVE:** We aimed to investigate if aberrant intracellular production of NADPH oxidase-derived reactive oxygen species (ROS) in neutrophils is a disease mechanism in the autoinflammatory disease SAPHO syndrome, characterized by synovitis, acne, pustulosis, hyperostosis and osteitis, as has previously been suggested based on a family with SAPHO syndrome-like disease.

**METHODS:** Neutrophil function was explored in a cohort of four patients with SAPHO syndrome, two of whom were sampled during both inflammatory and non-inflammatory phase. Intracellular neutrophil ROS production was determined by luminol-amplified chemiluminescence in response to phorbol myristate acetate.

RESULTS: Cells from all patients produced normal amounts of ROS, both intra- and extracellularly, when compared with internal controls as well as with a large collection of healthy controls assayed in the laboratory over time (showing an extensive inter-personal variability in a normal population). Further, intracellular production of ROS increased during the inflammatory phase. Neutrophil activation markers were comparable between patients and controls. CONCLUSION: Dysfunctional generation of intracellular ROS in neutrophils is not a generalizable feature in SAPHO syndrome. Secondly, serum amyloid A appears to be a more sensitive inflammatory marker than CRP during improvement and relapses in SAPHO syndrome.

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DOI: 10.1093/rheumatology/kew192

PMCID: PMC4957673

PMID: 27121779 [Indexed for MEDLINE]

1244. *Pediatr Rheumatol Online J.* 2016 Apr 27;14(1):28. doi: 10.1186/s12969-016-0089-1.

Vitamin D levels in children with familial Mediterranean fever.

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Comment in



**BACKGROUND:** This study aimed to determine whether vitamin D deficiency is more common in children with familial Mediterranean fever (FMF) than in healthy individuals.

**METHODS:** The study group consisted of 100 patients diagnosed with FMF and 50 healthy children. Serum baseline 25-hydroxyvitamin D levels and other related parameters were evaluated.

**RESULTS:** The mean (standard deviation [SD]) vitamin D levels in patients with FMF and healthy controls were 24.78 (8.35) and 28.70 (11.70) ng/mL, respectively. Patients with FMF had significantly decreased vitamin D levels compared with those in healthy controls ( $P = 0.039$ ). Vitamin D levels were similar in patients with FMF with different MEFV mutations ( $P = 0.633$ ). Age was significantly correlated with vitamin D levels ( $r = -0.235$ ,  $P = 0.019$ ). In addition, a negative correlation between parathyroid hormone and vitamin D levels was detected ( $r_s = -0.382$ ,  $P < 0.0001$ ).

**CONCLUSION:** This study demonstrated that vitamin D levels are lower in children with FMF than in healthy controls. We speculate that vitamin D levels should be carefully examined, and nutritional supplementation may be required in patients with FMF. Further studies with larger patient populations are needed to confirm the frequency of vitamin D deficiency in patients with FMF.

DOI: 10.1186/s12969-016-0089-1

PMCID: PMC4848823

PMID: 27121284 [Indexed for MEDLINE]

1245. Hautarzt. 2016 May;67(5):403-13. doi: 10.1007/s00105-016-3788-0.

[Neurophilic urticarial dermatosis].

[Article in German]

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Neurophilic urticarial dermatosis (NUD) is a new, important differential diagnosis of urticarial rashes. It is a clinical and histological response pattern that strongly correlates with systemic disease. Both autoinflammatory and autoimmune conditions can be present in patients with NUD. In this article the clinical and histological criteria of NUD, diagnostic considerations and the diseases most frequently associated with NUD are discussed.

DOI: 10.1007/s00105-016-3788-0

PMID: 27119369 [Indexed for MEDLINE]

1246. Curr Rheumatol Rep. 2016 Jun;18(6):36. doi: 10.1007/s11926-016-0580-1.

Management of Small Vessel Vasculitides.

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Inflammation mediated by cells of the immune system and necrosis are the most striking features observed at the histologic level in patients with vasculitides, clinical entities classified according to pathologic findings involving different organs, to etiology, or to size of vessels involved. Small vessel vasculitides (SVV) are a peculiar group of systemic disorders electively involving small intraparenchymal arteries, arterioles, capillaries, or venules and leading to different levels of vascular obstruction, tissue ischemia and risk of infarction;

they can be divided into anti-neutrophil cytoplasmic antibody-associated vasculitides and immune complex vasculitides. Despite the significant advances in understanding the whole disease process and pathophysiology of SVV, strong efforts are still needed to draft, share and spread guidelines in the therapeutic management of these protean disorders. After an accurate evaluation of different open or double-blind trials and cohort studies in this review, we analyze the actual medical tools suggested for treating granulomatosis with polyangiitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, Henoch-Schönlein purpura, cryoglobulinemic vasculitis, anti-glomerular basement membrane disease and hypocomplementemic urticarial vasculitis.

DOI: 10.1007/s11926-016-0580-1

PMID: 27118389 [Indexed for MEDLINE]

1247. Biologics. 2016 Apr 4;10:75-80. doi: 10.2147/BTT.S102954. eCollection 2016.

Efficacy of anti-IL-1 treatment in familial Mediterranean fever: a systematic review of the literature.

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**INTRODUCTION:** In 5%-10% of patients with familial Mediterranean fever (FMF), colchicine is not effective in preventing inflammatory attacks. Another 5%-10% of patients are intolerant to effective doses of colchicine and experience serious side effects. Treatment with anti-interleukin-1 (IL-1) drugs may be an alternative for these patients, although it is not reimbursed for this indication

in many countries.

**METHODS:** We systematically searched PubMed, Web of Science, and Scopus for reports of anti-IL-1 treatment in FMF patients.

**RESULTS:** Out of 284 potentially relevant articles, 27 eligible reports were identified and included in the data analysis.

**CONCLUSION:** A complete response to therapy without a single attack during treatment was reported in 76.5% of patients on anakinra treatment and in 67.5% of patients during canakinumab treatment. In patients with established type AA amyloidosis, anti-IL-1 treatment can reverse proteinuria. Anti-IL-1 therapy seems to be a safe and effective alternative for patients with FMF who do not respond to or cannot tolerate colchicine.

DOI: 10.2147/BTT.S102954

PMCID: PMC4831592

PMID: 27110096

1248. Nat Rev Rheumatol. 2016 Apr 25;12(5):256-8. doi: 10.1038/nrrheum.2016.55.

Autoinflammation: When is familial Mediterranean fever 'severe'?

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Comment on

Ann Rheum Dis. 2016 Jun;75(6):1051-6.

DOI: 10.1038/nrrheum.2016.55

PMID: 27108965 [Indexed for MEDLINE]

1249. Arch Rheumatol. 2016 Apr 26;31(3):265-271. doi: 10.5606/ArchRheumatol.2016.5750. eCollection 2016 Sep.

# Reliability and Factorial Validity of the Turkish Version of the Pain Disability Index in Rheumatic Patients With Chronic Pain.

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**Objectives:** This study aims to evaluate the reliability, factor structure, and validity of the Turkish version of the Pain Disability Index (PDI) in patients with chronic pain.

**Patients and methods:** The PDI Index was translated into Turkish according to the standard procedures and performed on 212 rheumatic patients with chronic pain (34 males, 178 females; mean age  $47.9 \pm 10.3$  years; range 19 to 65 years), with most common diagnoses including rheumatoid arthritis, seronegative spondyloarthropathies, and familial Mediterranean fever. Exploratory and confirmatory factor analyses were used for validation and Cronbach's alpha coefficient was determined as the internal reliability of the PDI. Correlations between each item and item-total score were also calculated.

**Results:** The Turkish form of the PDI revealed a two-factor model. Cronbach's alpha for the total scale was found as 0.86. All items were correlated significantly with the total score, with values ranging from 0.73 to 0.81. An analysis of the confirmatory factor revealed that the model fit was adequate.

**Conclusion:** The Turkish version of PDI had adequate psychometric properties in rheumatic patients with chronic pain. Thus, it may be useful in clinical practice to assist in better understanding of diseases characterized by chronic pain, providing objective measures for functional deficits, and monitoring treatment or rehabilitation effects.

DOI: 10.5606/ArchRheumatol.2016.5750

PMCID: PMC5827852

PMID: 29900947

**Conflict of interest statement:** Conflict of Interest: The authors declared no

conflicts of interest with respect to the authorship and/or publication of this article.

1250. Curr Rheumatol Rep. 2016 Jun;18(6):35. doi: 10.1007/s11926-016-0583-y.

SAPHO Syndrome: Current Developments and Approaches to Clinical Treatment.

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SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis) is a rare autoimmune disease which, due to its clinical presentation and symptoms, is often misdiagnosed and unrecognized. Its main features are prominent inflammatory cutaneous and articular manifestations. Treatments with immunosuppressive drugs have been used for the management of SAPHO with variable results. To date, the use of anti-TNF- $\alpha$  agents has proved to be an effective alternative to conventional treatment for unresponsive or refractory SAPHO cases. TNF- $\alpha$  is a pro-inflammatory cytokine and pivotal regulator of other cytokines, including IL-1  $\beta$ , IL-6, and IL-8, involved in inflammation, acute-phase response induction, and chemotaxis. IL-1 inhibition strategies with anakinra have shown efficacy as first and second lines of treatment. In this review, we will describe the main characteristics of biological drugs currently used for SAPHO syndrome. We also describe some of the promising therapeutic effects of ustekinumab, an antibody against the p40 subunit of IL-12 and IL-23, after failure of multiple drugs including anti-TNF- $\alpha$  and anakinra. We discuss the use and impact of the new anti-IL-1 antagonists involved in the IL-17 blockade, in particular for the most difficult-to-treat SAPHO cases.

1251. Curr Cardiol Rep. 2016 Jun;18(6):50. doi: 10.1007/s11886-016-0727-8.

Recurrent Pericarditis: Modern Approach in 2016.

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Recurrent pericarditis is one of the most troublesome complications of pericarditis occurring in about one third of patients with a previous attack of pericarditis. The pathogenesis is presumed to be autoimmune and/or autoinflammatory in most cases. The mainstay of therapy for recurrences is physical restriction and anti-inflammatory therapy based on aspirin or NSAID plus colchicine. Corticosteroids at low to moderate doses (e.g., prednisone 0.2 to 0.5 mg/kg/day) should be considered only after failure of aspirin/NSAID (and more than one of these drugs) or for specific indications (e.g., pregnancy, systemic inflammatory diseases on steroids, renal failure, concomitant oral anticoagulant therapy). One of the most challenging issues is how to cope with patients who have recurrences despite colchicine. A small subset of patients (about 5 %) may develop corticosteroid-dependence and colchicine resistance. Among the emerging treatments, the three most common and evidence-based therapies are based on azathioprine, human intravenous immunoglobulin (IVIG), and anakinra. After failure of all options of medical therapy or for those patients who do not tolerate medical therapy or have serious adverse events related to medical therapy, the last possible option is the surgical removal of the pericardium. Total or radical pericardiectomy is recommended in these cases in experienced centers performing this surgery. A stepwise approach is recommended starting from

NSAID and colchicine, corticosteroid and colchicine, a combination of the three options (NSAID, colchicine and corticosteroids), then azathioprine, IVIG, or anakinra as last medical options before pericardiectomy.

DOI: 10.1007/s11886-016-0727-8

PMID: 27108360 [Indexed for MEDLINE]

1252. BMC Genomics. 2016 Apr 23;17:299. doi: 10.1186/s12864-016-2619-0.

Absolute quantification reveals the stable transmission of a high copy number variant linked to autoinflammatory disease.

Olsson M(1), Kierczak M(2), Karlsson Å(2), Jabłońska J(2), Leegwater P(3), Koltoonian M(4), Abadie J(5), De Citres CD(6), Thomas A(6), Hedhammar Å(7), Tintle L(8), Lindblad-Toh K(2)(4), Meadows JR(9).

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**BACKGROUND:** Dissecting the role copy number variants (CNVs) play in disease pathogenesis is directly reliant on accurate methods for quantification. The Shar-Pei dog breed is predisposed to a complex autoinflammatory disease with numerous clinical manifestations. One such sign, recurrent fever, was previously shown to be significantly associated with a novel, but unstable CNV (CNV\_16.1). Droplet digital PCR (ddPCR) offers a new mechanism for CNV detection via absolute



quantification with the promise of added precision and reliability. The aim of this study was to evaluate ddPCR in relation to quantitative PCR (qPCR) and to assess the suitability of the favoured method as a genetic test for Shar-Pei Autoinflammatory Disease (SPAID).

**RESULTS:** One hundred and ninety-six individuals were assayed using both PCR methods at two CNV positions (CNV\_14.3 and CNV\_16.1). The digital method revealed a striking result. The CNVs did not follow a continuum of alleles as previously reported, rather the alleles were stable and pedigree analysis showed they adhered to Mendelian segregation. Subsequent analysis of ddPCR case/control data confirmed that both CNVs remained significantly associated with the subphenotype of fever, but also to the encompassing SPAID complex ( $p < 0.001$ ). In addition, harbouring CNV\_16.1 allele five (CNV\_16.1|5) resulted in a four-fold increase in the odds for SPAID ( $p < 0.001$ ). The inclusion of a genetic marker for CNV\_16.1 in a genome-wide association test revealed that this variant explained 9.7 % of genetic variance and 25.8 % of the additive genetic heritability of this autoinflammatory disease.

**CONCLUSIONS:** This data shows the utility of the ddPCR method to resolve cryptic copy number inheritance patterns and so open avenues of genetic testing. In its current form, the ddPCR test presented here could be used in canine breeding to reduce the number of homozygote CNV\_16.1|5 individuals and thereby to reduce the prevalence of disease in this breed.

DOI: 10.1186/s12864-016-2619-0

PMCID: PMC4841964

PMID: 27107962 [Indexed for MEDLINE]

1253. Clin Rheumatol. 2016 Nov;35(11):2757-2763. Epub 2016 Apr 23.

Evaluation of subclinical inflammation in familial Mediterranean fever patients: relations with mutation types and attack status: a retrospective study.

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Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disease of childhood and adulthood. Development of systemic amyloidosis and frequent attack influence quality of life and survival. There is sporadic evidence indicating subclinical inflammation in patients with FMF. We aimed to assess subclinical inflammation using neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and C-reactive protein (CRP) in pediatric patients with FMF in the attack-free period. In this retrospective study, we reviewed the files of all FMF patients in our pediatric rheumatology outpatient clinic in a tertiary center and enrolled those with sufficient clinical and laboratory data. We also enrolled 73 controls. We grouped the patients according to being in attack period or attack-free period. We compared CRP, NLR, PLR, and WBC (white blood cell) levels between different mutations and polymorphisms. We also compared patients in the attack period with those in attack-free period. We enrolled 61 patients in attack period, 509 patients in attack-free period, and 73 controls. There was no difference between patients with different mutations with respect to NLR or PLR levels in the attack-free period. However, CRP levels were higher in patients with homozygous exon 10 mutations, especially those with homozygous M694V mutations compared with other mutations. However, CRP levels were mostly normal in these patients. Our data are against the reported fact that patients with FMF have higher NLR or PLR levels in attack-free periods. However, CRP levels were higher in the presence of homozygous exon 10 mutations (in particular homozygous M694V mutations).

1254. Biochem Genet. 2016 Aug;54(4):448-456. doi: 10.1007/s10528-016-9731-3. Epub 2016 Apr 22.

Prevalence of Fabry Disease in Familial Mediterranean Fever Patients from Central Anatolia of Turkey.

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Fabry disease (FD) is a progressive, X-linked inherited disorder of glycosphingolipid metabolism due to deficient or absent lysosomal alpha-galactosidase A (AGALA) activity. FD and familial Mediterranean fever (FMF) have typical clinical similarities, and both diseases may progress to end-stage renal diseases. In this study, we aimed to determine the prevalence of FD in patients with FMF from Central Anatolia of Turkey. The study group consisted of 177 FMF patients, followed up by the Adult and Pediatric Nephrology Clinic of Cumhuriyet University Hospital. Screening for AGALA activity was performed by the dry blood spot method. Mutation analysis for GLA gene was carried out for patients having an AGALA enzyme activity value lower than the normal reference value. Low AGALA activity was detected in 23 (13 %) patients. Heterozygous GLA gene mutation c.[937G>T] p.[D313Y] was detected in one female patient (0.56 %).

The patient was a 53-year-old female with proteinuria and who had undergone left nephrectomy; her glomerular filtration rate (GFR) by scintigraphy was found to be 70 ml/min. She had M694V mutation and no clinical manifestation of FD. In our study, the prevalence rate of FD was found as 0.56 % in FMF patients. The similarities between the symptoms of FMF and FD might lead to a diagnostic dilemma in physicians at countries where FMF is observed frequently. Although the prevalence of FD is rare, physicians should keep in mind that FD has an ambiguous symptomology pattern of FMF.

DOI: 10.1007/s10528-016-9731-3

PMID: 27105876 [Indexed for MEDLINE]

1255. Science. 2016 Apr 22;352(6284):aaf1098. doi: 10.1126/science.aaf1098. Epub 2016 Apr 21.

Trained immunity: A program of innate immune memory in health and disease.

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The general view that only adaptive immunity can build immunological memory has recently been challenged. In organisms lacking adaptive immunity, as well as in mammals, the innate immune system can mount resistance to reinfection, a phenomenon termed "trained immunity" or "innate immune memory." Trained immunity is orchestrated by epigenetic reprogramming, broadly defined as sustained changes in gene expression and cell physiology that do not involve permanent genetic changes such as mutations and recombination, which are essential for adaptive immunity. The discovery of trained immunity may open the door for novel vaccine approaches, new therapeutic strategies for the treatment of immune deficiency states, and modulation of exaggerated inflammation in autoinflammatory diseases.

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DOI: 10.1126/science.aaf1098

PMCID: PMC5087274

PMID: 27102489 [Indexed for MEDLINE]

1256. Medicine (Baltimore). 2016 Apr;95(16):e3449. doi: 10.1097/MD.0000000000003449.

Multiple Serum Cytokine Profiling to Identify Combinational Diagnostic Biomarkers in Attacks of Familial Mediterranean Fever.

Koga T(1), Migita K, Sato S, Umeda M, Nonaka F, Kawashiri SY, Iwamoto N, Ichinose K, Tamai M, Nakamura H, Origuchi T, Ueki Y, Masumoto J, Agematsu K, Yachie A, Yoshiura K, Eguchi K, Kawakami A.

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The precise cytokine networks in the serum of individuals with familial Mediterranean fever (FMF) that are associated with its pathogenesis have been unknown. Here, we attempted to identify specific biomarkers to diagnose or assess disease activity in FMF patients. We measured serum levels of 45 cytokines in 75 FMF patients and 40 age-matched controls by multisuspension cytokine array. FMF in "attack" or "remission" was classified by Japan College of Rheumatology-certified rheumatologists according to the Tel Hashomer criteria. Cytokines were ranked by their importance by a multivariate classification algorithm. We performed a logistic regression analysis to determine specific biomarkers for discriminating FMF patients in attack. To identify specific molecular networks, we performed a cluster analysis of each cytokine. Twenty-nine of the 45 cytokines were available for further analyses. Eight cytokines' serum levels were significantly elevated in the FMF attack versus healthy control group. Nine cytokines were increased in FMF attack compared to FMF remission. Multivariate classification algorithms followed by a logistic regression analysis revealed that the combined measurement of IL-6, IL-18, and IL-17 distinguished FMF patients in attack from the controls with the highest accuracy (sensitivity 89.2%, specificity 100%, and accuracy 95.5%). Among the FMF patients, the combined measurement of IL-6, G-CSF, IL-10, and IL-12p40 discriminated febrile attack periods from remission periods with the highest accuracy (sensitivity 75.0%, specificity 87.9%, and accuracy 84.0%). Our data identified combinational diagnostic biomarkers in FMF patients based on the measurement of multiple cytokines. These findings help to improve the diagnostic performance of FMF in daily practice and extend our understanding of the activation of the inflammasome leading to enhanced cytokine networks.

DOI: 10.1097/MD.0000000000003449

PMCID: PMC4845848

PMID: 27100444 [Indexed for MEDLINE]

1257. Clin Transplant. 2016 Jul;30(7):787-90. doi: 10.1111/ctr.12749. Epub 2016 May 6.

Kidney transplantation for end-stage renal disease secondary to familial Mediterranean fever.

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Although kidney transplantation (KT) is widely used for treating renal amyloidosis secondary to familial Mediterranean fever (FMF), data concerning transplant outcome are limited and inconsistent. The aim of this study was to determine the long-term outcome of KT in patients with amyloidosis secondary to FMF. Kidney transplantation outcome in 24 patients with FMF was compared to that in 72 controls matched for age, gender of recipient, and type of the donor that underwent KT due to end-stage renal disease (ESRD) not caused by FMF. Mean follow-up time was  $80.3 \pm 55.1$  months in the FMF group, vs.  $86.5 \pm 47.6$  months in the control group. Death-censored graft survival at five and 10 yr in the FMF group was 95.8% and 78.4%, respectively, and was comparable to that in the control group. In the FMF group, five- and 10-yr patient survival (87.5 and 65.6%) was shorter than in the control group, but the difference was not statistically significant. The findings show that long-term outcome of KT in the patients with amyloidosis secondary to FMF was comparable to that in patients with ESRD not caused by FMF. Recurrence of amyloidosis in the allograft, gastrointestinal intolerance, and fatal infections remain as major complications during the post-transplant period.

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DOI: 10.1111/ctr.12749

PMID: 27101228 [Indexed for MEDLINE]

1258. JAMA Dermatol. 2016 Jul 1;152(7):825-8. doi: 10.1001/jamadermatol.2016.0751.

Therapeutic Efficacy of Interleukin 12/Interleukin 23 Blockade in Generalized Pustular Psoriasis Regardless of IL36RN Mutation Status.

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**IMPORTANCE:** Generalized pustular psoriasis von Zumbusch type (GPP) is the most severe manifestation of psoriasis. The etiology of GPP is only partially understood, and GPP lacks approved treatments. Loss-of-function mutations in the interleukin 36 (IL-36) receptor antagonist (IL36RN), an inhibitor of innate immune activation in the skin, and therapeutic efficacy of IL-1 blockade in a subset of patients with GPP are viewed as evidence for an autoinflammatory pathogenesis. A pathogenic role of T cells has not been considered.

**OBJECTIVE:** To test whether ustekinumab, a monoclonal antibody blocking IL-12 and IL-23, is an effective treatment modality for patients in whom GPP treatment with conventional psoriasis drugs or antagonists of tumor necrosis factor (TNF) has not been sufficiently effective, is contraindicated, or has lost efficacy.

**DESIGN, SETTING, AND PARTICIPANTS:** We treated a series of 4 patients with GPP with ustekinumab, which was applied on an outpatient basis according to the dosing regimen approved for psoriasis vulgaris. In 3 patients it was combined with low doses of the retinoid acitretin. IL36RN mutations were determined in all 4 patients by means of targeted sequencing of genomic DNA.

**MAIN OUTCOME MEASURES:** The response to therapy was assessed by clinical examination.

**RESULTS:** The 4 patients were female. Sequencing of IL36RN identified a homozygous mutation in case 1 (Pro76Leu). The other 3 patients carried no rare IL36RN variants. Overall GPP duration ranged from 50 to 146 months. Ustekinumab treatment is currently ongoing in all 4 patients without loss of efficacy, currently reaching treatment durations of 17 (case 1) to 44 months (case 3).

Ustekinumab treatment induced sustained remissions in all 4 GPP patients. This response was independent of IL36RN mutations and consolidated by combination with low doses of the retinoid acitretin.

**CONCLUSIONS AND RELEVANCE:** Ustekinumab-induced remissions suggest that T cells play a crucial role in GPP pathogenesis based on the documented role that IL-12 and IL-23 play in autoimmune diseases through differentiating helper T cell 1 (TH1) and maintaining TH17 responses. Acitretin treatment may support ustekinumab efficacy, possibly by suppressing TH17 responses through the retinoid-related orphan receptors, ROR $\gamma$ t and ROR $\alpha$ . Combining IL-12/IL-23 blockade and acitretin may constitute an efficient treatment modality interfering with GPP



pathomechanisms.

DOI: 10.1001/jamadermatol.2016.0751

PMID: 27096382 [Indexed for MEDLINE]

1259. Nature. 2016 May 5;533(7601):115-9. doi: 10.1038/nature17950. Epub 2016 Apr 20.

Noncanonical autophagy inhibits the autoinflammatory, lupus-like response to dying cells.

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Erratum in

Nature. 2016 Nov 3;539(7627):124.

Comment in

Ann Transl Med. 2016 Dec;4(24):513.

Nat Rev Nephrol. 2016 Jul;12(7):375.

Nat Rev Rheumatol. 2016 Jun;12(6):311.

Kidney Int. 2016 Aug;90(2):238-239.

Cell Death Differ. 2016 Aug;23(8):1267-8.

Defects in clearance of dying cells have been proposed to underlie the pathogenesis of systemic lupus erythematosus (SLE). Mice lacking molecules

associated with dying cell clearance develop SLE-like disease, and phagocytes from patients with SLE often display defective clearance and increased inflammatory cytokine production when exposed to dying cells in vitro. Previously, we and others described a form of noncanonical autophagy known as LC3-associated phagocytosis (LAP), in which phagosomes containing engulfed particles, including dying cells, recruit elements of the autophagy pathway to facilitate maturation of phagosomes and digestion of their contents. Genome-wide association studies have identified polymorphisms in the Atg5 (ref. 8) and possibly Atg7 (ref. 9) genes, involved in both canonical autophagy and LAP, as markers of a predisposition for SLE. Here we describe the consequences of defective LAP in vivo. Mice lacking any of several components of the LAP pathway show increased serum levels of inflammatory cytokines and autoantibodies, glomerular immune complex deposition, and evidence of kidney damage. When dying cells are injected into LAP-deficient mice, they are engulfed but not efficiently degraded and trigger acute elevation of pro-inflammatory cytokines but not anti-inflammatory interleukin (IL)-10. Repeated injection of dying cells into LAP-deficient, but not LAP-sufficient, mice accelerated the development of SLE-like disease, including increased serum levels of autoantibodies. By contrast, mice deficient in genes required for canonical autophagy but not LAP do not display defective dying cell clearance, inflammatory cytokine production, or SLE-like disease, and, like wild-type mice, produce IL-10 in response to dying cells. Therefore, defects in LAP, rather than canonical autophagy, can cause SLE-like phenomena, and may contribute to the pathogenesis of SLE.

DOI: 10.1038/nature17950

PMCID: PMC4860026

PMID: 27096368 [Indexed for MEDLINE]

1260. QJM. 2016 Jul;109(7):485-6. doi: 10.1093/qjmed/hcw059. Epub 2016 Apr 15.

Familial mediterranean fever-anticipated rise in Western Europe.

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DOI: 10.1093/qjmed/hcw059

PMID: 27083983

1261. Immunology. 2016 Aug;148(4):326-38. doi: 10.1111/imm.12611. Epub 2016 Jun 29.

MicroRNA223 promotes pathogenic T-cell development and autoimmune inflammation in central nervous system in mice.

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Multiple sclerosis (MS) is an incurable central nervous system autoimmune disease. Understanding MS pathogenesis is essential for the development of new MS therapies. In the present study, we identified a novel microRNA (miR) that regulates experimental autoimmune encephalomyelitis (EAE), an animal model of MS. Expression of miR223 was up-regulated specifically in spinal cords and lymphoid organs but not in other examined tissues. A global miR223 knockout (miR223(-/-) ) in mice led to a significant delay in EAE onset, reduction in spinal cord lesion, and lessening of neurological symptoms. These protective effects could be reproduced in bone marrow chimeras reconstituted with miR223(-/-) haematopoietic stem cells. We also found that miR223 deficiency reduced T helper type 1 (Th1) and Th17 infiltration into spinal cords. To address underlying mechanisms, we

investigated the role of miR223 in regulating the function, development and interaction of the major immune cells. Expression of the genes associated with dendritic cell (DC) activation (CD86 and MHC II) and Th1 and Th17 differentiation [interleukin-12 (IL-12) and IL-23, respectively] was significantly decreased in the spleens of miR223(-/-) mice bearing EAE. The miR223(-/-) DCs expressed significantly lower levels of basal and lipopolysaccharide-induced IL-12 and IL-23 compared with the wild-type DCs. These data are consistent with the observed lower efficiency of miR223(-/-) DCs to support Th1 and Th17 differentiation from naive T cells over-expressing an EAE antigen-specific T-cell receptor. Our data suggest that miR223 promotes EAE, probably through enhancing DC activation and subsequently the differentiation of naive T cells toward Th1 and Th17 effector cells.

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DOI: 10.1111/imm.12611

PMCID: PMC4948040

PMID: 27083389 [Indexed for MEDLINE]

1262. Reumatol Clin. 2017 Jan - Feb;13(1):57. doi: 10.1016/j.reuma.2016.03.007. Epub 2016 Apr 11.

Mevalonate kinase deficiency (hyper-IgD syndrome) overlap mutation familial Mediterranean fever.

[Article in English, Spanish]

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DOI: 10.1016/j.reuma.2016.03.007  
PMID: 27079959 [Indexed for MEDLINE]

1263. Semin Arthritis Rheum. 2016 Aug;46(1):e1-2. doi:  
10.1016/j.semarthrit.2016.03.006. Epub 2016 Mar 16.

Tocilizumab-induced exacerbation of mucosal ulcers in a patient with  
multi-refractory Behçet's disease.

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Comment on

Semin Arthritis Rheum. 2016 Jun;45(6):733-7.

DOI: 10.1016/j.semarthrit.2016.03.006  
PMID: 27079759 [Indexed for MEDLINE]

1264. Redox Rep. 2016 Nov;21(6):287-91. doi: 10.1080/13510002.2016.1168590. Epub 2016  
Mar 31.

Thiol/disulphide homeostasis in pregnant women with Familial Mediterranean fever.

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**OBJECTIVE:** To investigate the presence of oxidative stress (OS) in pregnant women with Familial Mediterranean fever (FMF) in the first trimester by evaluating thiol/disulphide homeostasis.

**STUDY DESIGN:** A total of 31 pregnant women with a diagnosis of FMF, between 11(0) and 13(6) weeks of gestation, were compared with 51 healthy pregnant controls at the same gestational weeks. A recently defined method was used to measure plasma native thiol, total thiol and disulphide levels.

**RESULTS:** There were no differences between groups in terms of maternal age, body mass index and numbers of gravida and parity. Antenatal complications (45.2% vs. 9.8%,  $P = 0.001$ ) and primary caesarean section (22.6% vs. 5.9%,  $P = 0.037$ ) were higher in the FMF group. Pregnant women with FMF had significantly lower first trimester serum levels of native thiol (297.5  $\mu\text{mol/l}$  (153.2-441.8) vs. 366.1  $\mu\text{mol/l}$  (288.7-432.4),  $P = 0.000$ ), total thiol (327.2  $\mu\text{mol/l}$  (171.0-471.0) vs. 389.9  $\mu\text{mol/l}$  (317.1-449.8),  $P = 0.000$ ) and higher levels of disulphide ( $14.2 \pm 4.5 \mu\text{mol/l}$  vs.  $12.4 \pm 3.4 \mu\text{mol/l}$ ,  $P = 0.045$ ). No differences were found in these parameters among FMF patients with and without antenatal complications.

**CONCLUSIONS:** The main outcome demonstrates a relation between OS and pregnant women with FMF in the first trimester of gestation. OS in the first trimester may be a major aetiological factor of unfavourable pregnancy outcomes in this group of patients.

DOI: 10.1080/13510002.2016.1168590

PMID: 27077456 [Indexed for MEDLINE]

1265. Clin Rev Allergy Immunol. 2018 Jun;54(3):446-453. doi: 10.1007/s12016-016-8537-8.

A Comprehensive Overview of the Hereditary Periodic Fever Syndromes.

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Innate immunity is a critical partner in the regulation of inflammation and some mutations in genes implied in innate immunity pathways can cause genetic disorders characterized by seemingly unprovoked self-limited inflammatory attacks. These rare conditions are collectively named "hereditary periodic fever syndromes" (HPFS), and protean pathogenetic mechanisms combined with several clinical phenotypes characterize at least four distinct conditions: (1) familial Mediterranean fever, which is the prototype and the most widely recognized among HPFS, inherited as an autosomal recessive disorder showing recurrent dysregulated inflammatory processes, caused by an abnormal interaction between cytoskeleton and inflammasome, a key-signaling platform that releases interleukin-1 $\beta$  (IL-1 $\beta$ ); (2) the group of cryopyrin-associated periodic syndrome, which upsets directly the production of IL-1 $\beta$ , with a dominant pattern of inheritance; (3) tumor necrosis factor receptor-associated periodic syndrome, which is an autosomal dominant disorder subverting the functions and traffic of a cell membrane protein; and (4) mevalonate kinase deficiency, which is an autosomal recessive metabolic disorder halting the biosynthesis of cholesterol. MEFV, NLRP3, TNFRSF1A, and MVK are respectively the four causing genes of these conditions, all resulting in excessive IL-1 $\beta$  signaling, though the encoded proteins act at different levels in cytoskeletal filament organization, apoptosis, and activation of the IL-1 $\beta$ -structured inflammasome. The differential diagnosis of HPFS can be challenging, as there are no universally accepted diagnostic algorithms, and near half of patients may have a specific disease without any genetic pathogenetic variant identified. Herein, we outline the most relevant aspects of HPFS at the crossroads between clinical medicine and immunology and all the most recent advances in their treatment, as the increasing use of IL-1 antagonists has achieved unexpected clinical results in a large number of patients.

DOI: 10.1007/s12016-016-8537-8  
PMID: 27068928 [Indexed for MEDLINE]

1266. Med Clin (Barc). 2016 Jul 1;147(1):46. doi: 10.1016/j.medcli.2016.02.020. Epub 2016 Apr 9.

[Familiar Mediterranean fever in a patient with ankylosing spondylitis].

[Article in Spanish]

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DOI: 10.1016/j.medcli.2016.02.020  
PMID: 27068785 [Indexed for MEDLINE]

1267. Joint Bone Spine. 2016 Jul;83(4):406-11. doi: 10.1016/j.jbspin.2015.08.017. Epub 2016 Apr 7.

Is colchicine an effective treatment in periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome?

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**INTRODUCTION:** PFAPA syndrome is the most frequent periodic fever syndrome in non-Mediterranean patients. The pathogenesis is unclear and the treatment is purely symptomatic and not standardized. The aim of this study was to assess colchicine's efficacy as prophylactic treatment in PFAPA syndrome and to identify factors able to predict response to treatment.

**METHODS:** We performed a retrospective, multicentric, cohort study of PFAPA patients under colchicine prophylaxis. PFAPA diagnosis was established according to Feder's criteria. Medical records were reviewed and analyzed for demographic, clinical and laboratory data. We distinguished one responder's group, defined as patients who had no more or twice fewer crises under colchicine and another one of non-responders. Subgroup analyses were performed using non-parametric Mann-Whitney test for quantitative data and calculating odds ratio and confidence interval for qualitative data. Difference between the two groups was considered significant for  $P\text{-value} < 0.05$  or a confidence interval different from 1.

**RESULTS-CONCLUSION:** Twenty children, 65% of whom were boys, were analyzed. Their mean age at disease onset was  $2.3 \pm 1.5$  years. Among the nine responder patients, five were MEFV (71%) heterozygotes: M694V mutation in four and V726A once. Heterozygous MEFV gene mutation tended to be more frequent in the responders group (71% versus 43%;  $OR = 0.3$  [0.03-2.7]). Non-responder patients had more chronic fatigue (82% versus 33%;  $OR = 9$  [1,14-71]) and had more oral aphthosis (82% versus 11%;  $OR = 36$  [1,7-141]) than the responders ones. Although not significant, colchicine treatment appeared more effective in patients with less complete PFAPA phenotype and MEFV heterozygosity.

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DOI: 10.1016/j.jbspin.2015.08.017

PMID: 27068612 [Indexed for MEDLINE]

1268. Clin Oral Investig. 2017 Jan;21(1):469-475. doi: 10.1007/s00784-016-1816-1. Epub 2016 Apr 11.

Evaluation of IL-1 $\beta$ , IL-1ra, and IL-10 levels and outcome of periodontal therapy in chronic periodontitis with familial Mediterranean fever.

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**OBJECTIVES:** This study aimed to examine the IL-1 $\beta$ , IL-1ra, and IL-10 cytokine levels in gingival crevicular fluid (GCF) and serum of familial Mediterranean fever (FMF) and chronic periodontitis (CP) patients, and their response to nonsurgical periodontal therapy.

**MATERIALS AND METHODS:** A total of 50 patients, 15 FMF patients with generalized chronic periodontitis (FMF-CP), 15 systemically healthy patients with generalized chronic periodontitis (CP), ten systemically and periodontal healthy controls (HC), and ten periodontally healthy FMF patients (FMF-HC) were enrolled in the study. The cytokine levels in GCF and serum were determined by ELISA. Probing depth, clinical attachment level, and gingival and plaque indices in each participant were also measured. The GCF and clinical parameters at baseline and 6 weeks were recorded.

**RESULTS:** The study indicated statistically significant healing of the clinical parameters in both FMF-CP and CP groups after periodontal treatment. GCF IL-1 $\beta$  levels at 6 weeks in FMF-CP group were significantly lower than the CP group ( $p < 0.05$ ), and GCF IL-1ra levels were significantly decreased at 6 week in the FMF-CP group ( $p < 0.05$ ). GCF IL-10 levels were significantly higher in the FMF-CP group than in the other groups at baseline and 6 weeks ( $p < 0.05$ ). There were no significant differences in serum-IL-1 $\beta$ , IL-1ra, and IL-10 levels either FMF-CP or

CP groups at baseline or 6 weeks ( $p > 0.05$ ).

**CONCLUSIONS:** The results of our study suggested that there was a positive correlation between gingival inflammation and serum cytokine levels in FMF patients and also colchicine treatment showed protective effects on GCF cytokine levels in FMF-CP group.

**CLINICAL RELEVANCE:** Following treatment, GCF IL-1 $\beta$  and GCF IL-1ra levels were decreased in FMF-CP group. GCF IL-10 levels were increased in FMF-CP group compared to other groups. Also, the serum cytokine levels associated with periodontal inflammation in FMF patients.

DOI: 10.1007/s00784-016-1816-1

PMID: 27068409 [Indexed for MEDLINE]

1269. Cell Mol Life Sci. 2016 Jun;73(11-12):2349-67. doi: 10.1007/s00018-016-2205-2. Epub 2016 Apr 11.

The intersection of cell death and inflammasome activation.

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Inflammasomes sense cellular danger to activate the cysteine-aspartic protease caspase-1, which processes precursor interleukin-1 $\beta$  (IL-1 $\beta$ ) and IL-18 into their mature bioactive fragments. In addition, activated caspase-1 or the related inflammatory caspase, caspase-11, can cleave gasdermin D to induce a lytic cell death, termed pyroptosis. The intertwining of IL-1 $\beta$  activation and cell death is further highlighted by research showing that the extrinsic apoptotic caspase, caspase-8, may, like caspase-1, directly process IL-1 $\beta$ , activate the NLRP3 inflammasome itself, or bind to inflammasome complexes to induce apoptotic cell

death. Similarly, RIPK3- and MLKL-dependent necroptotic signaling can activate the NLRP3 inflammasome to drive IL-1 $\beta$  inflammatory responses in vivo. Here, we review the mechanisms by which cell death signaling activates inflammasomes to initiate IL-1 $\beta$ -driven inflammation, and highlight the clinical relevance of these findings to heritable autoinflammatory diseases. We also discuss whether the act of cell death can be separated from IL-1 $\beta$  secretion and evaluate studies suggesting that several cell death regulatory proteins can directly interact with, and modulate the function of, inflammasome and IL-1 $\beta$  containing protein complexes.

DOI: 10.1007/s00018-016-2205-2

PMID: 27066895 [Indexed for MEDLINE]

1270. Arch Rheumatol. 2016 Apr 13;31(2):107-111. doi: 10.5606/ArchRheumatol.2016.5788. eCollection 2016 Jun.

Lack of the Association of the PTPN22 C1858T Gene Polymorphism With Susceptibility to Familial Mediterranean Fever.

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**Objectives:** This study aims to investigate whether the protein tyrosine phosphatase non-receptor type 22 (PTPN22) C1858T gene polymorphism plays a role in the pathogenesis of familial Mediterranean fever (FMF) through T-lymphocyte activation.

**Patients and methods:** We conducted a case-control study with 180 FMF patients (68 males, 112 females; mean age  $38.2 \pm 1.6$  years; range 16 to 81 years) and 184 healthy controls (86 males, 98 females; mean age  $32.9 \pm 9.2$  years; range 18 to 58 years). The PTPN22 C1858T polymorphism (rs2476601) was genotyped by polymerase chain reaction restriction fragment length polymorphism. In patients with FMF, clinical features, disease severity score, the frequencies of amyloidosis, positive family history, and Mediterranean fever gene mutations were determined. **Results:** The frequencies of heterozygous genotype (CT) were 4.5% in FMF patients and 2.8% in healthy controls, respectively. The frequencies of polymorphic homozygous genotypes (TT) were 0.5% in both FMF patients and healthy controls. There were no statistically significant differences in the frequencies of CT and TT genotypes between FMF patients and healthy controls (odds ratio: 1.65, 95% confidence interval: 0.53-5.14,  $p > 0.05$  for CT genotype). The frequencies of clinical features, sex, amyloidosis, positive family history, Mediterranean fever gene mutations, and disease severity score were not significantly different between the patients. **Conclusion:** The distribution of PTPN22 C1858T polymorphism did not reveal any association with FMF in a Turkish population.

DOI: 10.5606/ArchRheumatol.2016.5788

PMCID: PMC5827824

PMID: 29900952

**Conflict of interest statement:** Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

1271. Front Microbiol. 2016 Mar 31;7:456. doi: 10.3389/fmicb.2016.00456. eCollection 2016.

Update on Pyrin Functions and Mechanisms of Familial Mediterranean Fever.

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Mutations in the MEFV gene, which encodes the protein named pyrin (also called marenostrin or TRIM20), are associated with the autoinflammatory disease familial Mediterranean fever (FMF). Recent genetic and immunologic studies uncovered novel functions of pyrin and raised several new questions in relation to FMF pathogenesis. The disease is clinically heterogeneous reflecting the complexity and multiplicity of pyrin functions. The main functions uncovered so far include its involvement in innate immune response such as the inflammasome assemblage and, as a part of the inflammasome, sensing intracellular danger signals, activation of mediators of inflammation, and resolution of inflammation by the autophagy of regulators of innate immunity. Based on these functions, the FMF-associated versions of pyrin confer a heightened sensitivity to a variety of intracellular danger signals and postpone the resolution of innate immune responses. It remains to be demonstrated, however, what kind of selective advantage the heterozygous carriage conferred in the past to be positively selected and maintained in populations from the Mediterranean basin.

DOI: 10.3389/fmicb.2016.00456

PMCID: PMC4815028

PMID: 27066000

1272. Arthritis Care Res (Hoboken). 2016 Dec;68(12):1859-1865. doi: 10.1002/acr.22901.

Periodic Fever, Aphthosis, Pharyngitis, and Adenitis Syndrome: Analysis of Patients From Two Geographic Areas.

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**OBJECTIVE:** Periodic fever, aphthosis, pharyngitis, and adenitis (PFAPA) syndrome is a periodic fever syndrome of childhood with an unknown etiology. Our aim was to compare the features between PFAPA syndrome patients from Turkey and those from the US, and patients with and without MEFV variants, and to test the performance of the Eurofever criteria in excluding other autoinflammatory disorders.

**METHODS:** Seventy-one children with PFAPA syndrome, followed in Hacettepe University, in Ankara, Turkey, and 60 patients at Boston Children's Hospital in the US were enrolled. MEFV gene-variant analysis was performed in 56 patients with Sanger sequencing.

**RESULTS:** In patients from Turkey, symptom onset was at a younger age, fever attacks were of shorter duration, and pharyngitis was more frequent, whereas adenitis, headache, and nausea/vomiting were less frequent during attacks, when compared to patients from the US ( $P < 0.05$ ). More patients from the Turkish cohort were classified in the familial Mediterranean fever (FMF) group according to the Eurofever criteria than patients from the US (66.2% versus 10%;  $P < 0.001$ ). Two patients were diagnosed with FMF after MEFV analysis. Twenty-one patients (37.5%) had a single MEFV variant. No significant differences in phenotype were found between patients with and without MEFV variants.

**CONCLUSION:** The differences between patients from the Turkish and US cohorts may be due to epigenetic or environmental factors. In addition, the Eurofever FMF criteria may perform better in certain areas, if the weight of ethnic origin parameter or cutoff values were modified.

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DOI: 10.1002/acr.22901

PMID: 27059542 [Indexed for MEDLINE]

1273. Iran J Public Health. 2016 Jan;45(1):112-3.

Assessment of MEFV Gene Mutations in Exon 10 in Familial Mediterranean Fever Patients from Iranian Azeri and Turkish Population.

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PMCID: PMC4822383

PMID: 27057533

1274. Indian J Pediatr. 2016 Aug;83(8):890-1. doi: 10.1007/s12098-016-2101-7. Epub 2016 Apr 8.

Protracted Myalgia Syndrome as the Presenting Sign of Familial Mediterranean Fever: Is Group A  $\beta$ -Hemolytic Streptococcus Infection a Causative Factor?

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DOI: 10.1007/s12098-016-2101-7

PMID: 27056245 [Indexed for MEDLINE]

1275. Arthritis Res Ther. 2016 Apr 7;18:85. doi: 10.1186/s13075-016-0980-7.

Comparison of the efficacy of once- and twice-daily colchicine dosage in pediatric patients with familial Mediterranean fever--a randomized controlled



noninferiority trial.

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**BACKGROUND:** In this study, we examined the efficacy and safety of a once-daily dosage schema of colchicine compared with a twice-daily dosage schema in pediatric patients with familial Mediterranean fever (FMF).

**METHODS:** In this 24-week, multicenter, randomized controlled noninferiority trial, pediatric patients newly diagnosed with FMF carrying a homozygous or compound heterozygous mutation and not receiving any treatment were included. Patients were randomly assigned using a block randomization method to receive treatment with a once- or twice-daily dosage. Clinical and laboratory characteristics and medication side effects were recorded and compared between groups. The study was carried out in compliance with Good Clinical Practice and the Consolidated Standards for Reporting of Trials (CONSORT) statement.

**RESULTS:** A total of 92 patients were selected, and 79 patients completed the study. There were 42 patients in the once-daily dosage group and 37 in the twice-daily dosage group. The results indicated that the once-daily dosage was not inferior to the twice-daily dosage regarding decrease in attack frequency and duration as well as improvement in clinical findings and Mor severity scores. Alterations in laboratory findings indicating inflammation, such as erythrocyte sedimentation rate, C-reactive protein, and serum amyloid A, were similar in both groups. The rates of drug side effects were similar between the once- and twice-daily dosage groups, implying comparable safety of colchicine, with the exception of diarrhea, which was slightly higher in the once-daily dosage group.

**CONCLUSIONS:** Using colchicine with either a once- or twice-daily dosage provides similar clinical and laboratory improvements. Considering both efficacy and safety, colchicine can be prescribed with a once-daily dosage.

**TRIAL REGISTRATION ID:** ClinicalTrials.gov identifier NCT02602028 . Registered 5 November 2015.

DOI: 10.1186/s13075-016-0980-7

PMCID: PMC4823910

PMID: 27055417 [Indexed for MEDLINE]

1276. PLoS One. 2016 Apr 7;11(4):e0152720. doi: 10.1371/journal.pone.0152720. eCollection 2016.

A Single Amino Acid Substitution Prevents Recognition of a Dominant Human Aquaporin-4 Determinant in the Context of HLA-DRB1\*03:01 by a Murine TCR.

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**BACKGROUND:** Aquaporin 4 (AQP4) is considered a putative autoantigen in patients with Neuromyelitis optica (NMO), an autoinflammatory disorder of the central nervous system (CNS). HLA haplotype analyses of patients with NMO suggest a positive association with HLA-DRB1\* 03:01. We previously showed that the human (h) AQP4 peptide 281-300 is the dominant immunogenic determinant of hAQP4 in the context of HLA-DRB1\*03:01. This immunogenic peptide stimulates a strong Th1 and Th17 immune response. AQP4281-300-specific encephalitogenic CD4+ T cells should initiate CNS inflammation that results in a clinical phenotype in HLA-DRB1\*03:01 transgenic mice.

**METHODS:** Controlled study with humanized experimental animals. HLA-DRB1\*03:01 transgenic mice were immunized with hAQP4281-300, or whole-length hAQP4 protein emulsified in complete Freund's adjuvant. Humoral immune responses to both antigens were assessed longitudinally. In vivo T cell frequencies were assessed by tetramer staining. Mice were followed clinically, and the anterior visual pathway was tested by pupillometry. CNS tissue was examined histologically post-mortem. Flow cytometry was utilized for MHC binding assays and to immunophenotype T cells, and T cell frequencies were determined by ELISpot assay.

**RESULTS:** Immunization with hAQP4281-300 resulted in an in vivo expansion of antigen-specific CD4+ T cells, and an immunoglobulin isotype switch.

HLA-DRB1\*03:01 TG mice actively immunized with hAQP4281-300, or with whole-length

hAQP4 protein were resistant to developing a neurological disease that resembles NMO. Experimental mice show no histological evidence of CNS inflammation, nor change in pupillary responses. Subsequent analysis reveals that a single amino acid substitution from aspartic acid in hAQP4 to glutamic acid in murine (m)AQP4 at position 290 prevents the recognition of hAQP4<sub>281-300</sub> by the murine T cell receptor (TCR).

**CONCLUSION:** Induction of a CNS inflammatory autoimmune disorder by active immunization of HLA-DRB1\*03:01 TG mice with human hAQP4<sub>281-300</sub> will be complex due to a single amino acid substitution. The pathogenic role of T cells in this disorder remains critical despite these observations.

DOI: 10.1371/journal.pone.0152720

PMCID: PMC4824350

PMID: 27054574 [Indexed for MEDLINE]

1277. Scand J Rheumatol. 2016;45(3):215-8. doi: 10.3109/03009742.2015.1092580. Epub 2015 Nov 17.

Prevalence and significance of MEFV gene mutations in patients with sarcoidosis.

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**OBJECTIVES:** Sarcoidosis is a chronic granulomatous disease. Pyrin has anti-inflammatory activity in the regulation of inflammasomes and is encoded by the Mediterranean fever (MEFV) gene. MEFV gene mutations trigger the inflammatory cascade and cause familial Mediterranean fever (FMF). A relationship between

various rheumatic diseases and MEFV gene mutations has been demonstrated. The aim of this study was to determine the prevalence of the MEFV gene mutation in Turkish patients with sarcoidosis and to detect any possible correlation with disease phenotype.

**METHOD:** The study included 78 sarcoidosis patients and 85 healthy subjects matched for age, gender, and ethnicity. MEFV gene mutations were investigated with the FMF strip assay, which is based on reverse hybridization of biotinylated polymerase chain reaction (PCR) products.

**RESULTS:** Of the 78 patients with sarcoidosis, nine (11.5%) were found to be carriers of MEFV gene mutations. The distribution of these nine mutations were: three (3.8%) V726A, two (2.5%) E148Q, two (2.5%) M680I, one (1.3%) A744S, and one (1.3%) K695R. Carriers of M694V, M694I, R761H, and P369S were not detected in any of the sarcoidosis patients. None of the sarcoidosis patients were found to be compound heterozygous carriers. The prevalence of the MEFV gene mutation carrier detected in the healthy control group was 22.4%. The distribution of the 19 MEFV gene mutations found in the healthy controls was: nine (10.6%) E148Q, two (2.3%) M694V, one (1.2%) M694I, one (1.2%) M680I, two (2.3%) V726A, one (1.2%) A744S, two (2.3%) K695R, and one (1.2%) P369S. When compared with the control group, a lower prevalence of the MEFV gene mutation carrier was found in sarcoidosis patients but this was not statistically significant ( $p = 0.067$ ). In nine patients found to be MEFV gene mutation carriers, higher serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels and higher numbers patients with arthritis, enthesitis, and ankle arthritis were found ( $p = 0.01$ ,  $p = 0.04$ ,  $p = 0.028$ ,  $p = 0.05$ ,  $p = 0.05$ , respectively).

**CONCLUSIONS:** When we compared Turkish sarcoidosis patients with the healthy control group, we found a lower prevalence of MEFV gene mutations. In sarcoidosis patients, the MEFV gene mutation carrier was found to be related to high acute-phase responses, arthritis, and enthesitis. The existence of MEFV gene mutations may have a preventive role with regard to the development of sarcoidosis. Prospective studies that include larger patient populations are needed.

DOI: 10.3109/03009742.2015.1092580

PMID: 27053370 [Indexed for MEDLINE]

1278. J Inflamm Res. 2016 Mar 17;9:13-20. doi: 10.2147/JIR.S91352. eCollection 2016.

Familial Mediterranean fever: current perspectives.

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Familial Mediterranean fever (FMF) is the most frequent monogenic autoinflammatory disease, and it is characterized by recurrent attacks of fever and polyserositis. The disease is associated with mutations in the MEFV gene encoding pyrin, which causes exaggerated inflammatory response through uncontrolled production of interleukin 1. The major long-term complication of FMF is amyloidosis. Colchicine remains the principle therapy, and the aim of treatment is to prevent acute attacks and the consequences of chronic inflammation. With the evolution in the concepts about the etiopathogenesis and genetics of the disease, we have understood that FMF is more complicated than an ordinary autosomal recessive monogenic disorder. Recently, recommendation sets have been generated for interpretation of genetic testing and genetic diagnosis of FMF. Here, we have reviewed the current perspectives in FMF in light of recent recommendations.

DOI: 10.2147/JIR.S91352

PMCID: PMC4803250

PMID: 27051312

1279. Am J Forensic Med Pathol. 2016 Jun;37(2):57-9. doi: 10.1097/PAF.0000000000000225.

Colchicine-Induced Rhabdomyolysis: An Autopsy Case.

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Colchicine is derived from *Colchicum autumnale* and *Gloriosa superba* and is used to treat acute gout and familial Mediterranean fever (FMF). Musculoskeletal adverse effects range from myopathy to rhabdomyolysis. An 18-year-old woman, with a 2-year history of FMF treated with colchicine, took 9 colchicine pills (4.5 mg)

to relieve severe abdominal pain. On the sixth day of hospitalization, the patient's condition worsened, and she died. As this was a case of fatal poisoning, a forensic autopsy was performed, and the cause of death was determined to be complications of muscle destruction due to colchicine intoxication with the findings of myocytolysis, positive antimyoglobin antibody staining kidney tubules. Colchicine toxicity begins with gastrointestinal symptoms. Multiorgan effects follow the gastrointestinal effects. Serious outcomes of colchicine toxicity are rhabdomyolysis, bone marrow suppression, and disseminated intravascular coagulation. In chronic diseases that require lifelong treatment with medications, adverse effects can arise with long periods of use. Our patient had been treated for FMF with colchicine for 2 years but took too many colchicine pills to relieve her severe abdominal pain. Warning patients about the effects of high doses of drugs and providing information about their toxic effects and what to do "in case" of overuse could be lifesaving.

DOI: 10.1097/PAF.0000000000000225

PMID: 27049658 [Indexed for MEDLINE]

1280. Cell Mol Life Sci. 2016 Jun;73(11-12):2335-47. doi: 10.1007/s00018-016-2204-3. Epub 2016 Apr 5.

Inflammasomes as polyvalent cell death platforms.

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Inflammasomes are multi-protein platforms that are organized in the cytosol to cope with pathogens and cellular stress. The pattern recognition receptors NLRP1, NLRP3, NLRC4, AIM2 and Pyrin all assemble canonical platforms for caspase-1

activation, while caspase-11-dependent inflammasomes respond to intracellular Gram-negative pathogens. Inflammasomes are chiefly known for their roles in maturation and secretion of the inflammatory cytokines interleukin-(IL)1 $\beta$  and IL18, but they can also induce regulated cell death. Activation of caspases 1 and 11 in myeloid cells can trigger pyroptosis, a lytic and inflammatory cell death mode. Pyroptosis has been implicated in secretion of IL1 $\beta$ , IL18 and intracellular alarmins. Akin to these factors, it may have beneficial roles in controlling pathogen replication, but become detrimental in the context of chronic autoinflammatory diseases. Inflammasomes are increasingly implicated in induction of additional regulated cell death modes such as pyronecrosis and apoptosis. In this review, we overview recent advances in inflammasome-associated cell death research, illustrating the polyvalent roles of these macromolecular platforms in regulated cell death signaling.

DOI: 10.1007/s00018-016-2204-3

PMID: 27048821 [Indexed for MEDLINE]

1281. J Mol Med (Berl). 2016 Oct;94(10):1095-1102. Epub 2016 Apr 5.

The role of RNA editing by ADAR1 in prevention of innate immune sensing of self-RNA.

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The innate immune system is the first line of the cellular defence against invading pathogens. A critical component of this defence is the capacity to discriminate foreign RNA molecules, which are distinct from most cellular RNAs in structure and/or modifications. However, a series of rare autoimmune/autoinflammatory diseases in humans highlight the propensity for the innate immune sensing system to be activated by endogenous cellular



double-stranded RNAs (dsRNAs), underscoring the fine line between distinguishing self from non-self. The RNA editing enzyme ADAR1 has recently emerged as a key regulator that prevents innate immune pathway activation, principally the cytosolic dsRNA sensor MDA5, from inducing interferon in response to double-stranded RNA structures within endogenous RNAs. Adenosine-to-Inosine RNA editing by ADAR1 is proposed to destabilise duplexes formed from inverted repetitive elements within RNAs, which appear to prevent MDA5 from sensing these RNA as virus-like in the cytoplasm. Aberrant activation of these pathways has catastrophic effects at both a cellular and organismal level, contributing to one of the causes of the conditions collectively known as the type I interferonopathies.

DOI: 10.1007/s00109-016-1416-1

PMID: 27044320 [Indexed for MEDLINE]

1282. J Allergy Clin Immunol. 2016 Oct;138(4):1161-1169.e6. doi: 10.1016/j.jaci.2015.12.1338. Epub 2016 Mar 31.

Dysregulation of proinflammatory versus anti-inflammatory human TH17 cell functionalities in the autoinflammatory Schnitzler syndrome.

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**BACKGROUND:** TH17 cells have so far been considered to be crucial mediators of autoimmune inflammation. Two distinct types of TH17 cells have been described recently, which differed in their polarization requirement for IL-1 $\beta$  and in their cytokine repertoire. Whether these distinct TH17 phenotypes translate into distinct TH17 cell functions with implications for human health or disease has not been addressed yet.

**OBJECTIVE:** We hypothesized the existence of proinflammatory and anti-inflammatory human TH17 cell functions based on the differential expression of IL-10, which is regulated by IL-1 $\beta$ . Considering the crucial role of IL-1 $\beta$  in the pathogenesis of autoinflammatory syndromes, we hypothesized that IL-1 $\beta$  mediates the loss of anti-inflammatory TH17 cell functionalities in patients with Schnitzler syndrome, an autoinflammatory disease.

**METHODS:** To assess proinflammatory versus anti-inflammatory TH17 cell functions, we performed suppression assays and tested the effects of IL-1 $\beta$  dependent and independent TH17 subsets on modulating proinflammatory cytokine secretion by monocytes. Patients with Schnitzler syndrome were analyzed for changes in TH17 cell functions before and during therapy with IL-1 $\beta$ -blocking drugs.

**RESULTS:** Both TH17 cell subsets differ in their ability to suppress T-cell proliferation and their ability to modulate proinflammatory cytokine production by antigen-presenting cells because of their differential IL-10 expression properties. In patients with Schnitzler syndrome, systemic overproduction of IL-1 $\beta$  translates into a profound loss of anti-inflammatory TH17 cell functionalities, which can be reversed by anti-IL-1 $\beta$  treatment.

**CONCLUSION:** IL-1 $\beta$  signaling determines the differential expression pattern of IL-10, which is necessary and sufficient to induce proinflammatory versus anti-inflammatory TH17 cell functions. Our data introduce TH17 cell subsets as novel players in autoinflammation and thus novel therapeutic targets in autoinflammatory syndromes including other IL-1 $\beta$  mediated diseases. This demonstrates for the first time alterations in the adaptive immune system in patients with autoinflammatory syndromes.

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DOI: 10.1016/j.jaci.2015.12.1338

PMID: 27040374 [Indexed for MEDLINE]

10.1016/j.jaip.2016.02.016. Epub 2016 Mar 30.

NOD2-associated autoinflammatory disease and immune deficiency.

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DOI: 10.1016/j.jaip.2016.02.016

PMID: 27039238 [Indexed for MEDLINE]

1284. Arthritis Res Ther. 2016 Apr 1;18:78. doi: 10.1186/s13075-016-0977-2.

Patient-reported impact of spondyloarthritis on work disability and working life: the ATLANTIS survey.

Ramonda R(1), Marchesoni A(2), Carletto A(3), Bianchi G(4), Cutolo M(5), Ferraccioli G(6), Fusaro E(7), De Vita S(8), Galeazzi M(9), Gerli R(10), Matucci-Cerinic M(11), Minisola G(12), Montecucco C(13), Pellerito R(14), Salaffi F(15), Paolazzi G(16), Sarzi-Puttini P(17), Scarpa R(18), Bagnato G(19), Triolo G(20), Valesini G(21), Punzi L(22), Olivieri I(23); ATLANTIS study group.

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**BACKGROUND:** The aim was to establish how patients experience the impact of spondyloarthritis (SpA) on work disability and working life.

**METHODS:** The survey was performed in 17/20 regions in Italy (1 January to 31 March 2013). A multiple-choice questionnaire was published on the official website of the sponsor - the National Association of Rheumatic Patients (ANMAR) - and hard-copies were distributed at outpatient clinics for rheumatic patients.

**RESULTS:** Respondents (n = 770) were of both sexes (56 % men), educated (62 % at

high school or more), of working age (75 % aged  $\leq 60$  years), and affected by SpA. The most common types diagnosed were ankylosing spondylitis (AS) (39 %) and psoriatic arthritis (PsA) (36 %). Respondents were working full-time (45 %), part-time (8 %) or had retired (22 %); 15 % were unemployed (for reasons linked to the disease or for other reasons, students or housewives). Patients reported disability (39 %), were receiving disability benefits (34 %), were experiencing important limitations that were hindering their professional development/career (36 %) and some had to change/leave their job or lost it because of SpA (21 %). Employed respondents (n = 383) had worked on average 32.2 h in the last 7 days. More hours of work were lost over the last 7 days due to SpA (2.39 h vs 1.67 h). The indirect costs of the disease amounted to €106/week for patients reporting well-being/good physical conditions/improvement and €216/week for those reporting permanent impairment.

**CONCLUSIONS:** Most patients were in the midst of their productive years and were experiencing considerable difficulties in carrying out their job because of the disease: half of them reported disability and one third were experiencing important limitations in their career perspective.

DOI: 10.1186/s13075-016-0977-2

PMCID: PMC4818386

PMID: 27037139 [Indexed for MEDLINE]

1285. Sci Transl Med. 2016 Mar 30;8(332):332ra45. doi: 10.1126/scitranslmed.aaf1471.

Familial autoinflammation with neutrophilic dermatosis reveals a regulatory mechanism of pyrin activation.

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Pyrin responds to pathogen signals and loss of cellular homeostasis by forming an inflammasome complex that drives the cleavage and secretion of interleukin-1 $\beta$  (IL-1 $\beta$ ). Mutations in the B30.2/SPRY domain cause pathogen-independent activation of pyrin and are responsible for the autoinflammatory disease familial Mediterranean fever (FMF). We studied a family with a dominantly inherited autoinflammatory disease, distinct from FMF, characterized by childhood-onset recurrent episodes of neutrophilic dermatosis, fever, elevated acute-phase reactants, arthralgia, and myalgia/myositis. The disease was caused by a mutation in MEFV, the gene encoding pyrin (S242R). The mutation results in the loss of a 14-3-3 binding motif at phosphorylated S242, which was not perturbed by FMF mutations in the B30.2/SPRY domain. However, loss of both S242 phosphorylation and 14-3-3 binding was observed for bacterial effectors that activate the pyrin inflammasome, such as *Clostridium difficile* toxin B (TcdB). The S242R mutation thus recapitulated the effect of pathogen sensing, triggering inflammasome activation and IL-1 $\beta$  production. Successful therapy targeting IL-1 $\beta$  has been

initiated in one patient, resolving pyrin-associated autoinflammation with neutrophilic dermatosis. This disease provides evidence that a guard-like mechanism of pyrin regulation, originally identified for Nod-like receptors in plant innate immunity, also exists in humans.

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DOI: 10.1126/scitranslmed.aaf1471

PMID: 27030597 [Indexed for MEDLINE]

1286. J Pediatr Gastroenterol Nutr. 2016 Jul;63(1):130-55. doi: 10.1097/MPG.0000000000001188.

NASPGHAN Clinical Report: Surveillance, Diagnosis, and Prevention of Infectious Diseases in Pediatric Patients With Inflammatory Bowel Disease Receiving Tumor Necrosis Factor- $\alpha$  Inhibitors.

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Children and adolescents with inflammatory bowel disease (IBD) receiving therapy with tumor necrosis factor  $\alpha$  inhibitors (anti-TNF $\alpha$ ) pose a unique challenge to health care providers in regard to the associated risk of infection. Published experience in adult populations with distinct autoinflammatory and autoimmune diseases treated with anti-TNF $\alpha$  therapies demonstrates an increased risk of serious infections with intracellular bacteria, mycobacteria, fungi, and some viruses; however, there is a paucity of robust pediatric data. With a rising incidence of pediatric IBD and increasing use of biologic therapies, heightened



knowledge and awareness of infections in this population is important for primary care pediatricians, pediatric gastroenterologists, and infectious disease (ID) physicians. This clinical report is the result of a consensus review performed by pediatric ID and gastroenterology physicians detailing relevant published literature regarding infections in pediatric patients with IBD receiving anti-TNF $\alpha$  therapies. The objective of this document is to provide comprehensive information for prevention, surveillance, and diagnosis of infections based on current knowledge, until additional pediatric data are available to inform evidence-based recommendations.

DOI: 10.1097/MPG.0000000000001188

PMID: 27027903 [Indexed for MEDLINE]

1287. J Neuroinflammation. 2016 Mar 29;13(1):68. doi: 10.1186/s12974-016-0533-7.

Morvan's syndrome and myasthenia gravis related to familial Mediterranean fever gene mutations.

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**BACKGROUND:** We present the first case of Morvan's syndrome (MoS) and myasthenia gravis (MG) related to familial Mediterranean fever (FMF) gene mutations.

CASE PRESENTATION: A 40-year-old woman with a 1-year history of bilateral ptosis and limb muscle weakness presented to our hospital. She also had memory impairment, insomnia, hyperhidrosis, and muscle twitches. Electromyography confirmed widespread myokymia, and there was evidence of temporal region dysfunction on electroencephalography. Anti-voltage-gated potassium channel complex antibodies and anti-acetylcholine receptor antibodies were both positive. Edrophonium administration was effective for bilateral ptosis and muscle weakness. She and her family experienced self-limiting febrile attacks with arthralgia, which led us to suspect FMF. Genetic analyses revealed compound heterozygous mutations in exon 2 of the MEFV gene (L110P/E148Q). From these findings, a diagnosis of MoS and MG complicated with MEFV gene mutations was made. Intravenous high-dose corticosteroids, plasma exchange, and intravenous immunoglobulin resulted in only transient, limited improvement, and frequent relapses, especially in the myasthenic symptoms. Interleukin (IL)-6, IL-1 $\beta$ , and tumor necrosis factor- $\alpha$  were markedly elevated in the serum, which was considered to be derived from the MEFV mutations and responsible for the resistance to immunotherapy.

CONCLUSION: The present case illustrates a possible link between auto-inflammation and auto-antibody-mediated neurological diseases.

DOI: 10.1186/s12974-016-0533-7

PMCID: PMC4812638

PMID: 27026266 [Indexed for MEDLINE]

1288. Int J Mol Sci. 2016 Mar 25;17(4):448. doi: 10.3390/ijms17040448.

Recurrent Fever in Children.

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Children presenting with recurrent fever may represent a diagnostic challenge. After excluding the most common etiologies, which include the consecutive occurrence of independent uncomplicated infections, a wide range of possible causes are considered. This article summarizes infectious and noninfectious causes of recurrent fever in pediatric patients. We highlight that, when investigating recurrent fever, it is important to consider age at onset, family history, duration of febrile episodes, length of interval between episodes, associated symptoms and response to treatment. Additionally, information regarding travel history and exposure to animals is helpful, especially with regard to infections. With the exclusion of repeated independent uncomplicated infections, many infective causes of recurrent fever are relatively rare in Western countries; therefore, clinicians should be attuned to suggestive case history data. It is important to rule out the possibility of an infectious process or a malignancy, in particular, if steroid therapy is being considered. After excluding an infectious or neoplastic etiology, immune-mediated and autoinflammatory diseases should be taken into consideration. Together with case history data, a careful physical exam during and between febrile episodes may give useful clues and guide laboratory investigations. However, despite a thorough evaluation, a recurrent fever may remain unexplained. A watchful follow-up is thus mandatory because new signs and symptoms may appear over time.

DOI: 10.3390/ijms17040448

PMCID: PMC4848904

PMID: 27023528 [Indexed for MEDLINE]

1289. J Dermatol Sci. 2016 Jul;83(1):17-25. doi: 10.1016/j.jdermsci.2016.03.005. Epub 2016 Mar 10.

A differential gene expression study: Ptpn6 (SHP-1)-insufficiency leads to neutrophilic dermatosis-like disease (NDLD) in mice.

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**BACKGROUND:** Irradiated syngeneic wild-type mice developed the same neutrophilic dermatosis-like disease (NDLD) after adoptive transfer of bone marrow cells from Ptpn6(meb2/meb2) mutant mice.

**OBJECTIVE:** To analyze differentially expressed genes in the bone marrow of mice with NDLD to gain insight into the role of Ptpn6 in myelopoietic bone marrow pathology, and the mechanisms by which Ptpn6 insufficiency in the hematopoietic cells can lead to the development of skin lesions.

**METHODS:** As Ptpn6 is involved in a myriad of signaling pathways, we used a global approach with microarray technology for the first time to characterize changes in the bone marrow and skin of motheaten-type mice.

**RESULTS:** A total number of 1,511 probe sets in the bone marrow showed at least two-fold changes with FDR <0.05, of which 256 probe sets had over four-fold changes. A group of 63 genes in the bone marrow of NDLD mice had more than a 4-fold change with FDR <0.0001. From 503 genes encoding proteins with ITIM motif that binds to Ptpn6, 109 were up-regulated and 83 were down-regulated. We found that genes encoding hematopoietic receptors, neutrophil chemoattractants, Toll-like receptors (Tlr1, Tlr2 and Tlr4) and C-type lectin innate immunity receptors (Clec4e, Clec4d, Clec4n, Clec4a2 and Clec4a3) were significantly up-regulated in both NDLD bone marrow and skin. The Il1b gene was also significantly overexpressed in skin samples, confirming the importance of the IL-1/TLR pathway in the development of early skin inflammation in NDLD mice.

**CONCLUSION:** Our results suggest that innate immunity genes play a major role in development of neutrophilic dermatosis-like disease in mice.

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DOI: 10.1016/j.jdermsci.2016.03.005

PMID: 27020408 [Indexed for MEDLINE]

1290. Nat Immunol. 2016 May;17(5):495-504. doi: 10.1038/ni.3409. Epub 2016 Mar 28.

DNA polymerase- $\alpha$  regulates the activation of type I interferons through cytosolic RNA:DNA synthesis.

Starokadomskyy P(1), Gemelli T(2), Rios JJ(2)(3)(4), Xing C(2)(5), Wang RC(6), Li H(1), Pokatayev V(1), Dozmorov I(7), Khan S(7), Miyata N(1), Fraile G(8), Raj P(7), Xu Z(9), Xu Z(9), Ma L(9), Lin Z(10), Wang H(10)(11)(12), Yang Y(10)(11), Ben-Amitai D(13)(14), Orenstein N(15), Mussaffi H(14)(16), Baselga E(17), Tadini G(18)(19), Grunebaum E(20)(21), Sarajlija A(22)(23), Krzewski K(24), Wakeland EK(7), Yan N(1)(25), de la Morena MT(1)(4)(26), Zinn AR(1)(2), Burstein E(1)(27).

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Comment in

Nat Immunol. 2016 May;17(5):472-4.

Aberrant nucleic acids generated during viral replication are the main trigger for antiviral immunity, and mutations that disrupt nucleic acid metabolism can lead to autoinflammatory disorders. Here we investigated the etiology of X-linked reticulate pigmentary disorder (XLPDR), a primary immunodeficiency with autoinflammatory features. We discovered that XLPDR is caused by an intronic mutation that disrupts the expression of POLA1, which encodes the catalytic subunit of DNA polymerase- $\alpha$ . Unexpectedly, POLA1 deficiency resulted in increased production of type I interferons. This enzyme is necessary for the synthesis of RNA:DNA primers during DNA replication and, strikingly, we found that POLA1 is also required for the synthesis of cytosolic RNA:DNA, which directly modulates interferon activation. Together this work identifies POLA1 as a critical

regulator of the type I interferon response.

DOI: 10.1038/ni.3409

PMCID: PMC4836962

PMID: 27019227 [Indexed for MEDLINE]

1291. Rheumatology (Oxford). 2016 Jun;55(6):1147. doi: 10.1093/rheumatology/kew051. Epub 2016 Mar 27.

Comment on: Different disease subtypes with distinct clinical expression in familial Mediterranean fever: results of a cluster analysis.

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Comment in

Rheumatology (Oxford). 2016 Jun;55(6):1147-8.

Comment on

Rheumatology (Oxford). 2016 Feb;55(2):343-6.

DOI: 10.1093/rheumatology/kew051

PMID: 27018058 [Indexed for MEDLINE]

1292. Acta Clin Croat. 2015 Dec;54(4):516-20.

ORAL LICHEN PLANUS AND ORAL LICHENOID REACTION--AN UPDATE.

Rotim Z, Bolanca Z, Rogulj AA, Andabak M, Boras VV, Vrdoljak DV.

Oral lichen planus (OLP) and oral lichenoid reaction (OLR) are clinically and histopathologically similar diseases. Whereas OLP is a consequence of T cell

mediated autoinflammatory process to a still unknown antigen, OLR might be caused by drugs, dental restorative materials and dental plaque. Pubmed was searched and 24 publications published over the last three years regarding etiology, diagnosis and malignant alteration were included in this study. Patients with OLR who have amalgam fillings near lesions should have them replaced, i.e. when possible they should be referred to patch test, as well as when drug-induced OLR are suspected. OLR lesions induced by drugs should disappear when the offending drug has been discontinued. Histology finding in OLR consists of more eosinophils, plasma cells and granulocytes in comparison to OLP lesions. Furthermore, OLP lesions showed more p53, bcl-2 and COX-2 positivity when compared to OLR. OLP is characterized by infiltration, atrophic epithelium, rete pegs and Max Joseph spaces, while deep infiltration into connective tissue and hyperkeratosis were the criteria for making the diagnosis of OLR. The number of degranulated mastocytes in the reticular layer, as well as the number of capillaries was higher in OLR in comparison to OLP. It seems that OLR are more prone to malignant alteration in comparison to OLP.

PMID: 27017728 [Indexed for MEDLINE]

1293. Ocul Immunol Inflamm. 2016 Aug;24(4):477. doi: 10.3109/09273948.2016.1148173. Epub 2016 Mar 25.

Response to Letter from Dr. Salih Uzun et al. Regarding "Peripapillary Retinal Nerve Fiber Layer and Ganglion Cell-Inner Plexiform Layer Thickness in Children with Familial Mediterranean Fever".

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DOI: 10.3109/09273948.2016.1148173

PMID: 27015371

1294. *Pediatr Rheumatol Online J.* 2016 Mar 25;14(1):19. doi: 10.1186/s12969-016-0081-9.

Perinatal manifestation of mevalonate kinase deficiency and efficacy of anakinra.

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**BACKGROUND:** Mevalonate kinase deficiency is a metabolic autoinflammatory syndrome caused by mutations in the MVK gene, mevalonate kinase, the key enzyme in the non-sterol isoprenoid biosynthesis pathway. Two phenotypes of mevalonate kinase deficiency are known based on the level of enzymatic deficiency, mevalonic aciduria and hyperimmunoglobulinemia D syndrome, but a wide spectrum of intermediate phenotypes has been reported. Currently one of the most effective treatments is biological therapy (with interleukin-1 antagonist anakinra or tumour necrosis factor- $\alpha$  inhibitor etanercept).

**CASE PRESENTATION:** The patient in this case has a phenotype contributing to a severe disease that caused the symptoms to manifest very early, in the prenatal period. Mevalonate kinase deficiency was suspected on the basis of clinical (hydrops fetalis, hepatosplenomegaly, hypotonia) and laboratory signs (anaemia, intense acute phase reaction, increased urinary excretion of mevalonic acid). Mutation analysis of the MVK gene confirmed the biochemical diagnosis. Treatment with the interleukin-1 antagonist anakinra was started (minimal dose of 1 mg/kg/day) and revealed its efficacy after three days.

**CONCLUSIONS:** Our case highlights the need for a very detailed clinical and laboratory assessment in new-borns with any suggestion of autoinflammatory disorders. It is important that patients are diagnosed as early as possible to

provide better multidisciplinary follow-up and therapy when needed.

DOI: 10.1186/s12969-016-0081-9

PMCID: PMC4807578

PMID: 27012807 [Indexed for MEDLINE]

1295. Nephrology (Carlton). 2016 Sep;21(9):736-44. doi: 10.1111/nep.12785.

The NLRP3 inflammasome in kidney disease and autoimmunity.

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The NLRP3 inflammasome is an intracellular platform that converts the pro-inflammatory cytokines interleukin (IL)-1 $\beta$  and IL-18 to their active forms in response to 'danger' signals, which can be either host or pathogen derived, and mediates a form of inflammatory cell death called pyroptosis. This component of the innate immune system was initially discovered because of its role in rare autoinflammatory syndromes called cryopyrinopathies, but it has since been shown to mediate injurious inflammation in a broad range of diseases. Inflammasome activation occurs in both immune cells, primarily macrophages and dendritic cells, and in some intrinsic kidney cells such as the renal tubular epithelium. The NLRP3 inflammasome has been implicated in the pathogenesis of a number of renal conditions, including acute kidney injury, chronic kidney disease, diabetic nephropathy and crystal-related nephropathy. The inflammasome also plays a role in autoimmune kidney disease, as IL-1 $\beta$  and IL-18 influence adaptive immunity through modulation of T helper cell subsets, skewing development in favour of Th17 and Th1 cells that are important in the development of autoimmunity. Both IL-1 blockade and two recently identified specific NLRP3 inflammasome blockers, MCC950 and  $\beta$ -hydroxybutyrate, have shown promise in the treatment of inflammasome-mediated conditions. These targeted therapies have the potential to be of benefit in the growing number of kidney diseases in which the NLRP3

inflammasome has been implicated.

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DOI: 10.1111/nep.12785

PMID: 27011059 [Indexed for MEDLINE]

1296. Curr Treat Options Neurol. 2016 May;18(5):19. doi: 10.1007/s11940-016-0405-6.

Behçet's Disease and Nervous System Involvement.

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**OPINION STATEMENT:** Management of neuro-Behçet's disease can be divided into two stages: treatment of acute attacks and prevention of relapses. Treatment of acute attacks is accomplished by high-dose intravenous corticosteroids followed by maintenance treatment with oral steroids for 6-12 months depending on the type and severity of the neurological involvement. Relapses can be prevented by using immunosuppressants. Oral immunosuppressants such as azathioprine and mycophenolate are the most widely utilized agents for this purpose. Patients who are refractory or who cannot tolerate these medications can be managed by cyclophosphamide, interferon alpha, or anti-TNF- $\alpha$  monoclonal antibodies such as infliximab, etanercept, and adalimumab. Recent reports showed that newer agents such as tocilizumab, canakinumab, and anakinra, which exert their biological activity through IL-1 and IL-6 pathways, are also promising treatment alternatives for progressive or relapsing patients.

DOI: 10.1007/s11940-016-0405-6

PMID: 27007988

1297. Clin Rheumatol. 2016 Sep;35(9):2377. doi: 10.1007/s10067-016-3233-x. Epub 2016 Mar 23.

Is late-onset disease or the lower rate of M694V mutations associated with the mild disease phenotype?

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Comment on

Clin Rheumatol. 2016 Jul;35(7):1837-40.

DOI: 10.1007/s10067-016-3233-x

PMID: 27005935 [Indexed for MEDLINE]

1298. Pathol Int. 2016 Jun;66(6):351-3. doi: 10.1111/pin.12400. Epub 2016 Mar 22.

First autopsy case report of Familial Mediterranean fever in a Japanese man.

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DOI: 10.1111/pin.12400

PMID: 27004914 [Indexed for MEDLINE]

1299. Ocul Immunol Inflamm. 2016 Aug;24(4):476. doi: 10.3109/09273948.2016.1142575. Epub 2016 Mar 22.

Letter to: "Alim S, Özer S, Demir S, et al. Peripapillary Retinal Nerve Fiber Layer and Ganglion Cell-Inner Plexiform Layer Thickness in Children with Familial Mediterranean Fever".

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DOI: 10.3109/09273948.2016.1142575

PMID: 27002239

1300. Rheumatol Int. 2016 Jun;36(6):769-79. doi: 10.1007/s00296-016-3466-7. Epub 2016 Mar 21.

Serum biomarkers for the diagnosis and monitoring of chronic recurrent multifocal osteomyelitis (CRMO).

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Chronic recurrent multifocal osteomyelitis (CRMO), the most severe form of chronic nonbacterial osteomyelitis, is an autoinflammatory bone disorder. A timely diagnosis and treatment initiation is complicated by the absence of widely accepted diagnostic criteria and an incomplete pathophysiological understanding. The aim of this study was to determine biomarkers for the diagnosis and follow-up of CRMO. Serum of 56 CRMO patients was collected at the time of diagnosis. As controls, sera from treatment-naïve age-matched patients with Crohn's disease (N = 62) or JIA (N = 28) as well as healthy individuals (N = 62) were collected. Multiplex analysis of 25 inflammation markers was performed. Statistical analysis was performed using Kruskal-Wallis and Mann-Whitney U tests, canonical discriminant analysis, and mixed model variance analysis. Mostly monocyte-derived serum proteins were detectable and differed significantly between groups: IL-1RA, IL-2R, IL-6, IL-12, eotaxin, MCP-1, MIP-1b, RANTES. Multicomponent discriminant analysis allowed for the definition of algorithms differentiating between CRMO, Crohn's disease, and healthy controls. Persistently high levels of MCP-1, IL-12, sIL-2R correlated with incomplete remission in follow-up samples from CRMO patients. Discrimination algorithms allow differentiation between patients with CRMO or Crohn's disease, and healthy individuals. IL-12, MCP-1, and sIL-2R can act as markers for treatment response. Though confirmation of our findings in larger multiethnic cohorts is warranted, they may prove valuable to differentiate between otherwise healthy individuals or Crohn's disease patients with "bone pain" and CRMO patients. The elevation of mainly monocyte-derived pro-inflammatory serum proteins supports the hypothesis of pro-inflammatory monocyte/macrophages driving inflammation in CRMO.

DOI: 10.1007/s00296-016-3466-7

PMID: 27000045 [Indexed for MEDLINE]

1301. Rheumatology (Oxford). 2016 Jun;55(6):1147-8. doi: 10.1093/rheumatology/kew052. Epub 2016 Mar 18.

Comment on: different disease subtypes with distinct clinical expression in familial Mediterranean fever: results of a cluster analysis: reply.

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Comment on

Rheumatology (Oxford). 2016 Feb;55(2):343-6.

Rheumatology (Oxford). 2016 Jun;55(6):1147.

DOI: 10.1093/rheumatology/kew052

PMID: 26993879 [Indexed for MEDLINE]

1302. Oncotarget. 2016 Apr 12;7(15):19265-71. doi: 10.18632/oncotarget.8086.

Reduced serpinB9-mediated caspase-1 inhibition can contribute to autoinflammatory disease.

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Patients who suffer from autoinflammatory disease (AID) exhibit seemingly uncontrolled release of interleukin (IL)-1 $\beta$ . The presence of this inflammatory cytokine triggers immune activation in absence of pathogens and foreign material. The mechanisms that contribute to 'sterile inflammation' episodes in AID patients are not fully understood, although for some AIDs underlying genetic causes have been identified. We show that the serine protease inhibitor B9 (serpinB9) regulates IL-1 $\beta$  release in human monocytes. SerpinB9 function is more commonly known for its role in control of granzyme B. SerpinB9 however also serves to restrain IL-1 $\beta$  maturation through caspase-1 inhibition. We here describe an autoinflammatory disease-associated serpinB9 (c.985G>T, A329S) variant, which we discovered in a patient with unknown AID. Using patient cells and serpinB9 overexpressing monocytic cells, we show the A329S variant of serpinB9 exhibits unobstructed granzyme B inhibition, but compromised caspase-1 inhibition. SerpinB9 gene variants might contribute to AID development.

DOI: 10.18632/oncotarget.8086

PMCID: PMC4991381

PMID: 26992230 [Indexed for MEDLINE]

1303. Arthritis Rheumatol. 2016 Aug;68(8):2044-9. doi: 10.1002/art.39683.

Brief Report: Association of Tumor Necrosis Factor Receptor-Associated Periodic Syndrome With Gonosomal Mosaicism of a Novel 24-Nucleotide TNFRSF1A Deletion.

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**OBJECTIVE:** To investigate the molecular cause of persistent fevers in a patient returning from working overseas, in whom investigations for tropical diseases yielded negative results.

**METHODS:** DNA was extracted from the patient's whole blood, leukocyte subpopulations, saliva, hair root, and sperm. The TNFRSF1A gene was analyzed by polymerase chain reaction (PCR), allele-specific PCR, Sanger sequencing, and next-generation sequencing. In silico molecular modeling was performed to predict the structural and functional consequences of the tumor necrosis factor receptor (TNFR) type I protein mutation in the extracellular domain.

**RESULTS:** Sanger sequencing corroborated by allele-specific PCR detected a novel in-frame deletion of 24 nucleotides (c.255\_278del) in the TNFRSF1A gene, and this was subsequently confirmed using next-generation sequencing methods (targeted sequencing and amplicon-based deep sequencing). Results of amplicon-based deep sequencing revealed variable frequency of the mutant allele among different cell lines, including sperm, thus supporting the presence of gonosomal TNFRSF1A mosaicism. The patient had a complete response to treatment with interleukin-1 (IL-1) blockade, with resolution of symptoms and normalization of acute-phase protein levels.

**CONCLUSION:** We describe the first case of gonosomal TNFRSF1A mosaicism in a patient with TNFR-associated periodic syndrome (TRAPS), which was attributable to a novel, somatic 24-nucleotide in-frame deletion. The clinical picture in this patient, including the complete response to IL-1 blockade, was typical of that found in TRAPS. This case adds TRAPS to the list of dominantly inherited autoinflammatory diseases reported to be caused by somatic (or postzygotic) mutation.

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DOI: 10.1002/art.39683

PMID: 26992170 [Indexed for MEDLINE]

1304. ChemMedChem. 2016 Aug 19;11(16):1790-803. doi: 10.1002/cmdc.201600055. Epub 2016 Mar 17.

Design, Synthesis, and Evaluation of Acrylamide Derivatives as Direct NLRP3

## Inflammasome Inhibitors.

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NLRP3 inflammasome plays a key role in the intracellular activation of caspase-1, processing of pro-inflammatory interleukin-1 $\beta$  (IL-1 $\beta$ ), and pyroptotic cell death cascade. The overactivation of NLRP3 is implicated in the pathogenesis of autoinflammatory diseases, known as cryopyrin-associated periodic syndromes (CAPS), and in the progression of several diseases, such as atherosclerosis, type-2 diabetes, gout, and Alzheimer's disease. In this study, the synthesis of acrylamide derivatives and their pharmaco-toxicological evaluation as potential inhibitors of NLRP3-dependent events was undertaken. Five hits were identified and evaluated for their efficiency in inhibiting IL-1 $\beta$  release from different macrophage subtypes, including CAPS mutant macrophages. The most attractive hits were tested for their ability to inhibit NLRP3 ATPase activity on human recombinant NLRP3. This screening allowed the identification of 14, 2-(2-chlorobenzyl)-N-(4-sulfamoylphenethyl)acrylamide, which was able to concentration-dependently inhibit NLRP3 ATPase with an IC<sub>50</sub> value of 74  $\mu$ m. The putative binding pose of 14 in the ATPase domain of NLRP3 was also proposed.

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DOI: 10.1002/cmdc.201600055

PMID: 26990578 [Indexed for MEDLINE]

1305. Stem Cell Res. 2015 Nov;15(3):694-6. doi: 10.1016/j.scr.2015.10.018. Epub 2015 Nov 2.

Generation of integration-free induced pluripotent stem cells from a patient with Familial Mediterranean Fever (FMF).

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Fibroblasts from a Familial Mediterranean Fever (FMF) patient were reprogrammed with episomal vectors by using the Neon Transfection System for the generation of integration-free induced pluripotent stem cells (iPSCs). The resulting iPSC line was characterized to determine the expression of pluripotency markers, proper differentiation into three germ layers, the presence of normal chromosomal structures as well as the lack of genomic integration. A homozygous missense mutation in the MEFV gene (p.Met694Val), which lead to typical FMF phenotype, was shown to be present in the generated iPSC line.

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DOI: 10.1016/j.scr.2015.10.018

PMID: 26987928 [Indexed for MEDLINE]

1306. Medicine (Baltimore). 2016 Mar;95(11):e3027. doi: 10.1097/MD.0000000000003027.

Observational Study of a French and Belgian Multicenter Cohort of 23 Patients Diagnosed in Adulthood With Mevalonate Kinase Deficiency.

Durel CA(1), Aouba A, Bienvenu B, Deshayes S, Coppéré B, Gombert B, Acquaviva-Bourdain C, Hachulla E, Lecomte F, Touitou I, Ninet J, Philit JB, Messer L, Brouillard M, Girard-Madoux MH, Moutschen M, Raison-Peyron N, Hutin P, Duffau P, Trolliet P, Hatron PY, Heudier P, Cevallos R, Lequerré T, Brousse V, Lesire V, Audia S, Maucourt-Boulch D, Cuisset L, Hot A.

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The aim of this study was to describe the clinical and biological features of Mevalonate kinase deficiency (MKD) in patients diagnosed in adulthood. This is a French and Belgian observational retrospective study from 2000 to 2014. To constitute the cohort, we cross-check the genetic and biochemical databases. The clinical, enzymatic, and genetic data were gathered from medical records. Twenty-three patients were analyzed. The mean age at diagnosis was 40 years, with a mean age at onset of symptoms of 3 years. All symptomatic patients had fever. Febrile attacks were mostly associated with arthralgia (90.9%); lymphadenopathy, abdominal pain, and skin lesions (86.4%); pharyngitis (63.6%); cough (59.1%); diarrhea, and hepatosplenomegaly (50.0%). Seven patients had psychiatric symptoms (31.8%). One patient developed recurrent seizures. Three patients experienced renal involvement (13.6%). Two patients had angiomyolipoma (9.1%). All but one tested patients had elevated serum immunoglobulin (Ig) D level. Twenty-one patients had genetic diagnosis; most of them were compound heterozygote (76.2%).

p.Val377Ile was the most prevalent mutation. Structural articular damages and systemic AA amyloidosis were the 2 most serious complications. More than 65% of patients displayed decrease in severity and frequency of attacks with increasing age, but only 35% achieved remission. MKD diagnosed in adulthood shared clinical and genetic features with classical pediatric disease. An elevated IgD concentration is a good marker for MKD in adults. Despite a decrease of severity and frequency of attacks with age, only one-third of patients achieved spontaneous remission.

DOI: 10.1097/MD.0000000000003027

PMCID: PMC4839898

PMID: 26986117 [Indexed for MEDLINE]

1307. Curr Rheumatol Rep. 2016 Apr;18(4):18. doi: 10.1007/s11926-016-0567-y.

Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis (PFAPA) Syndrome: a Review of the Pathogenesis.

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PFAPA syndrome represents the most common cause of recurrent fever in children in European populations, and it is characterized by recurrent episodes of high fever, pharyngitis, cervical adenitis, and aphthous stomatitis. Many possible causative factors have been explored so far, including infectious agents, immunologic mechanisms and genetic predisposition, but the exact etiology remains unclear. Recent findings demonstrate a dysregulation of different components of innate immunity during PFAPA flares, such as monocytes, neutrophils, complement, and pro-inflammatory cytokines, especially IL-1 $\beta$ , suggesting an

inflammasome-mediated innate immune system activation and supporting the hypothesis of an autoinflammatory disease. Moreover, in contrast with previous considerations, the strong familial clustering suggests a potential genetic origin rather than a sporadic disease. In addition, the presence of variants in inflammasome-related genes, mostly in NLRP3 and MEFV, suggests a possible role of inflammasome-composing genes in PFAPA pathogenesis. However, none of these variants seem to be relevant, alone, to its etiology, indicating a high genetic heterogeneity as well as an oligogenic or polygenic genetic background.

DOI: 10.1007/s11926-016-0567-y

PMID: 26984802 [Indexed for MEDLINE]

1308. Autophagy. 2017 May 4;13(5):989-990. doi: 10.1080/15548627.2016.1154254.

TRIM-directed selective autophagy regulates immune activation.

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Selectivity of autophagy is achieved by target recognition; however, the number of autophagy receptors identified so far is limited. In this study we demonstrate that a subset of tripartite motif (TRIM) proteins mediate selective autophagy of key regulators of inflammatory signaling. MEFV/TRIM20, and TRIM21 act as autophagic receptors recognizing their cognate targets and delivering them for autophagic degradation. MEFV recognizes the inflammasome components NLRP3, CASP1 and NLRP1, whereas TRIM21 specifically recognizes the activated, dimeric form of IRF3 inducing type I interferon gene expression. MEFV and TRIM21 have a second activity, whereby they act not only as receptors but also recruit and organize key components of autophagic machinery consisting of ULK1, BECN1, ATG16L1, and mammalian homologs of Atg8, with a preference for GABARAP. MEFV capacity to organize the autophagy apparatus is affected by common mutations causing familial Mediterranean fever. These findings reveal a general mode of action of TRIMs as autophagic receptor-regulators performing a highly-selective type of autophagy

(precision autophagy), with MEFV specializing in the suppression of inflammasome and CASP1 activation engendering IL1B/interleukin-1 $\beta$  production and implicated in the form of cell death termed pyroptosis, whereas TRIM21 dampens type I interferon responses.

DOI: 10.1080/15548627.2016.1154254

PMCID: PMC5446080

PMID: 26983397 [Indexed for MEDLINE]

1309. Scand J Rheumatol. 2016 Jul;45(4):337-8. doi: 10.3109/03009742.2016.1139175. Epub 2016 Mar 16.

Effective treatment with azathioprine for renal amyloidosis secondary to familial Mediterranean fever.

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DOI: 10.3109/03009742.2016.1139175

PMID: 26982335 [Indexed for MEDLINE]

1310. HSS J. 2015 Oct;11(3):278-80. doi: 10.1007/s11420-015-9444-x. Epub 2015 May 12.

A Case Report of Familial Mediterranean Fever Diagnosed Following the Total Knee Arthroplasty.

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DOI: 10.1007/s11420-015-9444-x

PMCID: PMC4773695

PMID: 26981061

1311. Eur J Immunol. 2016 Apr;46(4):817-28. doi: 10.1002/eji.201545497.

Innate immune memory: Implications for host responses to damage-associated molecular patterns.

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Cells of the innate immune system build immunological memory via epigenetic reprogramming after stimulations with microbial ligands. This functional readjustment allows for enhanced nonspecific inflammatory responses upon secondary challenges, a process termed "trained immunity." The epigenomic blueprint of trained monocytes has been recently reported, which revealed several important immunologic and metabolic mechanisms that underlie these changes. Interestingly, similar long-term reprogramming of cytokine production has also been described to be induced by endogenous damage-associated molecular patterns (DAMPs). Here, we present an overview of the novel data showing that endogenous alarm signals associated with tissue damage and sterile inflammation can induce trained immunity through epigenetic regulation of transcriptional programs. We describe new and old evidence of persistent effects of DAMPs in driving inflammation and enforce the concept that the influence of tissue-derived signals is critical in adjusting the magnitude and type of immune response built by the host. The better characterization of trained immunity for the persistence of inflammation induced by DAMPs would provide new possibilities for intervention in aging and autoinflammatory disorders.



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DOI: 10.1002/eji.201545497

PMID: 26970440 [Indexed for MEDLINE]

1312. Arch Pediatr. 2016 Apr;23(4):437-41. doi: 10.1016/j.arcped.2016.01.005. Epub 2016 Mar 8.

[Juvenile idiopathic arthritis: Definition and classification].

[Article in French]

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Juvenile idiopathic arthritis (JIA) is a group of diseases defined by the presence of arthritis of more than 6 weeks duration in patients aged less than 16 years and with unknown etiology. The international classification based on clinical and biological criteria define each type of JIA: systemic, oligoarticular, polyarticular with and without rheumatoid factor, enthesitis-related arthritis, and psoriatic arthritis. However, some discussions persist concerning systemic-onset juvenile idiopathic arthritis, whose clinical symptoms and pathogenic mechanisms are quite similar to those observed in autoinflammatory diseases, arthritis with antinuclear factors (poly- and oligoarticular) that could be considered as a homogenous group, and a family history of psoriasis that frequently led to unclassified arthritis. Better knowledge of the pathogenic mechanisms should improve the initial clinical classification with more homogeneous groups of patients and reduce the number of unclassified cases of arthritis.

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DOI: 10.1016/j.arcped.2016.01.005

PMID: 26968301 [Indexed for MEDLINE]

1313. J Invest Dermatol. 2016 Jun;136(6):1283-1286. doi: 10.1016/j.jid.2016.02.801. Epub 2016 Mar 9.

Whole Genome Linkage Analysis Followed by Whole Exome Sequencing Identifies Nicastrin (NCSTN) as a Causative Gene in a Multiplex Family with  $\gamma$ -Secretase Spectrum of Autoinflammatory Skin Phenotypes.

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DOI: 10.1016/j.jid.2016.02.801

PMID: 26968259 [Indexed for MEDLINE]

1314. United European Gastroenterol J. 2016 Feb;4(1):92-6. doi: 10.1177/2050640615584536. Epub 2015 May 5.

# The association of endoplasmic reticulum aminopeptidase-1 (ERAP-1) with Familial Mediterranean Fever (FMF).

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**BACKGROUND:** The ERAP1 gene cleaves the receptors and reduces their ability to transmit chemical signals to the cell that affect the process of inflammation and, secondly, it cleaves many types of proteins into small peptides that are recognized by the immune system.

**OBJECTIVE:** ERAP-1 gene mutations may create a sensitivity for Familial Mediterranean Fever (FMF).

**METHOD:** We included 15 FMF patients with the M694 (+) mutation in the study in order to exclude patients without pyrin gene mutations and create a homogeneous study group. Fifteen patients with ulcerative colitis formed the control group.

**RESULTS:** There wasn't any case without ERAP-1 gene mutations. At least one mutation at exon 3 or exon 10 was found in all cases in both groups. There were 14 ERAP-1 gene mutations at exon 10 and 11 at exon 3 in patients with FMF.

Interestingly, if there were ERAP-1 gene mutations at exon 3, a p.Arg127 Pro (c.380 G>C) mutation always existed for three FMF patients with polymorphic mutations at this exon. There were 11 ERAP-1 gene mutations at exon 10 and 12 gene mutations at exon 3 in patients with ulcerative colitis. Exon 3 mutations were usually single p.Arg127 Pro (c.380 G>C) mutations for 12 patients with ulcerative colitis as seen in the patients with FMF. The single mutation was always p.Ser453 Ser (c.1359T>C) for patients with ulcerative colitis at exon 10.

**CONCLUSION:** There are more ERAP-1 mutations in the FMF group in comparison to the ulcerative colitis group. So, there may be a strong susceptibility to ERAP-1 gene mutations in FMF patients according to our results. However, further studies with larger study and control groups are needed.

PMCID: PMC4766545

PMID: 26966528

1315. Pract Neurol. 2016 Aug;16(4):304-7. doi: 10.1136/practneurol-2015-001342. Epub 2016 Mar 10.

Trapped without a diagnosis: Tumour necrosis factor receptor-associated periodic syndrome (TRAPS).

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Tumour necrosis factor receptor-associated periodic syndrome (TRAPS) is an autosomal dominant condition caused by mutations in the TNFRSF1A gene. It is characterised by recurrent episodes of myalgia, followed by prolonged fever, migratory rashes, headache, serositis, arthralgia, abdominal pain and periorbital oedema. We describe a 49-year-old man with a self-limiting episode of paraparesis who reported recurrent bouts of abdominal symptoms and headaches since childhood. He had a persistent inflammatory response with night sweats and weight loss. We diagnosed TRAPS 2 years after having identified a TNFRSF1A gene mutation. His symptoms and inflammatory response resolved dramatically with the interleukin-1 receptor antagonist anakinra.

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DOI: 10.1136/practneurol-2015-001342

PMID: 26965498 [Indexed for MEDLINE]

1316. Oral Dis. 2016 Nov;22(8):719-734. doi: 10.1111/odi.12472. Epub 2016 Apr 26.

The microbiome-systemic diseases connection.

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The human microbiome consists of all microorganisms occupying the skin, mucous membranes and intestinal tract of the human body. The contact of the mucosal immune system with the human microbiome is a balanced interplay between defence mechanisms of the immune system and symbiotic or pathogenic microbial factors, such as microbial antigens and metabolites. In systemic autoimmune diseases (SADs) such as rheumatoid arthritis, systemic lupus erythematosus and Sjögren's syndrome, the immune system is deranged to a chronic inflammatory state and autoantibodies are an important hallmark. Specific bacteria and/or a dysbiosis in the human microbiome can lead to local mucosal inflammation and increased intestinal permeability. Proinflammatory lymphocytes and cytokines can spread to the systemic circulation and increase the risk of inflammation at distant anatomical sites, such as the joints or salivary glands. Increased intestinal permeability increases antigen exposure and the risk of autoantibody production. If the human microbiome indeed plays such a critical role in SADs, this finding holds a great promise for new therapeutic strategies, such as diet interventions and probiotics and prebiotics. This review provides a background on the human microbiome and mucosal immunity in the gut and oral cavity and gives a summary of

the current knowledge on the microbiome-SADs connection.

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DOI: 10.1111/odi.12472

PMID: 26953630 [Indexed for MEDLINE]

1317. Arch Rheumatol. 2016 Mar 10;31(2):133-138. doi: 10.5606/ArchRheumatol.2016.5696. eCollection 2016 Jun.

Screening of Free Carnitine and Acylcarnitine Status in Children With Familial Mediterranean Fever.

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**Objectives:** This study aims to demonstrate the patterns of free carnitine (FC) and acylcarnitine (AC) esters in familial Mediterranean fever (FMF) patients.

**Patients and methods:** A total of 205 patients (106 males, 99 females; mean age 131.3±52.1 months; range 24 to 254 months) with FMF and 50 healthy controls (27 males, 23 females; mean age 125.7±49.6 months; range 32 to 217 months) were enrolled. Fasting dried blood samples were taken for showing FC and AC ester levels with tandem mass spectrometry from both patients and controls.

**Results:** Screening of AC profile revealed increased FC, 3-hydroxypalmitoylcarnitine (C16-OH), and 3-Hydroxy octadecanoylcarnitine (C18:2-OH) carnitine levels, while decreased acetyl-carnitine (C2), propionyl-carnitine (C3), butyryl-carnitine (C4), tiglyl-carnitine (C5:1), hexanoyl-carnitine (C6), octanoyl-carnitine (C8), decenoylcarnitine (C10:1), decadienoylcarnitine (C10:2), malonylcarnitine (C3DC), methylmalonylcarnitine

(C4DC), glutarylcarnitine (C5DC), hexadecenoylcarnitine (C16:1), 3-Hydroxy butyrylcarnitine (C4-OH), and 3-Hydroxy oleylcarnitine (C18:1-OH) carnitine levels in FMF patients compared to controls. Total AC levels ( $p<0.001$ ) and AC to FC ratio ( $p<0.001$ ) were also lower in FMF patients than the controls.

Conclusion: In this study, we were able to detect some of the AC profile variations in FMF patients; however, usage of carnitine in all patients with FMF is not recommended since we were not able to demonstrate secondary carnitine deficiency in FMF patients of this study.

DOI: 10.5606/ArchRheumatol.2016.5696

PMCID: PMC5827828

PMID: 29900937

Conflict of interest statement: Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

1318. Scand J Rheumatol. 2016;45(3):252-3. doi: 10.3109/03009742.2015.1127413. Epub 2016 Mar 7.

Anakinra for the treatment of familial Mediterranean fever-associated spondyloarthritis.

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DOI: 10.3109/03009742.2015.1127413

PMID: 26948937 [Indexed for MEDLINE]

1319. Clin Immunol. 2016 Apr;165:21-8. doi: 10.1016/j.clim.2016.03.002. Epub 2016 Mar 3.

Shaping the spectrum - From autoinflammation to autoimmunity.

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Historically, autoimmune-inflammatory disorders were subdivided into autoinflammatory vs. autoimmune diseases. About a decade ago, an immunological continuum was proposed, placing "classical" autoinflammatory disorders, characterized by systemic inflammation in the absence of high-titer autoantibodies or autoreactive T lymphocytes, at the one end, and autoimmune disorders at the other end. We provide an overview of recent developments and observations, filling in some of the gaps and showing strong interconnections between innate and adaptive immune mechanisms, indicating that disorders from both ends of the immunological spectrum indeed share key pathomechanisms. We focus on three exemplary disorders: i) systemic juvenile idiopathic arthritis representing "classical" autoinflammatory disorders; ii) psoriasis, a mixed pattern disease; and iii) systemic lupus erythematosus, a prototypical autoimmune disease. We summarize scientific observations suggesting that, depending on disease stages and/or duration, individualized treatment targeting innate or adaptive immune mechanisms in disorders from either end of the immunological spectrum may control disease activity.

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DOI: 10.1016/j.clim.2016.03.002

PMID: 26948930 [Indexed for MEDLINE]

1320. Cardiol Res Pract. 2016;2016:7840724. doi: 10.1155/2016/7840724. Epub 2016 Jan 31.

The Use of IL-1 Receptor Antagonist (Anakinra) in Idiopathic Recurrent Pericarditis: A Narrative Review.

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Recurrent pericarditis is a complication of acute pericarditis in 20-30% of the patients and is usually idiopathic in nature. The underlying pathogenesis of this condition remains unclear, although immune-mediated mechanisms seem likely. A subgroup of these patients with refractory symptoms can be challenging to manage, and multiple immunosuppressive medications have been used without consistent benefit. Anakinra, an interleukin-1 receptor antagonist, has been used in treatment of rheumatoid arthritis and autoinflammatory syndromes. Preliminary evidence suggests that anakinra could be a promising therapy for idiopathic recurrent pericarditis. In this narrative review, we summarize the current understanding of the etiopathogenesis of idiopathic recurrent pericarditis, mechanism of action of anakinra, and the preliminary evidence, supporting the use of anakinra in pericarditis.

DOI: 10.1155/2016/7840724

PMCID: PMC4752980

PMID: 26942035

1321. Clin Exp Rheumatol. 2016 May-Jun;34(3):531-8. Epub 2016 Feb 26.

Safety profile of anakinra in the management of rheumatologic, metabolic and autoinflammatory disorders.

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Anakinra is a biologic response modifier that competitively antagonises the biologic effects of interleukin-1, the ancestor pleiotropic proinflammatory cytokine produced by numerous cell types, found in excess in the serum, synovial fluid and any involved tissues of patients with many inflammatory diseases. The magnitude of the risk of different infections, including *Mycobacterium tuberculosis* (Mtb) infection, associated with the large use of anakinra in many rheumatologic, metabolic or autoinflammatory disorders is still unknown. In addition, it is unclear whether this effect is modified by the concomitant use of antirheumatic drugs and corticosteroids. The rates of development of Mtb disease in patients treated with anakinra due to rheumatoid arthritis, systemic autoinflammatory diseases, Schnitzler's syndrome, Behçet's disease, adult-onset Still disease, systemic juvenile idiopathic arthritis, gout and diabetes mellitus have been usually very low. However, clinicians must carefully weigh the benefits of biological drugs against their risks, particularly in patients prone to infections. Additional data are needed to understand whether this risk of Mtb infection and reactivation are representative of a class effect related to biologics or whether anakinra bears specifically an intrinsic lower risk in comparison with other biologic drugs.

PMID: 26940286 [Indexed for MEDLINE]

1322. Mod Rheumatol. 2016 Sep;26(5):637-41. doi: 10.3109/14397595.2016.1162261. Epub 2016 Apr 21.

Biologic therapy in familial Mediterranean fever.

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Comment in

Mod Rheumatol. 2016 Sep;26(5):805.

Familial Mediterranean fever (FMF) is the most common autoinflammatory hereditary disease characterized by self-limited attacks of fever and serositis. Although colchicine is the gold standard treatment for the attacks ~10% of cases of FMF are resistant or intolerant to effective doses of colchicine. In such cases, however, there are increasing numbers of case reports or clinical trials treated by biologic agents which directly target the proinflammatory cytokines. Anti-interleukin-1 (IL-1) treatment has proven beneficial in improving the inflammation in terms of clinical manifestations and laboratory findings in clinical trials. Furthermore, anti-tumor necrosis factor treatment has also revealed the efficacy and safety in patients with colchicine-resistant FMF. More recently, cases of successful treatment with IL-6 inhibitor, tocilizumab (TCZ), has been reported from Japan and Turkey. Of note, TCZ may be preferable in the treatment as well as the prevention of secondary amyloidosis of FMF patients since it significantly suppresses acute inflammatory response. In the present review, we summarize the literatures regarding the efficacy of biologic therapy in colchicine-resistant or -intolerant patients with FMF.

DOI: 10.3109/14397595.2016.1162261

PMID: 26939747 [Indexed for MEDLINE]

1323. Duodecim. 2016;132(2):145-51.

[Chronic nonbacterial osteomyelitis].

[Article in Finnish]

Keskitalo P, Remes-Pakarinen T, Vähäsalo P, Niinimäki J, Kröger L.

Chronic nonbacterial osteomyelitis is an autoinflammatory disease occurring mainly in children and adolescents, typically involving recurrent or persistent osteitic foci. The symptom is bone pain, possibly accompanied by soft tissue tenderness. Some patients exhibit symptoms of systemic inflammation. The precise etiology of the disease is not known, but an imbalance of inflammatory and

anti-inflammatory cytokines is presumed to play a role in the development of the disease. While an anti-inflammatory analgesic is in most cases sufficient to calm down the osteitis, the use of corticosteroids, anti- TNF- $\alpha$  inhibitors or bisphosphonates is required in some cases.

PMID: 26939487 [Indexed for MEDLINE]

1324. Mol Med Rep. 2016 Apr;13(4):3181-9. doi: 10.3892/mmr.2016.4918. Epub 2016 Feb 22.

Putative modifier genes in mevalonate kinase deficiency.

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Mevalonate kinase deficiency (MKD) is an autosomal recessive auto-inflammatory disease, caused by impairment of the mevalonate pathway. Although the molecular mechanism remains to be elucidated, there is clinical evidence suggesting that other regulatory genes may be involved in determining the phenotype. The identification of novel target genes may explain non-homogeneous genotype-phenotype correlations, and provide evidence in support of the hypothesis that novel regulatory genes predispose or amplify deregulation of the mevalonate pathway in this orphan disease. In the present study, DNA samples were obtained from five patients with MKD, which were then analyzed using whole exome sequencing. A missense variation in the PEX11 $\gamma$  gene was observed in homozygosis in P2, possibly correlating with visual blurring. The UNG rare gene variant was detected in homozygosis in P5, without correlating with a specific clinical phenotype. A number of other variants were found in the five analyzed DNA samples from the MKD patients, however no correlation with the phenotype was established. The results of the presents study suggested that further analysis, using next generation sequencing approaches, is required on a larger sample size of patients with MKD, who share the same MVK mutations and exhibit 'extreme' clinical

phenotypes. As MVK mutations may be associated with MKD, the identification of specific modifier genes may assist in providing an earlier diagnosis.

DOI: 10.3892/mmr.2016.4918

PMID: 26935981 [Indexed for MEDLINE]

1325. PLoS One. 2016 Mar 2;11(3):e0150693. doi: 10.1371/journal.pone.0150693. eCollection 2016.

Human Monocyte-Derived Osteoclasts Are Targeted by Staphylococcal Pore-Forming Toxins and Superantigens.

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*Staphylococcus aureus* is the leading cause of bone and joint infections (BJIs). Staphylococcal pathogenesis involves numerous virulence factors including secreted toxins such as pore-forming toxins (PFTs) and superantigens. The role of these toxins on BJI outcome is largely unknown. In particular, few studies have examined how osteoclasts, the bone-resorbing cells, respond to exposure to staphylococcal PFTs and superantigens. We investigated the direct impact of recombinant staphylococcal toxins on human primary mature monocyte-derived osteoclasts, in terms of cytotoxicity and cell activation with cell death and bone resorption assays, using macrophages of the corresponding donors as a reference. Monocyte-derived osteoclasts displayed similar toxin susceptibility profiles compared to macrophages. Specifically, we demonstrated that the Pantone-Valentine leukocidin, known as one of the most powerful PFT which lyses myeloid cells after binding to the C5a receptor, was able to induce the death of osteoclasts. The archetypal superantigen TSST-1 was not cytotoxic but enhanced

the bone resorption activity of osteoclasts, suggesting a novel mechanism by which superantigen-producing *S. aureus* can accelerate the destruction of bone tissue during BJI. Altogether, our data indicate that the diverse clinical presentations of BJIs could be related, at least partly, to the toxin profiles of *S. aureus* isolates involved in these severe infections.

DOI: 10.1371/journal.pone.0150693

PMCID: PMC4774977

PMID: 26934588 [Indexed for MEDLINE]

1326. Eur J Neurol. 2016 Jul;23(7):1145-51. doi: 10.1111/ene.12965. Epub 2016 Mar 2.

Neurology of the cryopyrin-associated periodic fever syndrome.

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**BACKGROUND AND PURPOSE:** The cryopyrin-associated periodic fever syndrome (CAPS) is an autosomal dominant autoinflammatory disorder caused by mutations in the NLRP3 gene and is typified by recurrent episodes of systemic inflammation resulting in fever, urticarial rash and arthralgia. In addition to these systemic aspects, CAPS has multiple neurological manifestations. The largest case series to date is presented focusing on the neurological features of this disorder.

**METHODS:** The case histories of a cohort of 38 UK patients with genetically proven CAPS who were treated with interleukin 1 $\beta$  (IL-1 $\beta$ ) inhibition as part of a national treatment programme and underwent detailed neurological assessment were reviewed.

**RESULTS:** Across the entire disease course neurological manifestations were present in 95% of patients; 84% had some form of headache; 66% sensorineural hearing loss; 60% myalgia; 34% papilloedema and 26% optic atrophy. Patients with the T348M mutation tended to have a more severe neurological phenotype with an earlier age of onset. Four patients had cerebrospinal fluid examination, three of

whom had evidence of aseptic meningitis. There was a marked response to IL-1 $\beta$  inhibition, which has revolutionized management of these patients (29/32 patients with headache responding).

CONCLUSION: Neurological symptoms are extremely common in CAPS and these results highlight the importance of increasing awareness amongst neurologists, particularly as highly effective therapies are available.

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DOI: 10.1111/ene.12965

PMID: 26931528 [Indexed for MEDLINE]

1327. Int J Rheum Dis. 2017 Dec;20(12):2230-2232. doi: 10.1111/1756-185X.12853. Epub 2016 Mar 1.

Is plasmapheresis a potential treatment for familial Mediterranean fever patients resistant or intolerant to colchicine?

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DOI: 10.1111/1756-185X.12853

PMID: 26929063 [Indexed for MEDLINE]

1328. Rev Med Chil. 2015 Dec;143(12):1560-8. doi: 10.4067/S0034-98872015001200009.

Familial Mediterranean Fever is associated with abnormal ventricular repolarization indices.

Ahbap E, Sakaci T, Kara E, Sahutoglu T, Ozturk S, Basturk T, Koc Y, Sevinc M, Akgol C, Ucar ZA, Kayalar AO, Caglayan FB, Gurbuz S, Unsal A.

BACKGROUND: Cardiac arrhythmias can be a part of cardiovascular involvement in

some rheumatic diseases, but data about familial Mediterranean fever (FMF) are conflicting.

AIM: To search for abnormalities in ventricular repolarization indices in FMF patients.

PATIENTS AND METHODS: Seventy seven FMF patients and 30 age/gender comparable healthy controls were included. All patients were attack free and subjects with disease or drugs that are known to alter cardiac electrophysiology were excluded. Electrocardiographic data were obtained and analyzed.

RESULTS: Twelve FMF patients had amyloidosis. QT and QTc intervals were within the normal ranges and similar between FMF patients and healthy controls. QT dispersion, peak to end interval of T wave (Tpe), Tpe/QT and Tpe/QTc ratios were significantly higher in FMF patients than in healthy controls. Patients with amyloidosis had significantly higher QT dispersion, Tpe, Tpe/QT and Tpe/QTc than their counterparts without FMF. Levels of proteinuria were moderately correlated with QT dispersion, Tpe, Tpe/QT and Tpe/QTc.

CONCLUSIONS: FMF patients may have an increased risk for arrhythmias.

DOI: 10.4067/S0034-98872015001200009

PMID: 26928618 [Indexed for MEDLINE]

1329. Pediatr Emerg Care. 2016 Mar;32(3):168-72. doi: 10.1097/PEC.0000000000000728.

Assessment of 17 Pediatric Cases With Colchicine Poisoning in a 2-Year Period.

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AIM: The aim of the study is to discuss clinical effects, treatments, and outcomes of pediatric colchicine poisoning.

METHOD: This study was designed as an observational case series study. The medical records of children aged between 0 and 18 years, who were hospitalized for colchicine poisoning at the Department of Pediatric Intensive Care Unit, Cumhuriyet University Faculty of Medicine, between January 2010 and January 2012, were retrospectively evaluated.



**RESULTS:** We presented 17 children with colchicine poisoning. The mean (SD, range) age of patients was 71.5 (69.19, 18-204) months. The period to apply to the hospital after taking the medications was 7.3 hours (7.97, 30 minutes-26 hours) on average. The use of colchicine was due to diagnosis of Familial Mediterranean fever (FMF) in the families of 8 patients, diagnosis of Behçet disease in 1 patient's father, diagnosis of Behçet disease in 1 patient herself, and diagnosis of FMF in 6 patients themselves. Thirteen patients had taken colchicine at the dose of less than 0.5 mg/kg known as subtoxic and 1 patient had taken colchicine at the dose of greater than 0.8 mg/kg, and doses taken by 3 patients were not known. Fourteen patients (82.4%) had involuntary drug intake. Fifty percent of them were symptomatic at the moment of application and all had gastrointestinal complaints. All patients were observed in intensive care unit upon first admission and received supportive care. One of patients showed total alopecia, one showed leucocytosis, and another one showed acute abdomen picture. None of the patients showed mortality.

**CONCLUSIONS:** Mortality of colchicine toxicity is high and quick assessment is absolutely required. In regions where FMF is common and the use of colchicine is high, clinicians should pay attention to symptoms and findings related to colchicine intoxication and keep them in mind in differential diagnosis.

DOI: 10.1097/PEC.0000000000000728

PMID: 26928096 [Indexed for MEDLINE]

1330. Arch Iran Med. 2016 Mar;19(3):225-8. doi: 0161903/AIM.0013.

Newly Diagnosed Crohn's Disease in Patient with Familial Mediterranean Fever.

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Chronic abdominal pain sometimes constitute a major challenge, specially when a patient has two diseases with dominant features of abdominal pain in both. At this point, clinicians face a daunting task both in diagnosing and treating an individual's chronic abdominal pain. Similarly, familial Mediterranean fever disease and Crohn's disease have the same clinical features in terms of chronic abdominal pain, and inflammatory properties of these diseases. The association of familial Mediterranean fever disease and Crohn's disease is very rare and may lead to a remarkable challenge in both diagnosis and treatment. Here, we report a young man with FMF disease presented with extraordinary and intolerable abdominal pain relieved only by excessive narcotic analgesics. The presented case was diagnosed with CD and successfully treated with anti-TNF (tumor necrosis factor) due to steroid refractory.

DOI: 0161903/AIM.0013

PMID: 26923897 [Indexed for MEDLINE]

1331. Dermatology. 2016;232(2):254-8. doi: 10.1159/000443648. Epub 2016 Feb 27.

PASS Syndrome: An IL-1-Driven Autoinflammatory Disease.

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PASS syndrome is a rare inflammatory disease characterized by a chronic-relapsing course of pyoderma gangrenosum, acne vulgaris, hidradenitis suppurativa and ankylosing spondylitis. Here, we describe a case of a patient with spontaneously recurrent purulent skin lesions along with seronegative spondylarthritis consistent with the PASS syndrome. During his disease exacerbation, the patient displayed episodes of fever along with elevated serum levels of interleukin (IL)-1 $\beta$ . Skin lesions were characterized by sterile neutrophilic infiltrates and showed a rapid response to the IL-1 receptor antagonist anakinra (Kineret®) consistent with the autoinflammatory nature of this disease. However, unlike other autoinflammatory diseases such as PAPA and PAPASH, we did not find mutations in the gene PSTPIP1, raising the possibility that other specific

mutations in the IL-1 pathway may be involved.

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DOI: 10.1159/000443648

PMID: 26919742 [Indexed for MEDLINE]

1332. Indian J Pediatr. 2016 Apr;83(4):322-7. doi: 10.1007/s12098-016-2060-z. Epub 2016 Feb 26.

Systemic Juvenile Idiopathic Arthritis: Diagnosis and Management.

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Systemic juvenile idiopathic arthritis (sJIA) is an inflammatory condition characterized by fever, lymphadenopathy, arthritis, rash and serositis. In sJIA, systemic inflammation has been associated with dysregulation of the innate immune system, suggesting that it is an autoinflammatory disorder. IL-1 and IL-6 play a major role in the pathogenesis of sJIA and treatment with IL-1 and IL-6 inhibitors has shown to be highly effective. Recent data suggests that early cytokine blockage might abrogate chronic, destructive, therapy resistant arthritis phase, reflecting a potential "window of opportunity" in the care of children with sJIA.

DOI: 10.1007/s12098-016-2060-z

PMID: 26916892 [Indexed for MEDLINE]

1333. Transplant Proc. 2016 Jan-Feb;48(1):265-6. doi: 10.1016/j.transproceed.2015.11.006.

Kidney Transplant in a Patient With Tumor Necrosis Factor Receptor-1 Syndrome (TRAPS): Case Report and Review of the Literature.

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Tumor necrosis factor receptor -1-associated periodic syndrome (TRAPS) is a rare disease that may result in chronic kidney disease due to secondary amyloidosis. We report a case of a patient with a history of TRAPS who received a kidney transplant 11 years ago and still has functioning kidney transplant despite recurrence of amyloidosis and proteinuria.

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DOI: 10.1016/j.transproceed.2015.11.006

PMID: 26915881 [Indexed for MEDLINE]

1334. PLoS One. 2016 Feb 25;11(2):e0150075. doi: 10.1371/journal.pone.0150075. eCollection 2016.

IDO1 Deficiency Does Not Affect Disease in Mouse Models of Systemic Juvenile Idiopathic Arthritis and Secondary Hemophagocytic Lymphohistiocytosis.

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**OBJECTIVES:** Indoleamine 2,3-dioxygenase-1 (IDO1) is an immune-modulatory enzyme that catalyzes the degradation of tryptophan (Trp) to kynurenine (Kyn) and is strongly induced by interferon (IFN)- $\gamma$ . We previously reported highly increased levels of IFN- $\gamma$  and corresponding IDO activity in patients with hemophagocytic lymphohistiocytosis (HLH), a hyper-inflammatory syndrome. On the other hand, IFN- $\gamma$  and IDO were low in patients with systemic juvenile idiopathic arthritis (sJIA), an autoinflammatory syndrome. As HLH can occur as a complication of sJIA, the opposing levels of both IFN- $\gamma$  and IDO are remarkable. In animal models for sJIA and HLH, the role of IFN- $\gamma$  differs from being protective to pathogenic. In this study, we aimed to unravel the role of IDO1 in the pathogenesis of sJIA and HLH.

**METHODS:** Wild-type and IDO1-knockout (IDO1-KO) mice were used in 3 models of sJIA or HLH: complete Freund's adjuvant (CFA)-injected mice developed an sJIA-like syndrome and secondary HLH (sHLH) was evoked by either repeated injection of unmethylated CpG oligonucleotide or by primary infection with mouse cytomegalovirus (MCMV). An anti-CD3-induced cytokine release syndrome was used as a non-sJIA/HLH control model.

**RESULTS:** No differences were found in clinical, laboratory and hematological features of sJIA/HLH between wild-type and IDO1-KO mice. As IDO modulates the immune response via induction of regulatory T cells and inhibition of T cell proliferation, we investigated both features in a T cell-triggered cytokine release syndrome. Again, no differences were observed in serum cytokine levels, percentages of regulatory T cells, nor of proliferating or apoptotic thymocytes and lymph node cells.

**CONCLUSIONS:** Our data demonstrate that IDO1 deficiency does not affect inflammation in sJIA, sHLH and a T cell-triggered cytokine release model. We hypothesize that other tryptophan-catabolizing enzymes like IDO2 and tryptophan 2,3-dioxygenase (TDO) might compensate for the lack of IDO1.

DOI: 10.1371/journal.pone.0150075

PMCID: PMC4767214

PMID: 26914138 [Indexed for MEDLINE]

# Episode of Familial Mediterranean Fever-Related Peritonitis in the Second Trimester of Pregnancy Followed by Acute Cholecystitis: Dilemmas and Pitfalls.

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**BACKGROUND:** Differential diagnosis of acute abdomen in pregnant patients is one of the greatest challenges for the clinician. Occurrence of Familial Mediterranean Fever (FMF) paroxysm of peritonitis and acute cholecystitis during pregnancy is a unique clinical entity that leads to serious diagnostic and therapeutic dilemmas.

**CASE REPORT:** We present the case of a 33-year-old Armenian patient at 16 weeks' gestational age with a history of FMF, who was admitted twice within 1 month with acute abdomen. The first episode was attributed to FMF and successfully treated conservatively with colchicine. The second episode was diagnosed as acute cholecystitis and led to emergent laparoscopic cholecystectomy and lysis of peritoneal adhesions from previous FMF attacks. The patient presented an uneventful postoperative clinical course and had a normal delivery of a healthy infant at the 39th week of gestation.

**CONCLUSIONS:** Pregnant patients with acute abdomen should be evaluated with open mind. To the best of our knowledge, this is the first published report of the coexistence of 2 different causes of acute abdomen during pregnancy. Meticulous history and thorough physical, laboratory, and radiologic examination are the keys to reach a correct diagnosis. Treatment of pregnant patients with acute abdomen should be individualized. Administration of colchicine should be continued during conception, pregnancy, and lactation in patients with FMF history. Laparoscopic intervention in pregnant patients with surgical abdomen such as acute cholecystitis is the optimal method of treatment.

PMID: 26907752 [Indexed for MEDLINE]

1336. J Clin Rheumatol. 2016 Mar;22(2):89-91. doi: 10.1097/RHU.0000000000000363.

### Is Bariatric Surgery a Trigger Factor for Systemic Autoimmune Diseases?

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Bariatric procedures are an effective option for weight loss and control of comorbidities in obese patients. Obesity is a proinflammatory condition in which some cytokines such as leptin, a proinflammatory protein, is elevated and adiponectin, an anti-inflammatory protein, is decreased. In patients undergoing weight reduction surgeries, these hormone levels behave paradoxically. It is not known whether bariatric surgery protects against development of autoinflammatory or autoimmune conditions; nevertheless, changes occurring in the immune system are incompletely understood. In this case series, we describe 4 patients undergoing bariatric surgery, who subsequently developed systemic autoimmune diseases. Patients in our case series were asymptomatic before surgery and developed an autoimmune disease within 11.2 months. Two women fulfilled criteria for systemic lupus erythematosus (one associated with antiphospholipid syndrome), and 2 men developed rheumatoid arthritis. A causal relationship is difficult to establish because factors that could trigger these diseases are multiple, including genetic susceptibility, time elapsed until achievement of ideal weight, and vitamin deficiencies, among others. However, clinicians must be attentive to this possible association.

DOI: 10.1097/RHU.0000000000000363

PMID: 26906303 [Indexed for MEDLINE]

1337. EMBO J. 2016 Apr 15;35(8):831-44. doi: 10.15252/emboj.201593339. Epub 2016 Feb 22.

Ribonuclease H2 mutations induce a cGAS/STING-dependent innate immune response.

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Comment in

EMBO J. 2016 Apr 15;35(8):796-7.

Aicardi-Goutières syndrome (AGS) provides a monogenic model of nucleic acid-mediated inflammation relevant to the pathogenesis of systemic autoimmunity. Mutations that impair ribonuclease (RNase) H2 enzyme function are the most frequent cause of this autoinflammatory disorder of childhood and are also associated with systemic lupus erythematosus. Reduced processing of either RNA:DNA hybrid or genome-embedded ribonucleotide substrates is thought to lead to activation of a yet undefined nucleic acid-sensing pathway. Here, we establish *Rnaseh2b*(A174T/A174T) knock-in mice as a subclinical model of disease, identifying significant interferon-stimulated gene (ISG) transcript upregulation that recapitulates the ISG signature seen in AGS patients. The inflammatory response is dependent on the nucleic acid sensor cyclic GMP-AMP synthase (cGAS) and its adaptor STING and is associated with reduced cellular ribonucleotide excision repair activity and increased DNA damage. This suggests that cGAS/STING is a key nucleic acid-sensing pathway relevant to AGS, providing additional insight into disease pathogenesis relevant to the development of therapeutics for this childhood-onset interferonopathy and adult systemic autoimmune disorders.

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DOI: [10.15252/emboj.201593339](https://doi.org/10.15252/emboj.201593339)

PMCID: PMC4855687

PMID: 26903602 [Indexed for MEDLINE]



1338. J Immunol. 2016 Apr 1;196(7):3124-34. doi: 10.4049/jimmunol.1501035. Epub 2016 Feb 22.

Mouse Cytomegalovirus Infection in BALB/c Mice Resembles Virus-Associated Secondary Hemophagocytic Lymphohistiocytosis and Shows a Pathogenesis Distinct from Primary Hemophagocytic Lymphohistiocytosis.

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Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening immunological disorder that is characterized by systemic inflammation, widespread organ damage, and hypercytokinemia. Primary HLH is caused by mutations in granule-mediated cytotoxicity, whereas secondary HLH occurs, without a known genetic background, in a context of infections, malignancies, or autoimmune and autoinflammatory disorders. Clinical manifestations of both HLH subtypes are often precipitated by a viral infection, predominantly with Herpesviridae. Exploiting this knowledge, we established an animal model of virus-associated secondary HLH by infecting immunocompetent wild-type mice with the  $\beta$ -herpesvirus murine CMV. C57BL/6 mice developed a mild inflammatory phenotype, whereas BALB/c mice displayed the

clinicopathologic features of HLH, as set forth in the Histiocyte Society diagnostic guidelines: fever, cytopenia, hemophagocytosis, hyperferritinemia, and elevated serum levels of soluble CD25. BALB/c mice also developed lymphadenopathy, liver dysfunction, and decreased NK cell numbers. Lymphoid and myeloid cells were in a hyperactivated state. Nonetheless, depletion of CD8(+) T cells could not inhibit or cure the HLH-like syndrome, highlighting a first dissimilarity from mouse models of primary HLH. Immune cell hyperactivation in BALB/c mice was accompanied by a cytokine storm. Notably, plasma levels of IFN- $\gamma$ , a key pathogenic cytokine in models of primary HLH, were the highest. Nevertheless, murine CMV-infected IFN- $\gamma$ -deficient mice still developed the aforementioned HLH-like symptoms. In fact, IFN- $\gamma$ -deficient mice displayed a more complete spectrum of HLH, including splenomegaly, coagulopathy, and decreased NK cell cytotoxicity, indicating a regulatory role for IFN- $\gamma$  in the pathogenesis of virus-associated secondary HLH as opposed to its central pathogenic role in primary HLH.

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DOI: 10.4049/jimmunol.1501035

PMID: 26903481 [Indexed for MEDLINE]

1339. Isr Med Assoc J. 2015 Dec;17(12):783-4.

Recurrent Pericarditis: An Autoinflammatory Disease?

Schichter-Konfino V, Vadasz Z, Toubi E.

PMID: 26897984 [Indexed for MEDLINE]

1340. Rinsho Byori. 2015 Oct;63(10):1207-12.

[Pathogenesis and Clinical Examination of Autoinflammatory Syndrome].

[Article in Japanese]

Ida H.

Autoinflammatory syndrome is characterized by: 1) episodes of seemingly unprovoked inflammation, 2) the absence of a high titer of autoantibodies or auto-reactive T cells, and 3) an inborn error of innate immunity. In this decade, many autoinflammatory syndromes have been reported in Japan, and so many Japanese physicians have become aware of this syndrome. Monogenic autoinflammatory syndromes present with excessive systemic inflammation including fever, rashes, arthritis, and organ-specific inflammation and are caused by defects in single genes encoding proteins that regulate innate inflammatory pathways. The main monogenic autoinflammatory syndromes are familial Mediterranean fever (FMF), TNF receptor-associated periodic syndrome (TRAPS), mevalonate kinase deficiency (MKD), cryopyrin-associated periodic syndrome (CAPS), Blau syndrome, and syndrome of pyogenic arthritis with pyoderma gangrenosum and acne (PAPA). We diagnosed these syndromes as clinical manifestations and performed genetic screening. Many serum cytokines are elevated in patients with autoinflammatory syndrome, but this is not disease-specific. The pathogeneses of many autoinflammatory syndromes are known to be related to inflammasomes, which are multiprotein complexes that serve as a platform for caspase 1 activation and interleukin-1 $\beta$ (IL-1 $\beta$ ) and IL-18 maturation. Especially, NLRP3 inflammasomes may play a crucial role in the initiation and progression of FMF and CAPS. Recently, it was reported that NETs (neutrophil extracellular traps) derived from neutrophils may also play an important role in the pathogenesis of FMF. In the future, we hope to discover new clinical examinations which can provide evidence of inflammasome activation independent of genetic screening. In this issue, I introduce autoinflammatory syndromes and discuss the pathogenesis and clinical examination of these syndromes.

PMID: 26897858 [Indexed for MEDLINE]

1341. J Clin Lab Anal. 2016 Sep;30(5):641-4. doi: 10.1002/jcla.21915. Epub 2016 Feb 18.

Is Turkish MEFV Mutations Spectrum Different Among Regions?

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**BACKGROUND:** Familial Mediterranean fever (FMF) is an autosomal recessive inherited inflammatory disease. The gene responsible for the disease, called MEFV, encodes a protein called pyrin or marenostrin. According to recent data, MEFV mutations are not the only cause of FMF, but genetic analysis of MEFV gene is needed for confirming the diagnosis of FMF. In the present study, we aimed to evaluate the molecular testing results of MEFV mutations.

**METHODS:** Molecular testing results of 1,435 patients were retrospectively evaluated over the last 4 years. These patients were identified as having FMF clinical symptoms. Patients were tested for 12 common mutations in the MEFV gene using a strip assay technique.

**RESULTS:** From all 1,435 patients, MEFV mutations were found in 776 patients (54.08%) and 659 patients (45.92%) did not carry any mutations. Patients with mutations were classified as homozygotes (n = 148), compound heterozygotes (n = 197), heterozygous (n = 427), and complex genotypes (n = 4, patients with three mutations). Allelic frequencies for the four most common mutations in the mutation-positive groups were 48.79% (M694V), 14.86% (M680I G/C), 13.70% (E148Q), and 12.35% (V726A). The remaining alleles (10.3%) showed rare mutations that were R761H, P369S, A744S, K695R, F479L, and M694I. No patient showed a I692del mutation that is sometimes evident in other Mediterranean populations.

**CONCLUSION:** It was found that the most common four mutations (M694V, M680I [G/C], E148Q, V726A) were similar to those previously reported from different regions of Turkey and this study might add some knowledge to the mutational spectrum data on FMF.

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DOI: 10.1002/jcla.21915

PMID: 26892483 [Indexed for MEDLINE]

1342. Clin Exp Rheumatol. 2016 Sep-Oct;34(5):961-962. Epub 2016 Feb 9.

Canakinumab in recessive dystrophic epidermolysis bullosa: a novel unexpected weapon for non-healing wounds?

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PMID: 26885873 [Indexed for MEDLINE]

1343. Med Hypotheses. 2016 Mar;88:10-1. doi: 10.1016/j.mehy.2015.12.024. Epub 2016 Jan 8.

The asymmetric protein expression hypothesis - Explaining the unilaterality of HLA-B27-positive acute anterior uveitides.

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For reasons still unclear, most HLA-B27-positive acute anterior uveitides occur unilaterally. Building upon the growing literature showing that left-right asymmetry exist at the biomolecular and at the cellular levels, we propose a new hypothesis to explain why HLA-B27-positive acute anterior uveitides tend to affect one eye selectively. We postulate that left and right uveal tissue may present quantitatively and qualitatively different proteins to the immune system, capable to trigger an autoimmune response, and that other variables, including anatomical, cellular and molecular barriers, as well as our own eye-derived immunological tolerance and immune suppressive intraocular microenvironment may also be unequally distributed, and impact differently the immune privileges of

the left and right eye. These same quantitative and qualitative differences might also explain why HLA-B27-positive acute anterior uveitides can flip-flop between the left and the right eye, after the first attack. By trying to figure out why one eye is targeted by an autoimmune reaction while the other is clinically unaffected, we might be able to better understand how and why an autoimmune reaction starts. Hopefully, this will help us devise better treatments for ocular autoimmune diseases, and contribute to the management of autoinflammatory conditions with a marked asymmetric clinical presentation in other fields.

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DOI: 10.1016/j.mehy.2015.12.024

PMID: 26880626 [Indexed for MEDLINE]

1344. Clin Rheumatol. 2016 Jul;35(7):1669-72. doi: 10.1007/s10067-016-3211-3. Epub 2016 Feb 13.

The significance of urinary beta-2 microglobulin level for differential diagnosis of familial Mediterranean fever and acute appendicitis.

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The clinical and laboratory parameters widely used are not specific to discriminate the abdominal pain due to FMF attack from that of acute appendicitis. The present study aims to investigate the urinary beta-2 microglobulin (U- $\beta$ 2M) level as a potential parameter to identify these two diseases mimicking each other. A total of 51 patients with established FMF diagnosis due to Tel Hashomer criteria on colchicine treatment (1-1.5 mg/day), 15 patients with acute appendicitis who had appropriate clinical picture and were also supported pathologically after the surgery, and 20 healthy controls were enrolled in the study. Of the 51 patients with FMF, 25 were at an attack period, while remaining 26 were not. For the diagnosis of acute attack, as well as physical examination, laboratory tests including white blood cell count, C-reactive protein, and erythrocyte sedimentation rate were performed. From urine specimens U- $\beta$ 2M, microalbumin, and N-acetyl glucosaminidase (U-NAG) were measured. U- $\beta$ 2M levels were significantly higher in acute appendicitis group compared to FMF attack, FMF non-attack, and control groups ( $p < 0.001$ ,  $p < 0.001$ , and  $p < 0.001$ , respectively). U-NAG and microalbuminuria were significantly higher in acute appendicitis, FMF attack, and FMF non-attack groups compared to controls (U-NAG  $p < 0.001$ ,  $p = 0.016$ ,  $p = 0.004$ , microalbuminuria  $p < 0.001$ ,  $p < 0.001$ ,  $p < 0.001$ , respectively). Microalbuminuria was significantly higher in acute appendicitis group compared to the FMF attack group ( $p = 0.004$ ). Determination of U- $\beta$ 2M levels may be helpful for differential diagnosis of peritonitis attacks of FMF patients on colchicine treatment and acute appendicitis. However, this finding should be substantiated with other studies.

DOI: 10.1007/s10067-016-3211-3

PMID: 26873102 [Indexed for MEDLINE]

1345. Br J Dermatol. 2016 Feb;174(2):262. doi: 10.1111/bjd.14258.

CARD14 alterations and psoriasis: are psoriasis and related disorders genetic autoinflammatory diseases?

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Comment on

Br J Dermatol. 2016 Feb;174(2):330-7.

DOI: 10.1111/bjd.14258

PMID: 26871918 [Indexed for MEDLINE]

1346. Korean J Intern Med. 2016 Mar;31(2):386-91. doi: 10.3904/kjim.2015.039. Epub 2016 Feb 11.

The role of neutrophil lymphocyte ratio to leverage the differential diagnosis of familial Mediterranean fever attack and acute appendicitis.

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**BACKGROUND/AIMS:** Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by attacks of fever and diffuse abdominal pain. The primary concern with this presentation is to distinguish it from acute appendicitis promptly. Thus, we aimed to evaluate the role of neutrophil lymphocyte ratio (NLR) to leverage the differential diagnosis of acute FMF attack with histologically proven appendicitis.

**METHODS:** Twenty-three patients with histologically confirmed acute appendicitis and 88 patients with acute attack of FMF were included in the study. NLR,



C-reactive protein and other hematologic parameters were compared between the groups.

RESULTS: Neutrophil to lymphocyte ratio was significantly higher in patients with acute appendicitis compared to the FMF attack group ( $8.24 \pm 6.31$  vs.  $4.16 \pm 2.44$ ,  $p = 0.007$ ). The performance of NLR in diagnosing acute appendicitis with receiver operating characteristic analysis with a cut-off value of 4.03 were; 78% sensitivity, 62% specificity, and area under the curve 0.760 (95% confidence interval, 0.655 to 0.8655;  $p < 0.001$ ).

CONCLUSIONS: This study showed that NLR, the simple and readily available inflammatory marker may have a useful role in distinguishing acute FMF attack from acute appendicitis.

DOI: 10.3904/kjim.2015.039

PMCID: PMC4773722

PMID: 26864298 [Indexed for MEDLINE]

1347. J Dermatolog Treat. 2016 Oct;27(5):436-8. doi: 10.3109/09546634.2015.1136048. Epub 2016 Feb 10.

Interleukin-1 receptor antagonist (anakinra) for Schnitzler syndrome.

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Schnitzler syndrome is a rare autoinflammatory disease, which is defined by the presence of two major criteria: chronic urticaria and monoclonal immunoglobulin M (IgM) or immunoglobulin G gammopathy, in combination with at least two additional minor criteria: recurrent fever, leukocytosis and/or elevated C-reactive protein (CRP), objective signs of abnormal bone remodelling and a neutrophilic infiltrate in skin biopsy. We report on a 68-year-old female patient with a 10-year medical

history of chronic urticaria, recurrent fever, severe arthralgia and increased CRP. Over the years, multiple diagnostic investigations were performed without conclusive findings, and therapeutic attempts with anti-histamines and several immunosuppressive agents had failed. The decision to initiate monotherapy with interleukin-1 (IL-1) receptor antagonist was based on immunohistochemical detection of the abundance of IL-1 $\beta$  positive cells in the patient's skin biopsy. After starting treatment with anakinra, disappearance of symptoms could be observed within 24 h. Discontinuation of the treatment resulted in a rapid relapse of the symptoms. Finally, already after the initiation of therapy with anakinra, the suspected diagnosis of Schnitzler syndrome could be confirmed by detection of IgM-gammopathy that was initially absent.

DOI: 10.3109/09546634.2015.1136048

PMID: 26864191 [Indexed for MEDLINE]

1348. *Ophthalmologica*. 2016;235(3):184. doi: 10.1159/000444061. Epub 2016 Feb 11.

Choroidal Changes in Patients with Familial Mediterranean Fever.

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Comment in

*Ophthalmologica*. 2016;235(3):185.

Comment on

*Ophthalmologica*. 2016;235(2):72-7.

DOI: 10.1159/000444061

PMID: 26863213 [Indexed for MEDLINE]

1349. *Ophthalmologica*. 2016;235(3):185. doi: 10.1159/000443850. Epub 2016 Feb 11.

Response to the Letter by Kosker et al. Entitled 'Choroidal Changes in Patients

with Familial Mediterranean Fever'.

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Comment on

Ophthalmologica. 2016;235(2):72-7.

Ophthalmologica. 2016;235(3):184.

DOI: 10.1159/000443850

PMID: 26863131 [Indexed for MEDLINE]

1350. Gene. 2016 May 15;582(2):173-7. doi: 10.1016/j.gene.2016.02.008. Epub 2016 Feb 6.

Interleukin-1Ra rs2234663 and Interleukin-4 rs79071878 Polymorphisms in Familial Mediterranean Fever.

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**OBJECTIVE:** Familial Mediterranean Fever (FMF) is an autosomal recessively inherited auto inflammatory disorder. MEFV gene, causing FMF, encodes pyrin that is associated with the interleukin-1 (IL-1) related inflammation cascade. The aim of this study was to investigate the relationship of interleukin-1 receptor antagonist (IL-1Ra) and interleukin-4 (IL-4) polymorphisms with the risk of FMF in the Turkish population.

**METHODS:** This study included 160 patients with FMF (74 men, 86 women) and 120 healthy controls (50 men, 70 women), respectively. Genotyping of IL-1Ra rs2234663 polymorphism was evaluated by gel electrophoresis after polymerase chain reaction (PCR). The IL-4 rs79071878 polymorphism was determined by PCR-based restriction fragment length polymorphism (PCR-RFLP) analysis. The results of analyses were evaluated for statistical significance.

**RESULTS:** There was no significant difference in IL-1Ra genotype and allele distributions between FMF and the control groups ( $p>0.05$ ). However, a significant association was observed between FMF patients and control groups according to IL-4 genotype distribution ( $p=0.016$ ), but no association was found in the allelic frequency of IL-4 between FMF patients and the controls ( $p>0.05$ , OR: 1.131, CI 95%: 0.71-1.81).

**CONCLUSIONS:** The IL-4 rs79071878 polymorphism, was associated whereas the IL-1Ra rs2234663 polymorphism was not associated with FMF risk in the Turkish population. Larger studies with different ethnicities are needed to determine the impact of IL-1Ra and IL-4 polymorphism on the risk of developing FMF.

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DOI: 10.1016/j.gene.2016.02.008

PMID: 26861613 [Indexed for MEDLINE]

1351. Curr Opin Rheumatol. 2016 May;28(3):197-203. doi: 10.1097/BOR.0000000000000266.

Anti-inflammatory panacea? The expanding therapeutics of interleukin-1 blockade.

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**PURPOSE OF REVIEW:** Blockade of interleukin (IL)-1 signaling is one of the oldest biologic therapies, yet the use of these agents is on the rise as the role of IL-1 activation is being recognized in a wide spectrum of inflammatory disorders. This review will cover established and emerging uses of IL-1 antagonism in rheumatic diseases.

**RECENT FINDINGS:** Expanding off-label indications for IL-1 blockade include

neutrophil-dominant skin diseases, including pyoderma gangrenosum, hidradenitis suppurativa, and pustular psoriasis. There is also increasing evidence for the use of IL-1 blockade in heart failure associated with rheumatic diseases. Somatic mosaicism in NLRP3 may explain the onset of later-in-life presentations of periodic fevers which are responsive to IL-1 blockade. Of importance, clinical response to anti-IL-1 therapy does not always denote protection from autoinflammatory disease complications such as macrophage activation syndrome or amyloidosis.

SUMMARY: Indications for IL-1 blocking therapies will likely continue to broaden, but given the rarity of many rheumatic diseases which respond to such treatment, rigorous, large clinical trials for each indication are unlikely to occur. Thus, recommended use of these medications will often fall to the discretion of the astute physician. However, medication cost and hurdles of insurance approval, rather than drug efficacy, may be the primary limitation for more widespread use.

DOI: 10.1097/BOR.0000000000000266

PMCID: PMC4901309

PMID: 26859478 [Indexed for MEDLINE]

1352. J Pharmacol Sci. 2016 Mar;130(3):143-50. doi: 10.1016/j.jphs.2015.12.007. Epub 2016 Jan 8.

Unique immunomodulatory effect of paeoniflorin on type I and II macrophages activities.

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It has been widely accepted that macrophages are divided into M1 "pro-inflammatory" macrophages and M2 "anti-inflammatory" macrophages and an uncontrolled macrophage polarization plays an important role in the pathogenesis of different diseases. As the main substance of total glucosides of peony, paeoniflorin (PF), has been widely used to treat autoimmune and autoinflammatory diseases for years. Mechanistically, PF has been found to alter activities of many immune cells, which could further reduce inflammation and tissue damage. However, whether and how PF affects macrophages activities in vitro remains unknown. In current study, using M1 and M2 cells generated from mouse bone marrow precursors, we explored the role of PF in regulating M1/M2 cells activity in vitro. The results showed that PF inhibited LPS-induced M1 activity by reducing iNOS expression and NO production via decreasing LPS/NF- $\kappa$ B signaling pathway; whereas, PF enhanced IL-4-provoked M2 function by up-regulating Arg-1 production and activity via increasing IL-4/STAT6 signaling pathway. Our new finding indicates that PF can suppress M1 cells activity and enhance M2 cells function simultaneously, which could help to ameliorate autoimmune and autoinflammatory diseases in clinical treatment.

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DOI: 10.1016/j.jphs.2015.12.007

PMID: 26852260 [Indexed for MEDLINE]

1353. Chem Res Toxicol. 2016 Mar 21;29(3):296-302. doi: 10.1021/acs.chemrestox.5b00461. Epub 2016 Feb 23.

Electrophilicities and Protein Covalent Binding of Demethylation Metabolites of Colchicine.

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Colchicine, an alkaloid existing in plants of Liliaceous colchicum, has been widely used in the treatment of gout and familial Mediterranean fever. The administration of colchicine was found to cause liver injury in humans. The mechanisms of colchicine-induced liver toxicity remain unknown. The objectives of this study were to determine the electrophilicities of demethylation metabolites of colchicine and investigate the protein adductions derived from the reactive metabolites of colchicine. Four demethylated colchicine (1-, 2-, 3-, and 10-DMCs), namely, M1-M4, were detected in colchicine-fortified microsomal incubations. Four N-acetyl cysteine (NAC) conjugates (M5-M8) derived from colchicine were detected in the microsomes in the presence of NAC. M5 and M6 were derived from 10-DMC. M7 resulted from the reaction of 2-DMC or 3-DMC with NAC, and M8 originated from 10-DMC. Microsomal protein covalent binding was observed after exposure to colchicine. Two cysteine adducts (CA-1 and CA-2) derived from 10-DMC were found in proteolytically digested microsomal protein samples after incubation with colchicine. The findings allow us to define the chemical property of demethylation metabolites of colchicine and the interaction between protein and the reactive metabolites of colchicine generated in situ.

DOI: 10.1021/acs.chemrestox.5b00461

PMID: 26845511 [Indexed for MEDLINE]

1354. Med Arch. 2015 Dec;69(6):417-20. doi: 10.5455/medarh.2015.69.417-420.

Genetic Profile of Patients with Familial Mediterranean Fever (FMF): Single Center Experience at King Hussein Medical Center (KHMC).

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**OBJECTIVE:** To describe the spectrum of genetic mutations in patients with clinical diagnosis of Familial Mediterranean Fever.

**METHOD:** This is a retrospective study of 3359 sera samples for patient with clinical diagnosis of FMF, over a period of 6 years. The samples were tested for

12 mutations of the MEFV gene by PCR& hybridization of the PCR product with Probes immobilized as an array of panel lines.

RESULTS: A total of 1868 (55.6%) samples were found negative, and one or more mutations were detected in 1491 (44.4%) distributed along the mutations. Of the positive results, the Frequency of the mutations was as follows, the M694V was the most common mutation 30%, followed by E 148Q 21.5%, V 726 A 20%, M680I G/C 9%, M694I 8.3%, P369S 3.7%, A744S 3.1% and 4.2% among the 4 remaining mutations.

CONCLUSION: Frequency of common mutations in our study show similar results in comparisons with Mediterranean countries like Egypt, Turkey, and Syria with the most common mutation in our study being M694V followed by E148 Q.

DOI: 10.5455/medarh.2015.69.417-420

PMCID: PMC4720465

PMID: 26843738 [Indexed for MEDLINE]

1355. Clin Rheumatol. 2016 Jul;35(7):1837-40. doi: 10.1007/s10067-016-3196-y. Epub 2016 Feb 3.

Late-onset disease is associated with a mild phenotype in children with familial Mediterranean fever.

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Comment in

Clin Rheumatol. 2016 Sep;35(9):2377.

Familial Mediterranean fever (FMF) is an autosomal recessive disease, characterised by recurrent, self-limited attacks of fever with serositis.



Recently, it was shown that patients with early disease onset during childhood period had more severe disease. The aim of this study was to describe the demographic, clinical and genetic features of FMF patients who had late-onset disease during childhood period and to compare them to those with earlier onset patients. Files of patients who had been seen in our department between January 2013 and January 2014 were retrospectively evaluated. Patients were divided into two groups according to age of disease onset (group I,  $\leq 8$  years; group II,  $> 8$  years), and clinical findings were compared between the two groups. The study group comprised 317 FMF patients. There were 267 patients in group I and 50 patients in Group II. Median attack frequency was 24/year in group I and 12/year in group II ( $p < 0.05$ ). Fever and M694V homozygosity were less frequently detected in group II ( $p = 0.003$  and  $p = 0.022$ ). Median delay in diagnosis was 24 months in group I and 12 months in group II ( $p = 0.002$ ). Disease severity scores and final colchicine dosages were lower in group II ( $p < 0.001$  and  $p = 0.003$ ). Only a small number of FMF patients had disease onset at older ages in childhood period. It seems that FMF patients with late-onset disease have milder illness. However, more readily expression of their clinical findings in older ages yields earlier diagnosis in this group.

DOI: 10.1007/s10067-016-3196-y

PMID: 26842301 [Indexed for MEDLINE]

1356. J Korean Med Sci. 2016 Feb;31(2):196-201. doi: 10.3346/jkms.2016.31.2.196. Epub 2016 Jan 26.

Clinical and Genetic Features of Korean Patients with Recurrent Fever and Multi-System Inflammation without Infectious or Autoimmune Evidence.

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Autoinflammatory disease (AID) is a newly proposed category of disorders characterized by unprovoked episodes of inflammation without any infectious or

autoimmune evidence. We aimed to characterize the clinical and genetic features of patients who had recurrent fever and multi-system inflammation but remain unclassified for any established AIDs. Medical records of 1,777 patients who visited our Rheumatology Clinic between March 2009 and December 2010 were reviewed to identify those who met the following criteria; 1) presence of fever, 2) inflammation in two or more organ systems, 3) recurrent nature of fever or inflammation, 4) no evidence of infection or malignancy, 5) absence of high titer autoantibodies, and 6) failure to satisfy any classification criteria for known AIDs. Genotyping was performed for common missense variants in MEFV, NOD2/CARD15, and TNFRSF1A. A small number of patients (17/1,777, 0.95%) were identified to meet the above criteria. Muco-cutaneous and musculoskeletal features were most common, but there was a considerable heterogeneity in symptom combination. Although they did not satisfy any established classification criteria for AIDs, substantial overlap was observed between the clinical spectrum of these patients and known AIDs. According to the newly proposed Eurofever criteria for periodic fevers, eleven of them were classified as TNF receptor-associated periodic syndrome and two as mevalonate kinase deficiency. However, no examined genetic variants including those in TNFRSF1A were found in these patients. A new set of classification criteria needs to be developed and validated for Asian patients with unclassified AIDs.

DOI: 10.3346/jkms.2016.31.2.196

PMCID: PMC4729498

PMID: 26839472 [Indexed for MEDLINE]

1357. Oral Dis. 2016 Oct;22(7):591-604. doi: 10.1111/odi.12448. Epub 2016 Apr 14.

Genetically defined autoinflammatory diseases.

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Autoinflammatory diseases are hyperinflammatory, immune dysregulatory conditions that typically present in early childhood with fever and rashes and disease-specific patterns of organ inflammation. This review provides a historic background of autoinflammatory disease research, an overview of the currently genetically defined autoinflammatory diseases, and insights into treatment strategies derived from understanding of the disease pathogenesis. The integrative assessment of autoinflammatory conditions led to the identification of innate pro-inflammatory cytokine 'amplification loops' as the cause of the systemic and organ-specific disease manifestations, which initially centered around increased IL-1 production and signaling. More recently, additional innate pro-inflammatory cytokine amplification loops resulting in increased Type I IFN, IL-17, IL-18, or IL-36 signaling or production have led to the successful use of targeted therapies in some of these conditions. Clinical findings such as fever patterns, type of skin lesions, genetic mutation testing, and the prevalent cytokine abnormalities can be used to group autoinflammatory diseases.

Published 2016. This article is a U.S. Government work and is in the public domain in the USA.

DOI: 10.1111/odi.12448

PMCID: PMC4970964

PMID: 26837051 [Indexed for MEDLINE]

1358. *Ophthalmologica*. 2016;235(2):123. doi: 10.1159/000443849. Epub 2016 Feb 3.

Temperature Control Function of the Choroid May Be the Reason for the Increase in Choroidal Thickness during the Acute Phase of Familial Mediterranean Fever.

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Comment in

*Ophthalmologica*. 2016;235(2):124.

Comment on

Ophthalmologica. 2016;235(2):72-7.

DOI: 10.1159/000443849

PMID: 26835683 [Indexed for MEDLINE]

1359. Australas J Dermatol. 2017 May;58(2):e54-e59. doi: 10.1111/ajd.12438. Epub 2016 Feb 2.

Pyoderma gangrenosum, acne, suppurative hidradenitis (PASH) and polycystic ovary syndrome: Coincidentally or aetiologically connected?

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The clinical triad of pyoderma gangrenosum, acne conglobata and hidradenitis suppurativa has been named PASH syndrome. Polycystic ovary syndrome (PCOS) is associated with hyperandrogenism and inflammation. Hidradenitis suppurativa, like acne vulgaris, may be a feature of hyperandrogenism. Obesity may be associated with both hidradenitis suppurativa and PCOS. We describe a possible association between PASH syndrome and PCOS.

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DOI: 10.1111/ajd.12438

PMID: 26831949 [Indexed for MEDLINE]

1360. Inflamm Bowel Dis. 2016 Mar;22(3):E12-3. doi: 10.1097/MIB.0000000000000702.

Triple Disease Combination: Familial Mediterranean Fever, Crohn's Disease, and

## Chronic Idiopathic Urticaria with Angioedema.

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DOI: 10.1097/MIB.0000000000000702

PMID: 26829407 [Indexed for MEDLINE]

1361. Ophthalmologica. 2016;235(2):124. doi: 10.1159/000443752. Epub 2016 Feb 2.

Reply to the Letter by Kaya et al. Entitled "Temperature Control Function of the Choroid May Be the Reason for the Increase in Choroidal Thickness During the Acute Phase of Familial Mediterranean Fever".

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### Comment on

Ophthalmologica. 2016;235(2):72-7.

Ophthalmologica. 2016;235(2):123.

DOI: 10.1159/000443752

PMID: 26828744 [Indexed for MEDLINE]

1362. Anal Chim Acta. 2016 Feb 18;908:150-60. doi: 10.1016/j.aca.2015.12.030. Epub 2016 Jan 6.

Multiplex localization of sequential peptide epitopes by use of a planar microbead chip.

Schmidt C(1), Rödiger S(2), Gruner M(3), Moncsek A(4), Stohwasser R(2), Hanack K(5), Schierack P(2), Schröder C(2).

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Epitope mapping is crucial for the characterization of protein-specific antibodies. Commonly, small overlapping peptides are chemically synthesized and immobilized to determine the specific peptide sequence. In this study, we report the use of a fast and inexpensive planar microbead chip for epitope mapping. We developed a generic strategy for expressing recombinant peptide libraries instead of using expensive synthetic peptide libraries. A biotin moiety was introduced in vivo at a defined peptide position using biotin ligase. Peptides in crude *Escherichia coli* lysate were coupled onto streptavidin-coated microbeads by incubation, thereby avoiding tedious purification procedures. For read-out we used a multiplex planar microbead chip with size- and fluorescence-encoded microbead populations. For epitope mapping, up to 18 populations of peptide-loaded microbeads (at least 20 microbeads per peptide) displaying the primary sequence of a protein were analyzed simultaneously. If an epitope was recognized by an antibody, a secondary fluorescence-labeled antibody generated a signal that was quantified, and the mean value of all microbeads in the population was calculated. We mapped the epitopes for rabbit anti-PA28 $\gamma$  (proteasome activator 28 $\gamma$ ) polyclonal serum, for a murine monoclonal antibody against PA28 $\gamma$ , and for a murine monoclonal antibody against the hamster polyoma

virus major capsid protein VP1 as models. In each case, the identification of one distinct peptide sequence out of up to 18 sequences was possible. Using this approach, an epitope can be mapped multiparametrically within three weeks.

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DOI: 10.1016/j.aca.2015.12.030

PMID: 26826697 [Indexed for MEDLINE]

1363. Ann Rheum Dis. 2016 Jun;75(6):1051-6. doi: 10.1136/annrheumdis-2015-208671. Epub 2016 Jan 28.

Development and initial validation of international severity scoring system for familial Mediterranean fever (ISSF).

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Comment in

Nat Rev Rheumatol. 2016 Apr 25;12 (5):256-8.

**OBJECTIVE:** To develop widely accepted international severity score for children and adult patients with familial Mediterranean fever (FMF) that can be easily applied, in research and clinical practice.

**METHODS:** Candidate severity criteria were suggested by several FMF expert physicians. After three rounds of Delphi survey, the candidate criteria, defined by the survey, were discussed by experts in a consensus meeting. Each expert brought data of clinical manifestations, laboratory findings and physician's global assessments (PGAs) of minimum 20 patients from their centres. We used the PGAs for disease severity as a gold standard. Logistic regression analysis was used to evaluate the predicting value of each item, and receiver operating characteristic curve analysis was performed to demonstrate the success of the criteria set.

**RESULTS:** A total of 281 patients consist of 162 children and 119 adults with FMF were enrolled and available for validity analysis: Nine domains were included in the final core set of variables for the evaluation of disease severity in FMF.

The International Severity Score for FMF (ISSF) may reach a maximum of 10 if all items are maximally scored. The threshold values to determine: severe disease  $\geq 6$ , intermediate disease 3-5, mild disease  $\leq 2$ . Area under the curve was calculated as 0.825 for this set in the whole group.

**CONCLUSIONS:** The initial validity of ISSF both in children and adult with FMF was demonstrated. We anticipate that it will provide a robust tool to objectively define disease severity for clinical trials, future research as well as for therapeutic decisions in managing patients with FMF.

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DOI: 10.1136/annrheumdis-2015-208671

PMID: 26823530 [Indexed for MEDLINE]



1364. Indian J Pediatr. 2016 Mar;83(3):242-7. doi: 10.1007/s12098-015-1985-y. Epub 2016 Jan 29.

Autoinflammatory Syndromes in Children.

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Systemic autoinflammatory diseases are rare disorders of innate immunity which usually present in childhood with recurrent or continuous attacks of fever and systemic inflammation. The discovery of the genetic defect underlying Familial Mediterranean fever in 1997 has proved exceptionally informative about the innate immune system and the regulation of pro inflammatory cytokines particularly IL-1. Although extremely rare, systemic autoinflammatory diseases are important to recognise as many can now be completely controlled by long term drug therapies. Diagnosis relies on clinical suspicion followed by genetic testing. This review will focus on the main systemic autoinflammatory diseases.

DOI: 10.1007/s12098-015-1985-y

PMID: 26821543 [Indexed for MEDLINE]

1365. Harefuah. 2015 Nov;154(11):716-9, 741.

[INTERLEUKIN 1 INHIBITORS--A NEW HORIZON IN THE TREATMENT OF FAMILIAL MEDITERRANEAN FEVER].

[Article in Hebrew]

Shouval R, Livneh A, Ben-Zvi I.

Familial Mediterranean Fever (FMF) is a common genetic auto-inflammatory disease in the Middle Eastern population. Colchicine is the only proven treatment for the

prevention of FMF attacks and reactive amyloidosis. However, 5-10% of FMF patients do not respond to colchicine, and an additional 5% are intolerant to it. Progress in the understanding of FMF and the recognition of the central role of IL-1 in its pathophysiology has led to the introduction of IL-1 inhibitors in FMF patients who are unresponsive to colchicine. In this paper we review the clinical experience gained with IL-1 inhibitors in FMF. Overall, it appears that IL-1 inhibitors are safe and may serve as an alternative in FMF patients resistant to colchicine.

PMID: 26821505 [Indexed for MEDLINE]

1366. Lupus. 2016 Aug;25(9):1062-3. doi: 10.1177/0961203315627872. Epub 2016 Jan 24.

Coexistence of systemic lupus erythematosus and familial Mediterranean fever in a pediatric patient.

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DOI: 10.1177/0961203315627872

PMID: 26811369 [Indexed for MEDLINE]

1367. Arthritis Rheumatol. 2016 Feb;68(2):516-20. doi: 10.1002/art.39482.

Brief Report: Severe Inflammation Following Vaccination Against Streptococcus pneumoniae in Patients With Cryopyrin-Associated Periodic Syndromes.

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Comment in

Arthritis Rheumatol. 2016 Feb;68(2):274-6.

**OBJECTIVE:** Pneumococcal vaccination is recommended for patients receiving immunosuppressive drugs. We describe unusually severe adverse reactions to pneumococcal vaccination in each of 7 consecutive patients with cryopyrin-associated periodic syndromes (CAPS).

**METHODS:** Seven consecutive patients with CAPS were vaccinated with pneumococcal polysaccharide or conjugate vaccines. Clinical information was collected retrospectively.

**RESULTS:** Within a few hours after the vaccination, all 7 patients developed severe local reactions at the injection site. Two patients had to be hospitalized for systemic reactions including fever. All symptoms resolved in a period of 3-17 days.

**CONCLUSION:** Our findings indicate that pneumococcal vaccines can trigger a severe local and systemic inflammatory reaction in patients with CAPS and possibly patients with other autoinflammatory diseases. Careful consideration is warranted when implementing current European League Against Rheumatism immunization guidelines in this patient population.

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DOI: 10.1002/art.39482

PMID: 26808830 [Indexed for MEDLINE]

1368. Autoimmun Rev. 2016 May;15(5):447-50. doi: 10.1016/j.autrev.2016.01.010. Epub 2016 Jan 22.

Impact of obesity on the clinical outcome of rheumatologic patients in biotherapy.

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There is raising interest in the scientific community about the impact of body mass on different rheumatologic diseases. A growing body of evidence suggests that the effect of obesity on joint structure goes beyond the simply overload but is based on a complex interwinding of cytokines, hormones, growth factors, and intracellular regulators that at different stages can modify the course of a rheumatologic disease and the clinical response to biotherapies. In these settings, psoriatic arthritis (PsA) and rheumatoid arthritis (RA) have been the more extensively studied. Intriguing is the finding that the interaction between obesity and diseases seems different for PsA or RA. Concerning PsA, epidemiologic studies have provided robust data about the association between obesity and prevalence of psoriasis or PsA. Yet obesity is associated with an increase in degree of disability and poor clinical outcome on treatment with anti-tumor necrosis factor (TNF) drugs. Nevertheless, there are clues suggesting that weight reduction above 5% from baseline increases the probability of achieving a good clinical response in PsA patients on anti-TNF drugs. On the contrary, the epidemiological association between obesity and RA seems to be restricted to some categories of patients with peculiar demographic and autoimmune status. Furthermore, obesity definitely impairs the clinical response of RA patients to anti-TNF treatment, and this might be an effect limited to TNF-blocking agents, as preliminary studies are not confirming these findings for abatacept or tocilizumab. However, the most puzzling aspect of the impact of obesity on RA is that obese patients tend to have a more clinical active disease, an impaired response to biotherapies, and a less radiographically evident joint damage over time. The latter is a very stimulating issue and the knowledge of the underlying mechanisms should be an auspicious challenge for the researchers, which will provide further insights on the overall management of RA.

1369. Ann Rheum Dis. 2016 Apr;75(4):644-51. doi: 10.1136/annrheumdis-2015-208690. Epub 2016 Jan 22.

EULAR recommendations for the management of familial Mediterranean fever.

Ozen S(1), Demirkaya E(2), Erer B(3), Livneh A(4), Ben-Chetrit E(5), Giancane G(6), Ozdogan H(7), Abu I(8), Gattorno M(9), Hawkins PN(10), Yuce S(11), Kallinich T(12), Bilginer Y(13), Kastner D(14), Carmona L(15).

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Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease, but many rheumatologists are not well acquainted with its management. The objective of this report is to produce evidence-based recommendations to guide rheumatologists and other health professionals in the treatment and follow-up of patients with FMF. A multidisciplinary panel, including rheumatologists, internists, paediatricians, a nurse, a methodologist and a patient representative, was assembled. Panellists came from the Eastern Mediterranean area, Europe and North America. A preliminary systematic literature search on the pharmacological treatment of FMF was performed following which the expert group convened to define aims, scope and users of the guidelines and established the need for additional reviews on controversial topics. In a second meeting, recommendations were discussed and refined in light of available evidence. Finally, agreement with the recommendations was obtained from a larger group of experts through a Delphi survey. The level of evidence (LoE) and grade of recommendation (GR) were then incorporated. The final document comprises 18 recommendations, each presented with its degree of agreement (0-10), LoE, GR and rationale. The degree of agreement was greater than 7/10 in all instances. The more controversial statements were those related to follow-up and dose change, for which supporting evidence is limited. A set of widely accepted recommendations for the treatment and monitoring of FMF is presented, supported by the best available evidence and expert opinion. It is believed that these recommendations will be useful in guiding physicians in the care of patients with FMF.

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DOI: 10.1136/annrheumdis-2015-208690

PMID: 26802180 [Indexed for MEDLINE]

1370. Proc Natl Acad Sci U S A. 2016 Feb 9;113(6):1612-7. doi: 10.1073/pnas.1518163113. Epub 2016 Jan 22.

Recruitment of A20 by the C-terminal domain of NEMO suppresses NF- $\kappa$ B activation

and autoinflammatory disease.

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Comment in

Nat Rev Rheumatol. 2016 Mar;12(3):134.

Receptor-induced NF- $\kappa$ B activation is controlled by NEMO, the NF- $\kappa$ B essential modulator. Hypomorphic NEMO mutations result in X-linked ectodermal dysplasia with anhidrosis and immunodeficiency, also referred to as NEMO syndrome. Here we describe a distinct group of patients with NEMO C-terminal deletion ( $\Delta$ CT-NEMO) mutations. Individuals harboring these mutations develop inflammatory skin and intestinal disease in addition to ectodermal dysplasia with anhidrosis and immunodeficiency. Both primary cells from these patients, as well as reconstituted cell lines with this deletion, exhibited increased I $\kappa$ B kinase (IKK) activity and production of proinflammatory cytokines. Unlike previously described

loss-of-function mutations,  $\Delta$ CT-NEMO mutants promoted increased NF- $\kappa$ B activation in response to TNF and Toll-like receptor stimulation. Investigation of the underlying mechanisms revealed impaired interactions with A20, a negative regulator of NF- $\kappa$ B activation, leading to prolonged accumulation of K63-ubiquitinated RIP within the TNFR1 signaling complex. Recruitment of A20 to the C-terminal domain of NEMO represents a novel mechanism limiting NF- $\kappa$ B activation by NEMO, and its absence results in autoinflammatory disease.

DOI: 10.1073/pnas.1518163113

PMCID: PMC4760784

PMID: 26802121 [Indexed for MEDLINE]

1371. Z Rheumatol. 2016 Apr;75(3):276-83. doi: 10.1007/s00393-015-0040-8.

[Translational research in pediatric rheumatology. Current research approaches to the innate immune system].

[Article in German]

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Translational research aims at closely linking basic research and clinical observations so that important mechanistic insights identified in one field should trigger progress in the other. Particularly in the field of pediatric rheumatology this approach has significantly improved the understanding and therapy of several diseases in recent years. One focus of our research in this respect is on the structure, release mechanisms and function of damage associated molecular patterns (DAMP), particularly S100 proteins. Due to their huge potential as inflammation biomarkers for more specific diagnostics these proteins are of particular clinical interest. Overactivated cells of the innate immune system play a crucial role in the development of rheumatic diseases. Innate mechanisms, such as the generation of neutrophil extracellular traps (NETosis)



were linked to the pathogenesis of inflammatory diseases, such as systemic lupus erythematosus and rheumatoid arthritis. Furthermore, it became increasingly more evident that various excessive sterile inflammatory mechanisms and reactions significantly contribute to an activation of adaptive immune responses and thus to the development of autoimmunity. Studying such potentially DAMP-dependent pathways at the interface between innate and adaptive immunity can provide a better understanding of autoinflammatory conditions in pediatric rheumatology and to identify novel targets for optimization of therapy.

DOI: 10.1007/s00393-015-0040-8

PMID: 26800663 [Indexed for MEDLINE]

1372. World J Nephrol. 2016 Jan 6;5(1):66-75. doi: 10.5527/wjn.v5.i1.66.

Secondary amyloidosis in autoinflammatory diseases and the role of inflammation in renal damage.

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The release of proinflammatory cytokines during inflammation represents an attempt to respond to injury, but it may produce detrimental effects. The inflammasome is a large, multiprotein complex that drives proinflammatory cytokine production in response to infection and tissue injury; the best-characterized inflammasome is the nod-like receptor protein-3 (NLRP3). Once activated, inflammasome leads to the active form of caspase-1, the enzyme required for the maturation of interleukin-1 $\beta$ . Additional mechanisms bringing to renal inflammatory, systemic diseases and fibrotic processes were recently reported, via the activation of the inflammasome that consists of NLRP3, apoptosis associated speck-like protein and caspase-1. Several manuscripts seem to identify NLRP3 inflammasome as a possible therapeutic target in the treatment of progressive chronic kidney disease. Serum amyloid A (SAA), as acute-phase protein with also proinflammatory properties, has been shown to induce the secretion of cathepsin B and inflammasome components from human macrophages. SAA

is a well recognised potent activator of the NLRP3. Here we will address our description on the involvement of the kidney in autoinflammatory diseases driven mainly by secondary, or reactive, AA amyloidosis with a particular attention on novel therapeutic approach which has to be addressed in suppressing underlying inflammatory disease and reducing the SAA concentration.

DOI: 10.5527/wjn.v5.i1.66

PMCID: PMC4707170

PMID: 26788465

1373. Turk J Med Sci. 2015;45(6):1198-206.

Familial Mediterranean fever in children from the Aegean region of Turkey: gene mutation frequencies and phenotype-genotype correlation.

Yilmaz E, Dinçel N, Sözeri B, Ozdemir K, Bulut IK, Berdeli A, Mir MS.

**BACKGROUND/AIM:** Familial Mediterranean fever (FMF) is diagnosed by fever episodes with sterile peritonitis, arthritis, pleurisy, and erysipelas-like erythema. The relationship between phenotype and genotype in FMF has not been adequately explained. The aim of this study was to characterize the phenotype and genotype correlation in FMF.

**MATERIALS AND METHODS:** Clinical diagnosis of FMF was conducted according to the Tel Hashomer criteria. Pras scoring was used to determine clinical severity. FMF strip assay analysis was used, and the hotspot regions were observed with PCR amplification and automatic DNA sequence analysis method.

**RESULTS:** We showed commonly seen mutations (most frequently M694V) in a study group of 191 patients. The disease severity score of patients with M694V mutation was high on the Pras scoring system. Patients with M694V mutation needed high colchicine dosages to control disease activity. R202Q was the most commonly seen polymorphism in 70 patients. The coexpression of R314R single nucleotide polymorphism on third exon was shown in our study. Moreover, D102D, G138G, and A165A subhaplotypes and E474E, Q476Q, and D510D subhaplotypes were also shown.

**CONCLUSION:** DNA sequence analysis should be a commonly used method for progress in the field of molecular genetics and for the better understanding of the FMF phenotype and genotype relationships in all populations.

1374. Autoimmun Rev. 2016 Apr;15(4):354-74. doi: 10.1016/j.autrev.2016.01.001. Epub 2016 Jan 7.

Smoke and autoimmunity: The fire behind the disease.

Perricone C(1), Versini M(2), Ben-Ami D(3), Gertel S(4), Watad A(5), Segel MJ(6), Ceccarelli F(1), Conti F(1), Cantarini L(7), Bogdanos DP(8), Antonelli A(9), Amital H(10), Valesini G(1), Shoenfeld Y(11).

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The association between smoke habit and autoimmunity has been hypothesized a long time ago. Smoke has been found to play a pathogenic role in certain autoimmune disease as it may trigger the development of autoantibodies and act on pathogenic mechanism possibly related with an imbalance of the immune system. Indeed, both epidemiological studies and animal models have showed the potential deleterious effect caused by smoke. For instance, smoke, by provoking oxidative stress, may contribute to lupus disease by dysregulating DNA demethylation, upregulating immune genes, thereby leading to autoreactivity. Moreover, it can alter the lung microenvironment, facilitating infections, which, in turn, may trigger the development of an autoimmune condition. This, in turn, may result in a dysregulation of immune system leading to autoimmune phenomena. Not only cigarette smoke but also air pollution has been reported as being responsible for the development of autoimmunity. Large epidemiological studies are needed to further explore the accountability of smoking effect in the pathogenesis of autoimmune diseases.

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DOI: 10.1016/j.autrev.2016.01.001

PMID: 26772647 [Indexed for MEDLINE]

1375. Curr Rheumatol Rep. 2016 Feb;18(2):8. doi: 10.1007/s11926-015-0558-4.

Current Research in Outcome Measures for Pediatric Rheumatic and Autoinflammatory Diseases.

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A rational management of children and adolescents with rheumatic and autoinflammatory diseases requires the regular assessment of the level of disease activity and of child health and well-being through the use of well-validated outcome measures. Ideally, such instruments should be simple and feasible and easily applicable in standard clinical practice. In recent years, a number of novel outcome measures have been developed and validated for use in pediatric patients with rheumatic and autoinflammatory illnesses. Furthermore, there has been an increased focus on the appraisal of child and parent perception of the disease impact. The new tools have markedly enlarged the spectrum of disorders and health domains that can be assessed in a standardized way. This progress will help to enhance the reliability of research studies and clinical trials. The aim of the present review is to provide an update of the recent advances in this field of research.

DOI: 10.1007/s11926-015-0558-4

PMID: 26769307 [Indexed for MEDLINE]

1376. Z Rheumatol. 2016 Mar;75(2):141-50. doi: 10.1007/s00393-015-0024-8.

[Causes and treatment of systemic amyloidosis].

[Article in German]

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BACKGROUND: Systemic amyloidoses are rare protein deposition disorders, which are

often diagnosed in an advanced stage of the disease due to non-specific symptoms.

Any chronic inflammatory disease can lead to an AA-type amyloidosis.

AIM: This paper summarizes the current state of the art of diagnosis and treatment of AA amyloidosis and presents data from the past 10 years of our amyloidosis center.

MATERIAL AND METHODS: Our data represents an analysis of our cohort of patients with amyloidosis and a selective research in the PubMed database for AA amyloidosis.

RESULTS: The underlying diseases comprise autoinflammatory syndromes, polyarthritis, and chronic inflammatory bowel and lung diseases. Renal organ involvement is the most prevalent in AA amyloidosis. It can be detected early through the evaluation of proteinuria. The treatment depends on the individual underlying disease. Patients without an associated inflammatory disease are considered to have idiopathic AA amyloidosis and empiric treatment is mandatory.

DISCUSSION: Survival of this fatal disease has recently improved due to the new diagnostic tools and treatment options; however, early diagnosis plays a crucial role in the prevention of end-stage renal failure. New therapeutic strategies aim to remove existing amyloid deposits.

DOI: 10.1007/s00393-015-0024-8

PMID: 26768274 [Indexed for MEDLINE]

1377. *Pediatr Rheumatol Online J.* 2015 Dec 12;13:59. doi: 10.1186/s12969-015-0057-1.

Relationship between clinical findings and genetic mutations in patients with familial Mediterranean fever.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is one of the most frequent genetic diseases encountered in the Mediterranean region. We aimed to investigate the correlation between genetic mutations and the clinical findings in 562 patients with FMF.

**METHODS:** In this retrospective cross-sectional study conducted with patients' files between 2006, and 2013, reverse hybridization assay for MEFV gene mutations was used and the 12 most frequent mutations were screened. Mutation types and clinical findings were compared with variance analysis.

**RESULTS:** The mean age was  $6.9 \pm 3.4$  years (range, 1.8-11.6 years). The most common symptom was fever (97.3%). Thirty-four of the patients (6.04%) were admitted with periodic fever only. Of these patients, M694V was the most common mutation type (73.5%). The percentage of the patients predominantly presenting

with recurrent abdominal pain was 77.78% and the most frequent mutations were M694V and E148Q. The rate of arthritis and arthralgia was significantly higher in patients with M694V and E148Q mutations. Chest pain was reported more often in patients homozygous for M694V (61.4%). Pericardial effusion was documented in the echocardiography of 10.9% of the 229 children with chest pain. Some patients had both FMF and Henoch Schönlein purpura (HSP), and were more likely to harbor either homozygote M694V or E148Q mutations. The frequency of episodes was higher in patients with homozygous M694V mutations (number of attacks =  $4.4 \pm 1.6$ /month). Proteinuria was detected in 106 patients of cases (29.2%), at an average of  $854 \pm 145$  mg/L. Most of the patients with proteinuria and elevated serum amyloid-A had homozygous M694V mutation.

**CONCLUSION:** The most common mutation in children in Turkey with FMF is the M694V mutation. Recurrent abdominal pain, arthritis or arthralgia, chest pain, and pericarditis were commonly seen in patients with M694V and E148Q mutations.

DOI: 10.1186/s12969-015-0057-1

PMCID: PMC4711108

PMID: 26759267 [Indexed for MEDLINE]

1378. Clin Rheumatol. 2016 Aug;35(8):2117-2123. doi: 10.1007/s10067-015-3164-y. Epub 2016 Jan 12.

A retrospective study of patients with adult-onset Still's disease: is pericarditis a possible predictor for biological disease-modifying anti-rheumatic drugs need?

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The aims of this study were to look for clinical or serological markers able to predict the use of biological disease-modifying anti-rheumatic drugs (bDMARDs) in patients with adult-onset Still's disease (AOSD) and to evaluate the efficacy and safety of bDMARDs in AOSD. In a single-center retrospective study, 39 patients with AOSD were divided into two groups according to whether they were ever treated with bDMARDs or not. Literature was searched for articles dealing with possible predictors of the use of bDMARDs in AOSD. Among the 18 AOSD patients who received at least one bDMARD, the prevalence of pericarditis was higher than that in the other patients [ $p = 0.014$ , odds ratio (OR) = 13.4, 95 % confidence interval (CI) = 1.45 to 122]. Literature search retrieved another paper dealing with predictors of bDMARDs need in AOSD: the analysis pooling data from our series and this previous report confirmed pericarditis at disease onset as a predictor of bDMARDs need ( $p = 0.028$ , OR = 3.62, 95 % CI = 1.22 to 10.7). A complete remission was observed in 17 out of 18 patients treated with bDMARDs, allowing withdrawal or tapering of corticosteroid therapy ( $p < 0.001$ ), but because of inefficacy or adverse events, some patients received more than one bDMARD during the course of the disease and 31 different trials of bDMARDs were needed. Pericarditis at disease onset may be a predictor of bDMARDs need in AOSD. These drugs have a good efficacy and safety profile and should be considered for patients not responding to conventional therapy.

DOI: 10.1007/s10067-015-3164-y

PMID: 26758435 [Indexed for MEDLINE]

1379. Clin Exp Immunol. 2016 May;184(2):197-207. doi: 10.1111/cei.12768. Epub 2016 Feb 24.

Immunometabolic biomarkers of inflammation in Behçet's disease: relationship with epidemiological profile, disease activity and therapeutic regimens.

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Behcet's disease (BD) is a systemic inflammatory disease with a still unclear pathogenesis. Although several inflammatory molecules have been studied, current biomarkers are largely insensitive in BD and unable to predict disease progression and response to treatment. Our primary aim was to explore serum levels of soluble CD40 L (sCD40L), soluble intracellular adhesion molecule (sICAM-1), monocyte chemoattractant protein-1 (MCP-1), myeloperoxidase (MPO), leptin, resistin, osteoprotegerin (OPG), soluble type 1 tumour necrosis factor receptor (sTNFR), interleukin (IL)-6 and serum amyloid A (SAA) serum concentration in a cohort of 27 BD patients. The secondary aim was to evaluate potential correlations between the putative circulating biomarkers, demographic profile of patients, the status of disease activity, the specific organ involvement at the time of sample collection and different therapeutic regimens. Serum concentrations of sTNFR ( $P = 0.008$ ), leptin ( $P = 0.0011$ ), sCD40L ( $P < 0.0001$ ) and IL-6 ( $P = 0.0154$ ) were significantly higher in BD patients than in HC, while no difference was found in MCP-1, MPO and resistin serum levels. Moreover, we observed significantly higher sTNFR serum concentrations in BD patients presenting inactive disease than HC ( $P = 0.0108$ ). A correlation between sTNFR and age was also found, with higher levels in patients over 40 years than HC ( $P = 0.0329$ ). Although further research is warranted to elucidate the role of circulating biomarkers, some of that may contribute to the understanding of the physiopathology processes underlying BD activity and damage as well as to provide useful tools for prognostic purposes and a personalized treatment approach.

DOI: 10.1111/cei.12768

PMCID: PMC4837234

PMID: 26756979 [Indexed for MEDLINE]

1380. Z Rheumatol. 2016 Mar;75(2):134-40. doi: 10.1007/s00393-015-0027-5.

[Type I interferonopathies. Systemic inflammatory diseases triggered by type I interferons].

[Article in German]

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Type I interferons mediate immune defense against viral infections. The induction of type I interferons has stimulating and modulating effects on the innate and adaptive immune systems thereby reducing tolerance against self-antigens. Genetic defects that result in an inadequate activation of the type I interferon system can cause a group of inflammatory disorders, which are collectively referred to as type I interferonopathies. While the clinical spectrum of type I interferonopathies is broad and heterogeneous, neurological and cutaneous symptoms are the most frequent manifestations. Some clinical and genetic features of type I interferonopathies are shared by multifactorial diseases, such as systemic lupus erythematosus and systemic vasculitis. Advances in understanding the disease mechanisms underlying type I interferonopathies have pinpointed novel targets for therapeutic interventions.

DOI: 10.1007/s00393-015-0027-5

1381. Biochem Genet. 2016 Apr;54(2):169-76. doi: 10.1007/s10528-015-9710-0. Epub 2016 Jan 7.

Association Between Vitamin D Receptor Polymorphism and Familial Mediterranean Fever Disease in Turkish Children.

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Familial Mediterranean fever (FMF) is an autosomal recessive, inherited autoinflammatory disease characterized by recurrent, self-limited attacks of fever, and inflammation of serosal surfaces. The aim of our study was to determine a possible relationship between Vitamin D receptor (VDR) gene polymorphisms and the risk of children with FMF. We investigated VDR FokI (rs10735810), TaqI (rs731236), BsmI (rs1544410), and ApaI (rs7975232) polymorphisms in 50 children with FMF and 150 age-matched healthy control subjects. This study was performed by polymerase chain reaction-based restriction fragment length polymorphism. There was no significant difference between patients and controls for VDR FokI, TaqI, BsmI, and ApaI genotypes and alleles ( $p > 0.05$ ). Results need to be supported by further investigations that define haplotype patterns for VDR gene polymorphisms in a larger group and different ethnic groups of FMF patients.

1382. PLoS One. 2016 Jan 6;11(1):e0146522. doi: 10.1371/journal.pone.0146522. eCollection 2016.

## Conformational Sampling and Binding Site Assessment of Suppression of Tumorigenicity 2 Ectodomain.

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Suppression of Tumorigenicity 2 (ST2), a member of the interleukin-1 receptor (IL-1R) family, activates type 2 immune responses to pathogens and tissue damage via binding to IL-33. Dysregulated responses contribute to asthma, graft-versus-host and autoinflammatory diseases and disorders. To study ST2 structure for inhibitor development, we performed the principal component (PC) analysis on the crystal structures of IL1-1R1, IL1-1R2, ST2 and the refined ST2 ectodomain (ST2ECD) models, constructed from previously reported small-angle X-ray scattering data. The analysis facilitates mapping of the ST2ECD conformations to PC subspace for characterizing structural changes. Extensive coverage of ST2ECD conformations was then obtained using the accelerated molecular dynamics simulations started with the IL-33 bound ST2ECD structure as instructed by their projected locations on the PC subspace. Cluster analysis of all conformations further determined representative conformations of ST2ECD ensemble in solution. Alignment of the representative conformations with the

ST2/IL-33 structure showed that the D3 domain of ST2ECD (containing D1-D3 domains) in most conformations exhibits no clashes with IL-33 in the crystal structure. Our experimental binding data informed that the D1-D2 domain of ST2ECD contributes predominantly to the interaction between ST2ECD and IL-33 underscoring the importance of the D1-D2 domain in binding. Computational binding site assessment revealed one third of the total detected binding sites in the representative conformations may be suitable for binding to potent small molecules. Locations of these sites include the D1-D2 domain ST2ECD and modulation sites conformed to ST2ECD conformations. Our study provides structural models and analyses of ST2ECD that could be useful for inhibitor discovery.

DOI: 10.1371/journal.pone.0146522

PMCID: PMC4703388

PMID: 26735493 [Indexed for MEDLINE]

1383. Ocul Immunol Inflamm. 2016 Aug;24(4):372-6. doi: 10.3109/09273948.2015.1100747. Epub 2016 Jan 5.

Peripapillary Retinal Nerve Fiber Layer and Ganglion Cell-Inner Plexiform Layer Thickness in Children with Familial Mediterranean Fever.

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**PURPOSE:** To evaluate the thickness of the peripapillary retinal nerve fiber layer (RNFL) and retinal ganglion cell-inner plexiform layer (GCIPL) in children with familial Mediterranean fever (FMF).

**METHODS:** The study included 39 FMF patients and 36 healthy controls. After detailed ocular examination, the thickness of the peripapillary RNFL and GCIPL were measured by spectral domain optic coherence tomography (SD-OCT). All

measurements were taken from the right eye of the patients and controls. According to their disease severity score (DSS), the patients were divided into two groups: patients with DSS  $\leq 5$  and those with DSS  $> 5$ .

RESULTS: There were no statistically significant differences in peripapillary RNFL and retinal GCIPL thickness between patients with FMF and controls.

CONCLUSION: It appears that FMF does not affect the RNFL and GCIPL thickness.

DOI: 10.3109/09273948.2015.1100747

PMID: 26730943 [Indexed for MEDLINE]

1384. J Immunol. 2016 Feb 1;196(3):1348-54. doi: 10.4049/jimmunol.1502130. Epub 2016 Jan 4.

Synergy between Hematopoietic and Radioresistant Stromal Cells Is Required for Autoimmune Manifestations of DNase II-/-IFN $\alpha$ R-/- Mice.

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Detection of endogenous nucleic acids by cytosolic receptors, dependent on STING, and endosomal sensors, dependent on Unc93b1, can provoke inflammatory responses that contribute to a variety of autoimmune and autoinflammatory diseases. In DNase II-deficient mice, the excessive accrual of undegraded DNA leads to both a STING-dependent inflammatory arthritis and additional Unc93b1-dependent autoimmune manifestations, including splenomegaly, extramedullary hematopoiesis, and autoantibody production. In this study, we use bone marrow chimeras to show that clinical and histological inflammation in the joint depends upon DNase II deficiency in both donor hematopoietic cells and host radioresistant cells.

Additional features of autoimmunity in these mice, known to depend on Unc93b1 and therefore endosomal TLRs, also require DNase II deficiency in both donor and host

compartments, but only require functional TLRs in the hematopoietic cells. Collectively, our data demonstrate a major role of both stromal and hematopoietic cells in all aspects of DNA-driven autoimmunity. These findings further point to the importance of cytosolic nucleic acid sensors in creating an inflammatory environment that facilitates the development of Unc93b1-dependent autoimmunity.

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DOI: 10.4049/jimmunol.1502130

PMCID: PMC4724517

PMID: 26729810 [Indexed for MEDLINE]

1385. Inflamm Allergy Drug Targets. 2015;14(2):94-8.

Vaccination and Induction of Autoimmune Diseases.

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Vaccines have been suspected of playing a role in inducing autoimmune disease (AID) for a long time. However, apart from certain specific vaccine strains and complications (such as the swine flu vaccine and Guillain-Barré syndrome in 1976, thrombocytopenia and the Measles-Mumps-Rubella vaccine), this role has not been established. In spite of this, many isolated cases or series of cases of arthritis, vasculitis, and central or peripheral nervous system symptoms following vaccination have been reported. These cases tend to be very infrequent and usually only the shortterm outcomes are described. This paper will examine the arguments for and against the relationship between vaccines and AID, bearing in mind that no association between the two has been clearly identified up to now. The role of adjuvants in vaccines has been described by other teams and in a more general syndrome (Autoimmune/Autoinflammatory Syndrome Induced by Adjuvants). Thus, cases of AID triggered by vaccines are highly rare and raise questions about the interaction between vaccines and/or their adjuvants and the genetic context of autoimmune disease. These observations should therefore not undermine the benefits of vaccination.



PMID: 26728772 [Indexed for MEDLINE]

1386. Iran J Med Sci. 2016 Jan;41(1):2-8.

Bone Mineral Density in Egyptian Children with Familial Mediterranean Fever.

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**BACKGROUND:** Familial Mediterranean fever (FMF) has episodic or subclinical inflammation that may lead to a decrease in bone mineral density (BMD). The objective of this study was to assess BMD in Egyptian children with FMF on genetic basis.

**METHODS:** A cross sectional study included 45 FMF patients and 25 control children of both sexes in the age range between 3-16 years old. The patients were reclassified into two groups, namely group I(A) with 23 cases using colchicine for 1 month or less, and group I(B) with 22 cases using colchicine for more than 6 months. For both the patients and control groups, MEFV mutations were defined using molecular genetics technique and BMD was measured by DXA at the proximal femur and lumbar spines.

**RESULTS:** Four frequent gene mutations were found in the patient group E148Q (35.6%), V726A (33.3%), M680I (28.9%), and M694V (2.2%). There were also four heterozygous gene mutations in 40% of the control children. Patients receiving colchicine treatment for less than 1 month had highly significant lower values of BMD at the femur and lumbar spines than the control children ( $P=0.007$ ,  $P<0.001$ ). Patients receiving colchicine treatment for more than 6 months had improved values of BMD at femur compared with the control, but there were still significant differences between them in lumbar spine ( $P=0.036$ ). There were insignificant effect of gene mutation type on BMD and the risk of osteopenia

among the patients.

CONCLUSION: FMF had a significant effect on BMD. However, regular use of colchicine treatment improves this effect mainly at the femur.

PMCID: PMC4691266

PMID: 26722138

1387. Curr Opin Chem Biol. 2016 Jun;32:1-9. doi: 10.1016/j.cbpa.2015.12.003. Epub 2015 Dec 23.

Preclinical characterization and clinical development of ILARIS<sup>®</sup> (canakinumab) for the treatment of autoinflammatory diseases.

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Interleukin-1beta (IL-1 $\beta$ ) is a pro-inflammatory cytokine which is part of the first line innate response in vertebrates and is induced in injury, infection, and immunity. While temporally limited induction of IL-1 $\beta$  is believed to protect the organisms against traumatic or infectious insults, its aberrant expression in chronic inflammation is detrimental. Therefore, pharmacological neutralization of IL-1 $\beta$  in chronic inflammatory diseases is a meaningful strategy to treat inflammation and to alleviate respective clinical symptoms in man. Canakinumab is a high-affinity human monoclonal antibody designed to target human IL-1 $\beta$  in inflammatory diseases. Indeed, canakinumab has shown excellent efficacy in rare genetic autoinflammatory diseases or pathological conditions associated with aberrant production of IL-1 $\beta$ . This review focuses on the molecular and clinical mode of action and pharmaceutical development of canakinumab in (auto)inflammatory diseases.

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DOI: 10.1016/j.cbpa.2015.12.003

PMID: 26720283 [Indexed for MEDLINE]

1388. Cytokine Growth Factor Rev. 2016 Apr;28:79-93. doi: 10.1016/j.cytogfr.2015.12.001. Epub 2015 Dec 15.

Secretory leukocyte protease inhibitor (SLPI), a multifunctional protein in the host defense response.

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Secretory leukocyte protease inhibitor (SLPI), a ~12kDa nonglycosylated cationic protein, is emerging as an important regulator of innate and adaptive immunity and as a component of tissue regenerative programs. First described as an inhibitor of serine proteases such as neutrophil elastase, this protein is increasingly recognized as a molecule that benefits the host via its anti-proteolytic, anti-microbial and immunomodulatory activities. Here, we discuss the diverse functions of SLPI. Moreover, we review several novel layers of SLPI-mediated control that protect the host from excessive/dysregulated inflammation typical of infectious, allergic and autoinflammatory diseases and that support healing responses through affecting cell proliferation, differentiation and apoptosis.

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DOI: 10.1016/j.cytogfr.2015.12.001

PMID: 26718149 [Indexed for MEDLINE]

1389. Klin Med (Mosk). 2016;94(6):470-3.

[Case report of a combination of periodic disease and irritable bowel syndrome].

[Article in Russian]

Pogromov AP, Mnatsakanyan MG, Kolosova KY.

The article reports a case of atypical picture of a combination of periodic disease and irritable bowel syndrome in a 52 year old patient.

PMID: 30289668 [Indexed for MEDLINE]

1390. Genet Couns. 2016;27(4):525-528.

A NOVEL MUTATION K447M (P.LYS447MET, C.1340 A>T) IDENTIFIED IN EXON 4 OF THE MEFV GENE.

Eroz R, Dogan M, Kocabay K.

PMID: 30226974 [Indexed for MEDLINE]

1391. Turk J Pediatr. 2016;58(5):562-565. doi: 10.24953/turkjped.2016.05.019.

Bone marrow aspiration complications: Iliopsoas abscess and sacroiliac osteomyelitis.

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After bone marrow aspiration procedure; some complications like pain and bleeding at the puncture site may be expected but some serious complications like osteomyelitis and soft tissue infections may also rarely occur. In this case we present a boy with recurrent fever. During etiologic investigation, familial Mediterranean fever (FMF) gene M694V mutation was +/+. Patient was treated with oral colchicine however fever persisted. The patient was considered as colchicine resistant FMF and steroid treatment was planned. Bone marrow aspiration procedure was executed to rule out malignancy. Three months after bone marrow aspiration, he was readmitted with complaint of left pelvic pain, difficulty in walking without support and standing on his left foot. Radiological imaging demonstrated left iliopsoas abscess and left sacroiliac osteomyelitis. Patient was successfully treated with intravenous ampicillin-sulbactam and clindamycin treatment for 6 weeks. Then oral amoxicillin-clavulanic acid treatment was continued for 2 weeks. Patient was discharged without any surgical procedure. On 1-year follow-up he could walk without any support.

DOI: 10.24953/turkjpmed.2016.05.019

PMID: 28621103 [Indexed for MEDLINE]

1392. Turk J Pediatr. 2016;58(3):327-330.

Familial Mediterranean fever associated with optic neuritis, successfully treated with anti-interleukin 1 agents.

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Familial Mediterranean fever (FMF) is an inherited periodic auto-inflammatory disease characterized by recurrent attacks of fever, synovitis and serositis. Ophthalmological manifestations of FMF are extremely rare. Here we described a

boy who has been followed-up for FMF and attended with a loss of vision during the course of the disease. He was diagnosed with optic neuritis. As the other etiologies were excluded his optic neuritis was attributed to the underlying auto inflammatory process. After pulse steroid therapy, his symptoms improved and a complete remission occurred. Afterwards he had two more optic neuritis attacks. Thereafter anti-interleukin 1 (IL-1) drugs were introduced and he did not develop further attacks of both optic neuritis and FMF. This case presentation highlights the possible association between FMF and optic nerve involvement.

PMID: 28266203 [Indexed for MEDLINE]

1393. Rheumatol Int. 2016 Apr;36(4):483-7. doi: 10.1007/s00296-015-3413-z. Epub 2015 Dec 28.

What is the best acute phase reactant for familial Mediterranean fever follow-up and its role in the prediction of complications? A systematic review.

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The most dreaded complication of familial Mediterranean fever (FMF) is amyloidosis; controversy exists as to what acute phase reactant (APR) should be monitored in these patients. To analyze the best acute phase reactant for FMF follow-up to help guide physicians to decide on what APR parameter to use, we also attempted to define the best APR in predicting the complications of FMF, specifically the development of amyloidosis. Systematic review based on a sensitive search to capture studies that: (1) included FMF patients; (2) measured serum amyloid A (SAA), CRP (C-reactive protein), proteinuria, or ESR (erythrocyte sedimentation rate); (3) amyloidosis were the outcome measure; (4) sensitivity,

specificity, predictive value, and other performance parameters could be calculated; and (5) had a longitudinal design. Of 1905 captured items, 26 were selected for detailed review, of which only two finally met the criteria, and the quality was only moderate; the articles did not analyzed the performance by means of sensitivity and specificity to predict, or even detect, amyloidosis, and thus had to be calculated based on text. The 26 screened studies were very heterogeneous in designs, parameters measured, and results, despite being set from research questions similar to ours. They were mainly descriptive, and it was very difficult to interpret the true performance of the tests. The correlation between the various APR is low. The evidence supporting the monitoring of FMF with any APR over the others is limited. Well designed longitudinal studies with a mixture of outcomes should be undertaken. Until them, recommending an APR over other would be based on expert opinion and indirect evidence.

DOI: 10.1007/s00296-015-3413-z

PMID: 26712372 [Indexed for MEDLINE]

1394. Curr Rheumatol Rep. 2016 Jan;18(1):3. doi: 10.1007/s11926-015-0549-5.

Relapsing Polychondritis: an Update on Pathogenesis, Clinical Features, Diagnostic Tools, and Therapeutic Perspectives.

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Relapsing polychondritis is a rare multisystemic disease widely accepted as a complex autoimmune disorder affecting proteoglycan-rich structures and cartilaginous tissues, especially the auricular pinna, cartilage of the nose, tracheobronchial tree, eyes, and heart's connective components. The clinical spectrum may vary from intermittent inflammatory episodes leading to unesthetic structural deformities to life-threatening cardiopulmonary manifestations, such as airway collapse and valvular regurgitation. The frequent association with other rheumatologic and hematologic disorders has been extensively reported over time, contributing to define its complexity at a diagnostic and also therapeutic level. Diagnosis of relapsing polychondritis is mainly based on clinical clues, while laboratory data have only a supportive contribution. Conversely, radiology is showing a relevant role in estimating the rate of systemic involvement as well as disease activity. The present review is aimed at providing an update on scientific data reported during the last 3 years about relapsing polychondritis in terms of pathogenesis, clinical features, diagnosis, and new treatment options.

DOI: 10.1007/s11926-015-0549-5

PMID: 26711694 [Indexed for MEDLINE]

1395. Cell Mol Life Sci. 2016 May;73(9):1741-64. doi: 10.1007/s00018-015-2123-8. Epub 2015 Dec 26.

NLR-regulated pathways in cancer: opportunities and obstacles for therapeutic interventions.

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NLRs (nucleotide-binding domain, leucine-rich repeat containing receptors) are pattern recognition receptors associated with immunity and inflammation in response to endogenous and exogenous pathogen and damage associated molecular



patterns (PAMPs and DAMPs respectively). Dysregulated NLR function is associated with several diseases including cancers, metabolic diseases, autoimmune disorders and autoinflammatory syndromes. In the last decade, distinct cell and organ specific roles for NLRs have been identified however; their roles in cancer initiation, development and progression remain controversial. This review summarizes the emerging role of NLRs in cancer and their possible future as targets for cancer therapeutics.

DOI: 10.1007/s00018-015-2123-8

PMID: 26708292 [Indexed for MEDLINE]

1396. Ren Fail. 2016;38(2):340-1. doi: 10.3109/0886022X.2015.1127707. Epub 2015 Dec 27.

Colchicine resistance and low vitamin D in familial Mediterranean fever.

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Comment on

Ren Fail. 2015 Aug;37(7):1122-5.

DOI: 10.3109/0886022X.2015.1127707

PMID: 26707648 [Indexed for MEDLINE]

1397. Curr Allergy Asthma Rep. 2016 Jan;16(1):2. doi: 10.1007/s11882-015-0578-1.

Recurrent Fevers for the Pediatric Immunologist: It's Not All Immunodeficiency.

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Autoinflammatory diseases are disorders of the innate immune system, characterized by systemic inflammation independent of infection and autoreactive antibodies or antigen-specific T cells. Similar to immunodeficiencies, these immune dysregulatory diseases have unique presentations, genetics, and available therapies. Given the presentation of fevers, rashes, and mucosal symptoms in many of the disorders, the allergist/immunologist is the appropriate medical home for these patients: to appropriately rule out immunodeficiencies, evaluate for allergic disease, and diagnose and treat recurrent fever disorders. However, many practicing physicians are unfamiliar with the clinical presentation, diagnosis, and treatment of autoinflammatory disorders. This review will focus on understanding the signs and symptoms of classic autoinflammatory disorders, introduce newly described monogenic and polygenic disorders, and address the approach to the patient with recurrent fevers to distinguish autoinflammation from immunodeficiency and autoimmunity.

DOI: 10.1007/s11882-015-0578-1

PMID: 26707379 [Indexed for MEDLINE]

1398. Joint Bone Spine. 2016 Jul;83(4):421-6. doi: 10.1016/j.jbspin.2015.11.001. Epub 2015 Dec 14.

Musculoskeletal manifestations of Fabry disease: A retrospective study.

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**OBJECTIVES:** Fabry disease is a rare X-linked metabolic disorder characterized by a deficiency in the enzyme alpha-galactosidase A. Both males and females can be affected. The main presenting symptom is pain in the extremities, whereas at a more advanced stage, the manifestations include hypertrophic cardiomyopathy, cardiac dysrhythmia, proteinuria, chronic kidney dysfunction, stroke, and hearing loss. When not diagnosed and treated, Fabry disease causes early death. No studies specifically designed to describe the musculoskeletal manifestations of Fabry disease are available.

**METHODS:** We conducted a single-center retrospective study of patients receiving follow-up at a Fabry disease referral center. We described the musculoskeletal manifestations and analyzed the differential diagnoses.

**RESULTS:** Our study included 40 patients belonging to 20 families, including 25 females with a mean age of 44.2 years (range, 20-76 years) and 15 males with a mean age of 40.1 years (range, 16-61 years). Mean age at the diagnosis of Fabry disease was 37.2 years (range, 7-71 years) in the females and 26.9 years (range, 9-51 years) in the males. Specific enzyme replacement therapy was given to 10 (40%) females and 12 (80%) males. Musculoskeletal manifestations were as follows: past or present pain in the extremities (13 females and 10 males), combined in some patients with vasomotor disorders in the extremities and telangiectasia; exercise intolerance (12 females and 12 males); osteoporotic fractures (2 brothers aged 45 and 44 years, respectively); osteoporosis (3 females, aged 57, 63, and 75 years, respectively), which contributed to death in the oldest patient; osteopenia (2 females aged 38 and 47 years, respectively; and 1 male aged 43 years); Charcot foot and lymphedema with serious infectious complications (4 males older than 40 years), with avascular osteonecrosis of the lower limbs in 2 cases; toe amputations (3 cases); bilateral lower-limb amputation (1 case); abnormally slender lower limbs (5 females and 8 males); acute gout (3 males with severe chronic kidney failure); and carpal tunnel syndrome (1 female and 1 male, both younger than 40 years). Mistaken diagnoses that were made at an early stage, contributing to delay the identification of Fabry disease, included rheumatic fever (2 females and 2 males), growing pains (2 males), pain with paralysis (1 female), chilblains of the lower limbs (1 female), and erythralgia (1 female). In adulthood, the following mistaken diagnoses were made: Sjögren's syndrome and/or sicca syndrome (6 females), systemic sclerosis (1 male), dysautonomia (1 female), and familial Mediterranean fever (1 female).

**CONCLUSION:** The diagnosis of Fabry disease is usually delayed, due to confusion with more common disorders. Musculoskeletal manifestations may constitute the

presenting symptoms. Past or present pain in the extremities is typical. Osteoporosis may develop early and become severe. Together with the family history, the presence of musculoskeletal manifestations can lead to the correct diagnosis by prompting alpha-galactosidase assays in males and genetic testing in females. Fabry disease is often responsible for musculoskeletal manifestations, of which the most common are pain in the extremities and osteoporosis. These manifestations can be inaugural and lead to diagnostic wanderings. They require specific treatment strategies.

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DOI: 10.1016/j.jbspin.2015.11.001

PMID: 26697993 [Indexed for MEDLINE]

1399. J Genet. 2015 Dec;94(4):629-35.

Frequency of mutations in Mediterranean fever gene, with gender and genotype-phenotype correlations in a Turkish population.

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Familial Mediterranean fever (FMF) is the most common hereditary inflammatory periodic disease, characterized by recurrent episodes of fever, abdominal pain, synovitis and pleurisy. The aim of this study was to determine the frequency and distribution of Mediterranean fever (MEFV) gene mutations and to investigate the clinical characteristics and genotype-phenotype correlation in patients with FMF in Aydin, a province in western Anatolia, Turkey. Therefore, we retrospectively analysed MEFV gene mutations in 383 patients with suspected FMF and the clinical features of 327 among them. The MEFV gene mutations were investigated using the reverse dot-blot hybridization technique. We detected 26 different genotypes and 11 different mutations. The most common mutations in our cohort were p.M694V (41.15%), p.E148Q (20.35%), p.M680I(G/C) (12.39%) and p.R761H (9.73%). Abdominal pain (86.2%), fever (80.7%), arthralgia (57.2%), vomiting (36.1%), arthritis

(34.6%), fatigue (31.5%), anorexia (22.9%) and chest pain (19.0%) were the most prevalent clinical features in our patients. This is the first study from Aydin in which the distribution of MEFV gene mutations and clinical features were evaluated in patients with FMF. We found that the most common mutation was p.M694V in our region, while the frequency of the p.R761H mutation was higher compared to other regions of Turkey with respect to extracted data from previous similar studies. Presented results supported the clinical findings in the literature that the homozygous p.M694V and compound heterozygous genotype were associated with more severe courses in FMF patients.

PMID: 26690517 [Indexed for MEDLINE]

1400. Rheumatol Int. 2016 Mar;36(3):325-31. doi: 10.1007/s00296-015-3408-9. Epub 2015 Dec 19.

Efficacy and safety of treatments in Familial Mediterranean fever: a systematic review.

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Familial Mediterranean fever (FMF) is an autoinflammatory disease, which can be well controlled with lifelong use of colchicine. Since studies dealing with the efficacy and safety of colchicine were conducted mainly in the sixties and seventies of the previous century, it seems that this topic needs to be updated. Recently, an international expert panel was undertaken for the establishment of recommendations on how to manage FMF. We aimed to summarize the efficacy and safety of the current treatments available to prevent FMF attacks and to avert

the appearance of amyloidosis secondary to FMF. A systematic review was performed. Two reviewers and methodologist established the protocol of the review and the epidemiological questions in PICO terms. MEDLINE through PubMed, Embase, and Cochrane Central Trials Register all up to May 31, 2014, were searched, and only randomized controlled trials or quasicontrolled trials were accepted. For each study, a judgment on risk of bias was then rated as high, moderate, or low. Of 1222 initially captured publications, 153 articles were studied in detail. Finally, only seven studies met all criteria and were included. Among these seven studies, four were randomized crossover clinical trials of colchicine including a total of 57 patients, one RCT of *Andrographis paniculata* Herba Nees extract employed in 24 patients, one randomized crossover clinical trial of Rilonacept used in 12 patients, and one RCT of interferon treating 34 acute abdominal attacks in 22 patients. The quality of the colchicine trials was low compared with the other drugs trials. Safety was not clearly mentioned in the trials. Colchicine is an effective treatment in FMF.

DOI: 10.1007/s00296-015-3408-9

PMID: 26687683 [Indexed for MEDLINE]

1401. West Indian Med J. 2015 May 11;65(2):281-286. doi: 10.7727/wimj.2014.173.

Clinical Profile of Familial Mediterranean Fever in a Paediatric Population in Eastern Turkey.

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Objective: Clinical and genetic findings of familial Mediterranean fever (FMF) may vary in different populations. Environmental factors may also affect phenotypic features of FMF. In this study, we investigated demographic, clinical and mutational features of FMF patients treated in a single reference hospital in

Turkey.

**Subjects and Methods:** One hundred and ninety-seven patients were included. The 11 mutations most frequently seen in FMF were investigated in these patients.

Patients were assessed as homozygous, heterozygous, compound heterozygous or non-mutation bearing. Clinical and laboratory examinations in the attack and attack-free periods were recorded. A disease severity score was calculated for each patient.

**Results:** One hundred patients were female and 97 male. The most commonly seen mutations in our region was M694V (51.7%). The most frequent clinical findings in our patients was gastric pain (90.1%), followed by fever (82.2%). The highest disease severity score was determined in patients with homozygous M694V. Sedimentation values were significantly high in patients with homozygous M694V mutation, while no statistically significant difference was determined among other acute phase reactants and haemoglobin and leukocyte values.

**Conclusion:** Changes in acute phase reactants in attack and attack-free periods are used as diagnostic tools in FMF. Severity and frequency of attacks are clearly correlated with mutations. However, the fact that the clinical course can differ even in individuals with mutations reveals the importance of environmental factors.

DOI: 10.7727/wimj.2014.173

PMID: 26684158

1402. Medicine (Baltimore). 2015 Dec;94(50):e2301. doi: 10.1097/MD.0000000000002301.

Cytokine and Chemokine Profile in Amicrobial Pustulosis of the Folds: Evidence for Autoinflammation.

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Autoinflammation has recently been suggested in the pathogenesis of neutrophilic dermatoses but systematic studies on their cytokine profile are lacking. Notably, amicrobial pustulosis of the folds (APF), classified among neutrophilic dermatoses, has been studied only in small case series. In our University Hospital, we conducted an observational study on 15 APF patients, analyzing their clinical and laboratory features with a follow-up of 9 months to 20 years. Skin cytokine pattern of 9 of them was compared to that of 6 normal controls. In all patients, primary lesions were pustules symmetrically involving the skin folds and anogenital region with a chronic-relapsing course and responding to corticosteroids. Dapsone, cyclosporine, and tumor necrosis factor blockers were effective in refractory cases. In skin samples, the expressions of interleukin (IL)-1 $\beta$ , pivotal cytokine in autoinflammation, and its receptors I and II were significantly higher in APF ( $P=0.005$ ,  $0.018$ , and  $0.034$ , respectively) than in controls. Chemokines responsible for neutrophil recruitment such as IL-8 ( $P=0.003$ ), CXCL 1/2/3 (C-X-C motif ligand 1/2/3) ( $P=0.010$ ), CXCL 16 ( $P=0.045$ ), and RANTES (regulated on activation, normal T cell expressed and secreted) ( $P=0.034$ ) were overexpressed. Molecules involved in tissue damage like matrix metalloproteinase-2 (MMP-2) ( $P=0.010$ ) and MMP-9 ( $P=0.003$ ) were increased. APF is a pustular neutrophilic dermatosis with a typical distribution in all patients. The disorder may coexist with an underlying autoimmune/dysimmune disease but is often associated only with a few autoantibodies without a clear autoimmunity. The overexpression of cytokines/chemokines and molecules amplifying the inflammatory network supports the view that APF has an important autoinflammatory component.

DOI: 10.1097/MD.0000000000002301

PMCID: PMC5058939

PMID: 26683967 [Indexed for MEDLINE]

Conflict of interest statement: The authors have no conflicts of interest to disclose.

1403. Reumatol Clin. 2016 Sep-Oct;12(5):299-300. doi: 10.1016/j.reuma.2015.09.004. Epub 2015 Dec 3.

Case of familial Mediterranean fever presenting with constant abdominal pain.

[Article in English, Spanish]



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DOI: 10.1016/j.reuma.2015.09.004

PMID: 26670740 [Indexed for MEDLINE]

1404. Sci Rep. 2015 Dec 11;5:17935. doi: 10.1038/srep17935.

Genipin inhibits NLRP3 and NLRC4 inflammasome activation via autophagy suppression.

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Inflammasomes are cytoplasmic, multiprotein complexes that trigger caspase-1 activation and IL-1 $\beta$  maturation in response to diverse stimuli. Although inflammasomes play important roles in host defense against microbial infection, overactive inflammasomes are deleterious and lead to various autoinflammatory diseases. In the current study, we demonstrated that genipin inhibits the induction of IL-1 $\beta$  production and caspase-1 activation by NLRP3 and NLRC4 inflammasomes. Furthermore, genipin specifically prevented NLRP3-mediated, but not NLRC4-mediated, ASC oligomerization. Notably, genipin inhibited autophagy, leading to NLRP3 and NLRC4 inflammasome inhibition. UCP2-ROS signaling may be involved in inflammasome suppression by genipin. In vivo, we showed that genipin inhibited NLRP3-dependent IL-1 $\beta$  production and neutrophil flux in LPS- and alum-induced murine peritonitis. Additionally, genipin provided protection

against flagellin-induced lung inflammation by reducing IL-1 $\beta$  production and neutrophil recruitment. Collectively, our results revealed a novel role in inhibition of inflammatory diseases for genipin that has been used as therapeutics for centuries in herb medicine.

DOI: 10.1038/srep17935

PMCID: PMC4675967

PMID: 26659006 [Indexed for MEDLINE]

1405. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2015 Sep;29(17):1569-70.

[Adult onset Still's disease with the initial symptom of pharyngalgia: a case report].

[Article in Chinese]

Zhou E, Chen X, Zhang J.

Adult onset Still's disease is a rare inflammatory disease characterized by spiking fevers, arthritis/ arthralgias, typical salmon-colored bumpy rash, pharyngalgia, myalgia and possible involvement of visceral organs. The diagnosis is exclusively based on clinical symptoms, according to the criteria, after the exclusion of well-known infectious, neoplastic, or other autoimmune/autoinflammatory disorders. This report includes one case of adult onset Still's disease with the initial symptom of pharyngalgia.

PMID: 26647549 [Indexed for MEDLINE]

1406. Gut Microbes. 2015;6(6):392-7. doi: 10.1080/19490976.2015.1107697.

Advancing the use of Lactobacillus acidophilus surface layer protein A for the treatment of intestinal disorders in humans.

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Intestinal immunity is subject to complex and fine-tuned regulation dictated by interactions of the resident microbial community and their gene products with host innate cells. Deterioration of this delicate process may result in devastating autoinflammatory diseases, including inflammatory bowel disease (IBD), which primarily comprises Crohn's disease (CD) and ulcerative colitis (UC). Efficacious interventions to regulate proinflammatory signals, which play critical roles in IBD, require further scientific investigation. We recently demonstrated that rebalancing intestinal immunity via the surface layer protein A (SlpA) from *Lactobacillus acidophilus* NCFM potentially represents a feasible therapeutic approach to restore intestinal homeostasis. To expand on these findings, we established a new method of purifying bacterial SlpA, a new SlpA-specific monoclonal antibody, and found no SlpA-associated toxicity in mice. Thus, these data may assist in our efforts to determine the immune regulatory efficacy of SlpA in humans.

DOI: 10.1080/19490976.2015.1107697

PMCID: PMC4826124

PMID: 26647142 [Indexed for MEDLINE]

1407. West Indian Med J. 2015 May 6;65(1):165-169. doi: 10.7727/wimj.2014.202.

Can Mean Platelet Volume Be a Surrogate Marker of Inflammation in Rheumatic Diseases?

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**Background:** In humans, it has been suggested that low-level mean platelet volume (MPV) may be related to secondary thrombosis due to inflammation. For this reason, MPV can be used as a marker showing inflammation in the body.

**Objectives:** To evaluate the association of MPV with erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Disease Activity Score-28 (DAS-28), and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) in patients with rheumatic diseases.

**Methods:** The study consisted of 261 patients with rheumatoid arthritis (203 females, 77.8%; 58 males, 22.2%), 85 patients with ankylosing spondylitis (57 males, 67.1%; 28 females, 32.9%), 56 patients with familial Mediterranean fever (32 females, 57.1%; 24 males, 42.9%) and 194 patients (139 females, 71.6%; 55 males, 28.4%) with other rheumatic diseases (Behçet's disease, psoriatic arthritis, spondyloarthropathy, systemic lupus erythematosus, systemic sclerosis, or undifferentiated connective tissue disease).

**Results:** There was an inversely significant correlation between MPV and ESR and CRP in patients with rheumatoid arthritis ( $r = -0.164$ ,  $p = 0.008$ ). Mean platelet volume was negatively correlated with DAS-28-ESR/CRP ( $r = -0.393$ ,  $p < 0.001$ ) in rheumatoid arthritis. Mean platelet volume was inversely correlated with BASDAI ( $r = -0.580$ ,  $p < 0.001$ ) in ankylosing spondylitis. In the group with familial Mediterranean fever (especially M694V homozygous), there was a negative correlation between MPV and ESR and CRP ( $p < 0.001$ ). Mean platelet volume and CRP were negatively correlated in psoriatic arthritis ( $r = -0.599$ ,  $p = 0.011$ ). Mean platelet volume and ESR were inversely related in patients with systemic lupus erythematosus ( $r = -0.421$ ,  $p = 0.045$ ). There was a negative correlation between MPV and ESR ( $r = -0.219$ ,  $p = 0.002$ ), and between MPV and CRP ( $r = -0.208$ ,  $p = 0.004$ ) in other rheumatic diseases.

**Conclusions:** The lower MPV level surrogates active and/or chronic inflammatory state in the body. Thus, MPV may be used as a negative acute-phase reactant in rheumatic diseases.

DOI: 10.7727/wimj.2014.202

PMID: 26645595

1408. Nat Genet. 2016 Jan;48(1):67-73. doi: 10.1038/ng.3459. Epub 2015 Dec 7.

Loss-of-function mutations in TNFAIP3 leading to A20 haploinsufficiency cause an early-onset autoinflammatory disease.

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Systemic autoinflammatory diseases are driven by abnormal activation of innate immunity. Herein we describe a new disease caused by high-penetrance heterozygous germline mutations in *TNFAIP3*, which encodes the NF- $\kappa$ B regulatory protein A20, in six unrelated families with early-onset systemic inflammation. The disorder resembles Behçet's disease, which is typically considered a polygenic disorder with onset in early adulthood. A20 is a potent inhibitor of the NF- $\kappa$ B signaling pathway. Mutant, truncated A20 proteins are likely to act through haploinsufficiency because they do not exert a dominant-negative effect in overexpression experiments. Patient-derived cells show increased degradation of I $\kappa$ B $\alpha$  and nuclear translocation of the NF- $\kappa$ B p65 subunit together with increased expression of NF- $\kappa$ B-mediated proinflammatory cytokines. A20 restricts NF- $\kappa$ B signals via its deubiquitinase activity. In cells expressing mutant A20 protein, there is defective removal of Lys63-linked ubiquitin from TRAF6, NEMO and RIP1 after stimulation with tumor necrosis factor (TNF). NF- $\kappa$ B-dependent proinflammatory cytokines are potential therapeutic targets for the patients with this disease.

DOI: 10.1038/ng.3459

PMCID: PMC4777523

PMID: 26642243 [Indexed for MEDLINE]

1409. Ophthalmologica. 2016;235(2):72-7. doi: 10.1159/000442216. Epub 2015 Dec 5.

Choroidal Thickness Changes in the Acute Attack Period in Patients with Familial Mediterranean Fever.

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Comment in

Ophthalmologica. 2016;235(2):123.

Ophthalmologica. 2016;235(2):124.

Ophthalmologica. 2016;235(3):185.

Ophthalmologica. 2016;235(3):184.

**PURPOSE:** The aim of this study was to evaluate choroidal thickness changes during acute attacks of familial Mediterranean fever (FMF).

**METHODS:** Fifty patients with FMF and 50 healthy controls were included. Choroidal thickness of each participant was measured at the foveola and horizontal nasal and temporal quadrants at 500- $\mu$ m intervals to 1,500  $\mu$ m from the foveola using spectral-domain optical coherence tomography. White blood cell count, erythrocyte sedimentation rate (ESR) and serum levels of fibrinogen and C-reactive protein (CRP) were evaluated. The clinical findings (peritonitis, arthritis and pleuritis) were noted.

**RESULTS:** Choroidal thickness was significantly thicker at all measurement points in FMF patients compared to healthy controls during an acute attack ( $p < 0.05$ ).

There were positive correlations between the choroidal thickness and ESR, fibrinogen and, particularly, CRP levels. Clinical findings did not change the choroidal thickness significantly ( $p > 0.05$ ).

**CONCLUSIONS:** Increased choroidal thickness in the acute phase of FMF is possibly related to the inflammatory edematous changes in the choroid.

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DOI: 10.1159/000442216

PMID: 26637112 [Indexed for MEDLINE]

1410. Clin Rheumatol. 2016 Mar;35(3):565-72. doi: 10.1007/s10067-015-3132-6. Epub 2015 Dec 3.

Lights and shadows in autoinflammatory syndromes from the childhood and adulthood perspective.

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In a high percentage of cases, the monogenic autoinflammatory syndromes (AIS), caused by subversion in the inflammasome homeostasis leading to cytokine oversecretion and characterized by multiple inflammatory pictures, start in childhood. However, the description of tardive manifestations, veiled phenotypes, and atypical clinical signs beginning in adulthood has been more and more reported in recent times, requiring that many specialists become confident with concepts, details, and management strategies of AIS. Differences between child- and adult-onset syndromes raise the question of whether pathogenic mechanisms might differ when the timetable of AIS onset diverges, but show that carefulness is needed to establish a straightforward diagnosis.

DOI: 10.1007/s10067-015-3132-6

PMID: 26631101 [Indexed for MEDLINE]

1411. Semin Immunopathol. 2016 Jan;38(1):45-56. doi: 10.1007/s00281-015-0549-6. Epub 2015 Nov 30.

Neutrophilic dermatoses and autoinflammatory diseases with skin involvement--innate immune disorders.

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Neutrophilic dermatoses (NDs) such as Sweet's syndrome and pyoderma gangrenosum were first described more than 50 years ago and grouped based on their clinical features combined with the typical, neutrophil-rich cutaneous inflammation. In contrast, the recently identified autoinflammatory diseases (ADs) that are also associated with neutrophil granulocyte infiltration of the skin were first characterized based on their genetic architecture. Though both the older ND and the newer AD encompass distinct conditions, they can be seen as parts of a spectrum of innate inflammation. Both groups of diseases show so many overlapping clinical, pathogenetic, histologic, and genetic features that together they should likely be considered as innate immune disorders.

DOI: 10.1007/s00281-015-0549-6

PMID: 26620372 [Indexed for MEDLINE]

1412. Semin Arthritis Rheum. 2016 Apr;45(5):633-7. doi: 10.1016/j.semarthrit.2015.10.012. Epub 2015 Oct 29.

Adult autoinflammatory disease frequency and our diagnostic experience in an adult autoinflammatory clinic.

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OBJECTIVE: Systemic autoinflammatory diseases (SAIDs) mainly include monogenic hereditary periodic fever syndromes, and NOD2-associated AID (NAID) is a polygenic SAID. Our aim was to study the disease frequency and report our

diagnostic experience.

**METHODS:** A total of 266 adult patients with clinical phenotypes suspicious for SAIDs were studied at the Cleveland Clinic between November 2009 and February 2015. All patients were genotyped for NOD2 mutations or periodic fever syndrome panel. The definite diagnosis of each disease was deemed to be present if both clinical phenotypes and genetic confirmation were met.

**RESULTS:** Of the 266 patients, 79 (29.7%) were diagnostic of SAIDs, including 54 cases of NAID, 13 familial Mediterranean fever (FMF), 6 tumor necrosis factor receptor-associated periodic syndrome (TRAPS), 5 cryopyrin-associated periodic disease (CAPS), and 1 hyper IgD periodic syndrome (HIDS). NOD2 genotyping had a higher concordance rate with the clinical phenotype for the diagnosis of NAID. Of 29 patients, 13 (44.8%) were clinically suspicious for FMF and had positive genetic testing. Of 66 patients, 6 (9%) were tested positive for TRAPS. Out of 23 patients, 5 (21.7%) were tested positive for CAPS. Only 1 patient tested positive for HIDS. The concordance between the working clinical diagnosis and positive genetic testing varied among the SAIDs.

**CONCLUSIONS:** Our study demonstrates that NAID and FMF are relatively common in adults. TRAPS and HIDS are extremely rare, and the concordance between the working clinical diagnosis and positive genetic testing is considerably disproportional for TRAPS. Ordering of genetic testing for SAIDs should highly consider both the disease frequency and stringent phenotypes.

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DOI: 10.1016/j.semarthrit.2015.10.012

PMID: 26620106 [Indexed for MEDLINE]

1413. J Pediatr. 2016 Feb;169:188-93. doi: 10.1016/j.jpeds.2015.10.081. Epub 2015 Nov 23.

Developing a Predictive Score for Chronic Arthritis among a Cohort of Children with Musculoskeletal Complaints--The Chronic Arthritis Score Study.

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**OBJECTIVE:** To explore if features obtained from a carefully taken medical history can be predictors of the final diagnosis in children with musculoskeletal complaints.

**STUDY DESIGN:** We collected detailed clinical information on 178 children referred to our Pediatric Immunology and Rheumatology Unit by their primary care pediatrician for musculoskeletal complaints; a univariate logistic analysis was performed to identify variables correlated with the diagnosis of chronic arthritis. The variables identified were combined in a linear score that indicates the probability for a patient with musculoskeletal pain to receive the diagnosis of chronic arthritis.

**RESULTS:** The joint swelling pattern ( $P < .0001$ ), the precipitating factors of pain ( $P = .001$ ), the duration of morning stiffness ( $P < .0001$ ) and the frequency of pain ( $P < .0001$ ), were found to be independently correlated with the diagnosis of chronic arthritis and were used to develop a diagnostic score. This score had a sensitivity of 90.9% and specificity of 95.3%.

**CONCLUSIONS:** We developed a score that could be useful in the daily clinical routine to correctly direct the differential diagnosis in a child with musculoskeletal complaints, rationalizing time and resources necessary to reach a definitive diagnosis.

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DOI: 10.1016/j.jpeds.2015.10.081

PMID: 26616250 [Indexed for MEDLINE]

1414. Pharmaceuticals (Basel). 2015 Nov 25;8(4):793-815. doi: 10.3390/ph8040793.

Therapeutic Potential of Interferon- $\gamma$  and Its Antagonists in Autoinflammation: Lessons from Murine Models of Systemic Juvenile Idiopathic Arthritis and

## Macrophage Activation Syndrome.

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Interferon- $\gamma$  (IFN- $\gamma$ ) affects immune responses in a complex fashion. Its immunostimulatory actions, such as macrophage activation and induction of T helper 1-type responsiveness, are widely acknowledged, however, as documented by a large body of literature, IFN- $\gamma$  has also the potential to temper inflammatory processes via other pathways. In autoimmune and autoinflammatory disorders, IFN- $\gamma$  can either play a disease-enforcing role or act as protective agent, depending on the nature of the disease. In animal models of any particular autoimmune disease, certain changes in the induction procedure can reverse the net outcome of introduction or ablation of IFN- $\gamma$ . Here, we review the role of endogenous IFN- $\gamma$  in inflammatory disorders and related murine models, with a focus on systemic juvenile idiopathic arthritis (sJIA) and macrophage activation syndrome (MAS). In particular, we discuss our recent findings in a mouse model of sJIA, in which endogenous IFN- $\gamma$  acts as a regulatory agent, and compare with results from mouse models of MAS. Also, we elaborate on the complexity in the activity of IFN- $\gamma$  and the resulting difficulty of predicting its value or that of its antagonists as treatment option.

DOI: 10.3390/ph8040793

PMCID: PMC4695810

PMID: 26610523

1415. Nat Rev Immunol. 2015 Dec;15(12):760-70. doi: 10.1038/nri3921.

STING: infection, inflammation and cancer.

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The rapid detection of microbial agents is essential for the effective initiation of host defence mechanisms against infection. Understanding how cells detect cytosolic DNA to trigger innate immune gene transcription has important implications - not only for comprehending the immune response to pathogens but also for elucidating the causes of autoinflammatory disease involving the sensing of self-DNA and the generation of effective antitumour adaptive immunity. The discovery of the STING (stimulator of interferon genes)-controlled innate immune pathway, which mediates cytosolic DNA-induced signalling events, has recently provided important insights into these processes, opening the way for the development of novel immunization regimes, as well as therapies to treat autoinflammatory disease and cancer.

DOI: 10.1038/nri3921

PMCID: PMC5004891

PMID: 26603901 [Indexed for MEDLINE]

Conflict of interest statement: statement The author declares no competing interests.

1416. J Leukoc Biol. 2016 May;99(5):761-9. doi: 10.1189/jlb.3A0915-399R. Epub 2015 Nov 23.

Differential impact of high and low penetrance TNFRSF1A gene mutations on conventional and regulatory CD4+ T cell functions in TNFR1-associated periodic syndrome.

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TNFR-associated periodic syndrome is an autoinflammatory disorder caused by autosomal-dominant mutations in TNFRSF1A, the gene encoding for TNFR superfamily 1A. The lack of knowledge in the field of TNFR-associated periodic syndrome biology is clear, particularly in the context of control of immune self-tolerance. We investigated how TNF- $\alpha$ /TNFR superfamily 1A signaling can affect T cell biology, focusing on conventional CD4(+)CD25(-) and regulatory CD4(+)CD25(+) T cell functions in patients with TNFR-associated periodic syndrome

carrying either high or low penetrance TNFRSF1A mutations. Specifically, we observed that in high penetrance TNFR-associated periodic syndrome, at the molecular level, these alterations were secondary to a hyperactivation of the ERK1/2, STAT1/3/5, mammalian target of rapamycin, and NF-κB pathways in conventional T cells. In addition, these patients had a lower frequency of peripheral regulatory T cells, which also displayed a defective suppressive phenotype. These alterations were partially found in low penetrance TNFR-associated periodic syndrome, suggesting a specific link between the penetrance of the TNFRSF1A mutation and the observed T cell phenotype. Taken together, our data envision a novel role for adaptive immunity in the pathogenesis of TNFR-associated periodic syndrome involving both CD4(+) conventional T cells and Tregs, suggesting a novel mechanism of inflammation in the context of autoinflammatory disorders.

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DOI: 10.1189/jlb.3A0915-399R

PMID: 26598380 [Indexed for MEDLINE]

1417. Z Rheumatol. 2015 Dec;74(10):863-6, 868-72, 874-7. doi: 10.1007/s00393-015-0014-x.

[Childhood vasculitis].

[Article in German]

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**BACKGROUND:** The primary vasculitides are rare conditions in childhood. The most common disease subtypes are Schönlein-Henoch purpura and Kawasaki's syndrome, which frequently have a self-limiting course. In the majority of vasculitides, the etiology remains unknown. Environmental exposure, including infections, is suspected to trigger an autoinflammatory response in predisposed individuals.

**GOAL:** The aim of this review is to present the various aspects of childhood vasculitis.

**MATERIALS AND METHODS:** Reviews and special original papers on childhood vasculitis, published classification criteria and current therapy guidelines were reviewed and summarized.

**RESULTS:** The classification of vasculitides in childhood has been modified from the previous adult Chapel Hill classification for vasculitides in 2008. Most therapy recommendations for children are adapted from results of studies in adults. This review covers the current classifications, pathogenesis, clinical manifestations and therapy recommendations for children.

**DISCUSSION:** Although etiology and pathogenesis of many vasculitides in childhood are still unknown, clarifying diagnostic methods and effective therapeutic options are available. The knowledge about various forms of disease manifestation may contribute to an early diagnosis and timely initiation of treatment, which may prevent devastating irreversible impairment.

DOI: 10.1007/s00393-015-0014-x

PMID: 26597725 [Indexed for MEDLINE]

1418. Klin Med (Mosk). 2015;93(7):37-9.

[ANTIBIOTIC RESISTANCE OF ESCHERICHIA COLI OF THE INTESTINAL MICROBIOTA IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER].

[Article in Russian]

Pepoyan AZ, Balayan MA, Atrutyunyan NA, Grigoryan AG, Tsaturyan VV, Manvelyan AM, Dilanyan E, Pitseno I, Torok T.

We used clinical bacteriological analysis and high-density DNA-microchips (PhyloChip) to study the quality and the quantity of commensal bacteria of the genus *Escherichia* in patients with familial mediterranean fever (periodic



disease). The intestinal microbiota of these patients contained a large number of operational taxonomic units of these bacteria. The study of antibiotic resistance of *Escherichia coli* from the intestinal microbiota in patients with familial mediterranean fever revealed a large number of resistant and multiresistant isolates. Therapy with commercial probiotic Narine (Vitamax-E, Armenia) reduced the number of operational taxonomic units of commensal bacteria and the frequency of multiresistant isolates. The mechanism of action of Narine probiotic on intestinal bacteria and their resistance to antibiotics is discussed

PMID: 26596057 [Indexed for MEDLINE]

1419. Autoimmunity. 2016;49(1):12-6. doi: 10.3109/08916934.2015.1113404. Epub 2015 Nov 22.

Sequence analysis of TMEM173 exon 5 in patients with systemic autoimmune diseases.

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**BACKGROUND:** Overactivation of the interferon pathways has been demonstrated in patients suffering from different systemic autoimmune diseases (SADs). Genetic associations have been described for many genes involved in these pathways. Gain-of-function mutations in the TMEM173 gene have recently been reported in patients with autoinflammatory diseases that share some clinical features with SADs.

**METHODS:** We aimed at detecting the reported three mutations of transmembrane protein 173 (TMEM173) exon 5 in 100 patients suffering from: systemic lupus erythematosus (SLE) (n = 22), primary antiphospholipid syndrome (PAPS) (n = 20), systemic sclerosis (SSc) (n = 20), dermatomyositis (DM) (n = 20), and vasculitis (n = 18). Samples from 19 healthy controls were also included. Sequence analyses were performed from the derived TMEM173 exon 5 PCR fragment amplified from DNA obtained from whole blood.

RESULTS: Neither mutations nor single nucleotide polymorphisms (SNPs) in the exon 5 of the TMEM173 gene were detected. Just the rs7380272 SNP, located in the intronic region upstream exon 5, was detected in some patients and controls. The allele frequency of this SNP, though, was not statistically different between the patients groups and the control group.

CONCLUSIONS: Our study demonstrates the lack of association between the presence of SADs and mutations in exon 5 of the TMEM173 gene. SADs are complex multifactorial diseases in which not just one but probably many different genetic alterations may coexist. Although we cannot rule out the possibility that other variations may exist in other regions of this gene, we think that studies must be directed towards the analysis of other genes which, as TMEM173, also code for nucleic acid sensors that activate the nucleic-acid induced type I IFN pathway.

DOI: 10.3109/08916934.2015.1113404

PMID: 26593864 [Indexed for MEDLINE]

1420. J Ophthalmic Inflamm Infect. 2015 Dec;5(1):34. doi: 10.1186/s12348-015-0065-9. Epub 2015 Nov 21.

Successful resolution of stromal keratitis and uveitis using canakinumab in a patient with chronic infantile neurologic, cutaneous, and articular syndrome: a case study.

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**BACKGROUND:** Cryopyrin-associated periodic syndrome (CAPS) is a group of rare autoinflammatory diseases, and of these, chronic infantile neurologic, cutaneous, and articular/neonatal-onset multisystem inflammatory disease (CINCA/NOMID) syndrome has the most severe phenotype. Canakinumab, a monoclonal antibody that targets interleukin-1 $\beta$ , has been shown to be an effective treatment for resolving systemic inflammation. However, its efficacy for treating ophthalmic symptoms of this disorder remains unclear.

**FINDINGS:** A 64-year-old female reported episodes of nonpruritic urticaria, fever, aseptic meningitis, and bilateral sensorineural deafness. Her son had experienced similar symptoms. She was initially referred for ophthalmologic treatment for an infectious corneal ulcer. Examination of her right eye by slit lamp biomicroscopy showed diffuse conjunctival injection, corneal infiltrates, a corneal ulcer, and hypopyon. She was therefore treated aggressively with topical and systemic antibiotics in addition to antifungal medications. However, this was ineffective. Genetic analysis detected the heterozygous germline p.Asp303Asn mutation in the NLRP3 gene in both our patient and her son. She was therefore diagnosed with CINCA/NOMID syndrome based on her clinical manifestations. All of the patient's physical and ophthalmic symptoms were resolved within a few days after the initiation of canakinumab treatment. During an 18-month follow-up period, no adverse events or severe infections were observed.

**CONCLUSIONS:** Our case report indicates that canakinumab is effective not only for the treatment of systemic inflammation but also for treating ophthalmic involvement, such as recurrent stromal keratitis and anterior uveitis.

DOI: 10.1186/s12348-015-0065-9

PMCID: PMC4654730

PMID: 26590045

1421. *Pediatr Rheumatol Online J.* 2015 Nov 20;13:50. doi: 10.1186/s12969-015-0047-3.

Gene-expression analysis of adult-onset Still's disease and systemic juvenile idiopathic arthritis is consistent with a continuum of a single disease entity.

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**BACKGROUND:** Adult-onset Still's disease (AOSD), a rare autoinflammatory disorder, resembles systemic juvenile idiopathic arthritis (SJIA). The superimposable systemic clinical features of AOSD and SJIA suggest both clinical phenotypes represent the same disease continuum with different ages of onset. To further characterize the similarity between AOSD and SJIA at the molecular level, 2

previously identified response gene sets in SJIA were used to investigate how genes that respond to interleukin (IL)-1 $\beta$  inhibition with canakinumab in SJIA patients behave in AOSD patients with active disease prior to IL-1 $\beta$  targeting therapy, relative to healthy subjects.

FINDINGS: All genes downregulated in SJIA patients following canakinumab treatment were upregulated in most patients with active AOSD prior to canakinumab treatment, relative to healthy subjects. A few patients with milder AOSD had expectedly gene-expression patterns that resembled those in healthy subjects. Comparison of the gene-expression patterns with neutrophil counts showed a correlation between elevated neutrophil numbers and upregulation of canakinumab-responsive genes. Correspondingly, most genes upregulated following canakinumab treatment in patients with SJIA patients were downregulated in the majority of AOSD patients.

CONCLUSIONS: These results further support the concept of a Still's disease continuum that includes both a pediatric/juvenile onset (SJIA) and adult onset (AOSD) form.

DOI: 10.1186/s12969-015-0047-3

PMCID: PMC4654831

PMID: 26589963 [Indexed for MEDLINE]

1422. Iran J Public Health. 2015 Aug;44(8):1143-5.

Recurrent Macroscopic Hematuria and Abdominal Pain: Questions and Answers.

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A 6.5 yr old girl was admitted with a category of clinical signs and symptoms including recurrent gross hematuria, abdominal pain, and fever. After different examinations including genetic analysis, the disease was diagnosed as Familial Mediterranean fever (FMF). It is suggested to consider FMF as a rare cause of recurrent gross hematuria, which is responsive to colchicine treatment.

1423. Eur J Med Genet. 2015 Dec;58(12):668-73. doi: 10.1016/j.ejmg.2015.11.007. Epub 2015 Nov 14.

Study of the association of IL-1 $\beta$  and IL-1RA gene polymorphisms with occurrence and severity of Familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is a recessive autoinflammatory disorder. The balance between the pro-inflammatory cytokine IL-1 $\beta$  and its receptor antagonist IL-1RA plays an important role in the development of FMF. In order to determine a possible association of polymorphisms in IL-1 $\beta$  and IL-1RA genes with occurrence and/or severity of the disease, 42 genetically confirmed FMF patients and 42 controls were genotyped for IL-1 $\beta$ (-511C/T), IL-1 $\beta$ (-31T/C), IL1-1 $\beta$ (+3954T/C) and IL-1RA VNTR polymorphisms. IL-1 $\beta$  and IL-1RA levels were evaluated by multiplex ELISA in supernatants of PBMC cultures of 30 FMF patients with and without 24h stimulation of monocytes by LPS. The CC genotype and C allele at positions -31 and + 3954 of IL-1 $\beta$  gene were more frequent in FMF patients than in controls. FMF patients carriers of IL-1 $\beta$ (-31) CC genotype were associated with a 2-fold increase in LPS-induced IL-1 $\beta$  secretion as well as a higher disease severity score ( $11.2 \pm 2.9$ ) when compared to patients carrying the TC and TT genotypes ( $6.1 \pm 2.1$  and  $4.5 \pm 2.4$ , respectively). These results indicate that IL-1 $\beta$  gene polymorphisms at positions -31 and + 3954 may be associated with an increased risk for FMF. IL-1 $\beta$ (-31) contributes also to the severity of the disease, probably by modulating IL-1 $\beta$  synthesis.

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DOI: 10.1016/j.ejmg.2015.11.007

PMID: 26585190 [Indexed for MEDLINE]

1424. J Am Acad Dermatol. 2016 Jan;74(1):186-9. doi: 10.1016/j.jaad.2015.10.007. Epub 2015 Nov 14.

Failure to thrive, interstitial lung disease, and progressive digital necrosis with onset in infancy.

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Key teaching points • SAVI is a recently described interferonopathy resulting from constitutive action of STING and up-regulation of IFN- $\beta$  signaling. • SAVI is characterized by facial erythema with telangiectasia, acral/cold-sensitive tissue ulceration and amputations, and interstitial lung disease. It has overlapping features with Aicardi-Goutières syndrome and familial chilblain lupus. • Traditional immunosuppressive medications and biologic therapies appear to be of limited benefit, but JAK inhibitors may impact disease progression.

Published by Elsevier Inc.

DOI: 10.1016/j.jaad.2015.10.007

1425. Clin Rheumatol. 2016 Jan;35(1):19-23. doi: 10.1007/s10067-015-3120-x. Epub 2015 Nov 19.

Efficacy and safety of combination therapy for preventing bone damage in rheumatoid arthritis.

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The main outcomes of the therapies for rheumatoid arthritis (RA) must be preventing, or at least lessening, the development of structural damage. Biological disease-modifying anti-rheumatic drugs (bDMARDs), targeting tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) or other key steps (IL-1, IL-6, T cells, B cells) in the pathogenesis of RA, have given clues to be effective and safe as treatments for RA, being capable of improving disease activity, ameliorating functional ability and halting joint damage. A large body of evidence, stemming from randomized clinical trials, observational studies, and registries, has shown that the beneficial effects of the bDMARDs become optimal when combined with synthetic (s)-DMARDs, mainly methotrexate (MTX). Despite combination therapy is advocated by the international guidelines for the management of RA, data from the daily standard of care indicate that almost one third of RA patients are treated with bDMARDs as monotherapy. Many reasons may be taken into account to explain this gap from official recommendations, among which the fact that in real-life



settings, the assessment of clinical outcomes is exclusively based on clinical indices, disregarding the evolution of bone damage. Furthermore, some bDMARDs have been launched in the market with the official approval to be used as monotherapy. But even for the latter, there is no conclusive proof that monotherapy regimen is comparable to co-therapy with MTX in preventing articular damage. In conclusion, the most recent published data show that combination therapy with bDMARDs and MTX represents the best therapeutic option for the treatment of RA since it can stop or at least slow the progression of disabling structural damage.

DOI: 10.1007/s10067-015-3120-x

PMID: 26581205 [Indexed for MEDLINE]

1426. Clin Exp Rheumatol. 2015 Nov-Dec;33(6):906-9. Epub 2015 Nov 17.

Efficacy of intravenous cyclosporine in a case of cytophagic histiocytic panniculitis complicated by haemophagocytic syndrome after visceral leishmania infection.

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Cytophagic histiocytic panniculitis (CHP) is a rare panniculitis characterized by systemic features, due to histiocytic infiltration along with haemophagocytosis, which may also appear in bone marrow, spleen, lymph nodes, and liver.

Haemophagocytic lymphohistiocytosis (HLH) is a group of autoinflammatory disorders, which include macrophage activation syndrome, sometimes observed in the course of systemic autoimmune diseases, such as juvenile chronic

polyarthritis, systemic lupus erythematosus or vasculitis, and infection-associated haemophagocytic syndrome; if not promptly recognised and treated, HLH can be fatal. Visceral leishmaniasis (VL) is a systemic disease caused by different forms of *Leishmania* spp., an intracellular protozoa. VL is endemic in tropical countries such as in the Middle East and the Mediterranean. The typical clinical and laboratory features are fever, hepato-splenomegaly, hypergammaglobulinaemia and pancytopenia. The features of VL may mimic some haematologic diseases. We report a case of cytophagic histiocytic panniculitis and HLH, triggered by a previous visceral leishmania infection. Cyclosporine was quickly effective in this case, after failure of high-dose glucocorticoids, anakinra and etoposide.

PMID: 26575530 [Indexed for MEDLINE]

1427. Immunol Invest. 2015;44(8):777-802. doi: 10.3109/08820139.2015.1093912.

Immunotherapeutic Biologic Agents in Autoimmune and Autoinflammatory Diseases.

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In recent decades, innovative strategies to treat patients with inflammatory, immunologically based diseases have advanced in concert with our increased understanding of molecular immunology. Recognition of the spectrum and pathophysiology of autoimmune and autoinflammatory disorders has allowed for the development of cutting-edge therapies for such patients. In this review, key immunotherapeutic approaches for treating inflammatory autoimmune disorders, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), as well as genetic autoinflammatory diseases, such as cryopyrin associated periodic syndromes, are addressed. Indications, risks and additional considerations in the use of these agents are reviewed.

DOI: 10.3109/08820139.2015.1093912

1428. Med Sci Monit. 2015 Nov 17;21:3547-54.

# Killer Cell Immunoglobulin-Like Receptor (KIR) Genotype Distribution in Familial Mediterranean Fever (FMF) Patients.

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**BACKGROUND** Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disease predominantly affecting Mediterranean populations. The gene associated with FMF is the MEFV gene, which encodes for a protein called pyrin. Mutations of pyrin lead to uncontrolled attacks of inflammation, and subclinical inflammation continues during attack-free intervals. Killer cell immunoglobulin-like receptor (KIR) genes encode HLA class I receptors expressed by NK cells. The aim this study was to look for immunogenetic determinants in the pathogenesis of FMF and find out if KIR are related to susceptibility to disease or complications like renal amyloidosis. **MATERIAL AND METHODS** One hundred and five patients with FMF and 100 healthy individuals were involved in the study. Isolated DNA from peripheral blood was amplified by sequence specific PCR probes and analyzed by Luminex for KIR genotypes. Fisher Exact test was used to evaluate the variation of KIR gene distribution. **RESULTS** All patients and healthy controls expressed the framework genes. An activator KIR gene, KIR2DS2, was significantly more frequent in FMF patients ( $p=0.036$ ). Renal amyloidosis and presence of arthritis were not associated with KIR genes and genotype. KIR3DL1 gene was more common in patients with high serum CRP ( $p=0.016$ ). **CONCLUSIONS** According to our findings, we suggest that presence of KIR2DS2, which is an activator gene for NK

cell functions, might be related to the autoinflammation in FMF. The potential effect of KIR genes on amyloidosis and other clinical features requires studies with larger sample sizes.

PMCID: PMC4655612

PMID: 26574972 [Indexed for MEDLINE]

1429. Curr Med Chem. 2016;23(1):60-86.

Colchicine, Biologic Agents and More for the Treatment of Familial Mediterranean Fever. The Old, the New, and the Rare.

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Familial Mediterranean Fever (FMF) is a rare autosomal recessive autoinflammatory disorder involving the innate immunity and affecting almost exclusively populations with Mediterranean origin. Clinical features include recurrent episodes of fever, leukocytosis, serositis (peritonitis or pleuritis, arthritis), myalgia or erysipelas-like skin lesions, lasting 12-72 hrs. The MEFV gene mutations on chromosome 16p13.3 encodes the abnormal pyrin (marenostrin), a protein expressed in granulocytes, monocytes, serosal and synovial fibroblasts and involved in the activation of caspase-1 and the processing and release of active pro-inflammatory IL-1 $\beta$ . Since the first report in 1972, maintenance therapy with colchicine, a tricyclic neutral alkaloid, remains the mainstay of treatment in symptomatic FMF patients since it reduces the disease activity and prevents the development of secondary amyloidosis and renal damage. Adjunctive symptomatic therapy to colchicine includes nonsteroidal antiinflammatory drugs and corticosteroids. In a small group of colchicine-intolerant or colchicine-resistant FMF patients, alternative treatments must be considered. Evolving experiences have focussed on the potential effectiveness of biologic agents working as TNF- $\alpha$  inhibitors (etanercept, infliximab), IL-1 trap (Rilonacept), IL-1 inhibitors (Anakinra, Canakinumab) and IL-6 receptor antibody (Tocilizumab). Interferon- $\alpha$  and thalidomide have also been employed in FMF

patients. Still, clinical trials are mainly uncontrolled and restricted to few cases, thus requiring definitive conclusions. Old, and new treatments are discussed in the rare FMF disease, with the concept that any ideal treatment has to stand the test of time.

PMID: 26572612 [Indexed for MEDLINE]

1430. J Rheumatol. 2016 Jan;43(1):154-60. doi: 10.3899/jrheum.141249. Epub 2015 Nov 15.

Performance of Different Diagnostic Criteria for Familial Mediterranean Fever in Children with Periodic Fevers: Results from a Multicenter International Registry.

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**OBJECTIVE:** Our aims were to validate the pediatric diagnostic criteria in a large international registry and to compare them with the performance of previous criteria for the diagnosis of familial Mediterranean fever (FMF).

**METHODS:** Pediatric patients with FMF from the Eurofever registry were used for the validation of the existing criteria. The other periodic fevers served as controls: mevalonate kinase deficiency (MKD), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndrome (CAPS), aphthous stomatitis, pharyngitis, adenitis syndrome (PFAPA), and undefined periodic fever from the same registry. The performances of Tel Hashomer, Livneh, and the Yalcinkaya-Ozen criteria were assessed.

**RESULTS:** The FMF group included 339 patients. The control group consisted of 377 patients (53 TRAPS, 45 MKD, 32 CAPS, 160 PFAPA, 87 undefined periodic fevers). Patients with FMF were correctly diagnosed using the Yalcinkaya-Ozen criteria with a sensitivity rate of 87.4% and a specificity rate of 40.7%. On the other hand, Tel Hashomer and Livneh criteria displayed a sensitivity of 45.0 and 77.3%, respectively. Both of the latter criteria displayed a better specificity than the Yalcinkaya-Ozen criteria: 97.2 and 41.1% for the Tel Hashomer and Livneh criteria, respectively. The overall accuracy for the Yalcinkaya-Ozen criteria was 65 and 69.6% (using 2 and 3 criteria), respectively. Ethnicity and residence had no effect on the performance of the Yalcinkaya-Ozen criteria.

**CONCLUSION:** The Yalcinkaya-Ozen criteria yielded a better sensitivity than the other criteria in this international cohort of patients and thus can be used as a tool for FMF diagnosis in pediatric patients from either the European or eastern Mediterranean region. However, the specificity was lower than the previously suggested adult criteria.

DOI: 10.3899/jrheum.141249

PMID: 26568587 [Indexed for MEDLINE]

1431. Eur J Pediatr. 2016 May;175(5):735-40. doi: 10.1007/s00431-015-2668-4. Epub 2015 Nov 14.

CANDLE syndrome: chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature-a rare case with a novel mutation.

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We described herein a patient with chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome and a novel mutation in PSMB8 gene. This patient had multiple visceral inflammatory involvements, including rare manifestations, such as Sweet syndrome and pericarditis. A 3-year-old male, Caucasian, was born to consanguineous healthy parents. At the age of 11 months, he presented daily fever (temperature >40 °C), irritability, hepatomegaly, splenomegaly; and tender and itching, erythematous papular and edematous plaque lesions. Echocardiogram showed mild pericarditis. Skin biopsy revealed a neutrophil infiltrate without vasculitis suggesting Sweet syndrome. Mutational screening of PSMB8 gene revealed homozygous c.280G>C, p.A94P mutation. He responded partially to high doses of oral glucocorticoid and intravenous methylprednisolone. Colchicine, azathioprine, methotrexate, cyclosporine, and intravenous immunoglobulin were not efficacious. At the age of 3 years and 1 month, tocilizumab was administered resulting in remission of daily fever and irritability. However, there was no improvement of the skin tenderness and itching lesions. CONCLUSION: A new mutation in a CANDLE syndrome patient was

reported with pericarditis and mimicking Sweet syndrome. The disease manifestations were refractory to immunosuppressive agents and partially responsive to tocilizumab therapy.

WHAT IS KNOWN: • Proteasome-associated autoinflammatory syndromes (PRAAS) include four rare diseases. • Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome was seldom reported. What is New: • We described a Brazilian patient with CANDLE syndrome possessing a novel mutation in the PSMB8 gene. • This patient had multiple visceral inflammatory involvements, including rare manifestations, such as pericarditis and mimicking Sweet syndrome.

DOI: 10.1007/s00431-015-2668-4

PMID: 26567544 [Indexed for MEDLINE]

1432. World J Clin Pediatr. 2015 Nov 8;4(4):106-12. doi: 10.5409/wjcp.v4.i4.106. eCollection 2015 Nov 8.

Fever tree revisited: From malaria to autoinflammatory diseases.

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Over the centuries the idea of recurrent fevers has mainly been associated with malaria, but many other fevers, such as typhoid and diphtheria were cause for concern. It is only in recent times, with the more severe forms of fever from infectious origin becoming less frequent or a cause for worry that we started noticing recurrent fevers without any clear infectious cause, being described as having a pathogenesis of autoinflammatory nature. The use of molecular examinations in many cases can allow a diagnosis where the cause is monogenic. In other cases, however the pathogenesis is likely to be multifactorial and the diagnostic-therapeutic approach is strictly clinical. The old fever tree paradigm developed to describe fevers caused by malaria has been revisited here to describe today's periodic fevers from the periodic fever adenitis pharyngitis aphthae syndrome to the more rare autoinflammatory diseases. This model may allow us to place cases that are yet to be identified which are likely to be of



multifactorial origin.

DOI: 10.5409/wjcp.v4.i4.106

PMCID: PMC4637800

PMID: 26566482

1433. Child Neuropsychol. 2017 Apr;23(3):332-342. doi: 10.1080/09297049.2015.1108397. Epub 2015 Nov 12.

Evaluation of executive functions in children and adolescents with familial Mediterranean fever.

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The aim of the present study was to investigate neuropsychological test performance in children and adolescents with familial Mediterranean fever (FMF). A total of 88 children and adolescents aged 8 to 17 years were included, 52 with FMF and 36 healthy controls. After the participants were administered the Children Depression Inventory (CDI) and the Screen for Child Anxiety Related Emotional Disorders (SCARED), they completed the battery tests of the Central Nervous System Vital Signs (CNSVS), a neurocognitive test battery, via computer. The battery calculates seven domain scores (Memory, Psychomotor Speed, Processing Speed, Reaction Time, Complex Attention, Executive Function, and Cognitive Flexibility) and a summary score (Neurocognition Index [NCI]). A statistically significant difference between the FMF and control groups was found in six out of seven domains, where the scores of the participants with FMF were found to be significantly lower than those of the control participants ( $p < .05$ ). Although the mean Reaction Time score of the participants with FMF was found to be lower than that of the control participants, the finding was not statistically significant ( $p > .05$ ). The mean CDI and SCARED scores of the participants with

FMF were found to be significantly higher than those of the control participants ( $p < .05$ ). Low scores in the Processing Speed and Psychomotor Speed domains of the CNSVS were significantly correlated with higher SCARED scores ( $r = -.37$ ,  $p = .01$ ). Impaired cognitive functions should be taken into consideration in children and adolescents with FMF when assessing and managing this population.

DOI: 10.1080/09297049.2015.1108397

PMID: 26563732 [Indexed for MEDLINE]

1434. *Pediatr Nephrol*. 2016 Apr;31(4):633-40. doi: 10.1007/s00467-015-3249-5. Epub 2015 Nov 12.

Anti-interleukin 1 treatment in secondary amyloidosis associated with autoinflammatory diseases.

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**BACKGROUND:** Amyloidosis may complicate autoinflammatory diseases (AID). We aimed to evaluate the renal biopsy findings, and clinical and laboratory parameters in patients with AID-associated amyloidosis who have responded to anti-interleukin 1(IL1) treatment.

**METHODS:** Two children with systemic juvenile idiopathic arthritis and one with cryopyrin-associated periodic syndrome diagnosed as having reactive amyloidosis were treated with anti-IL1 drugs. The renal histopathological findings at the time of diagnosis of amyloidosis and after the onset of anti-IL1 were evaluated according to the amyloid scoring/grading system.

**RESULTS:** The median age of disease onset and diagnosis of amyloidosis were 3 and 12 years, respectively. Anakinra was started in all; however, anakinra caused a

local cutaneous reaction in one, thus canakinumab was commenced. Proteinuria improved in all. Control renal biopsies were performed a median of 3 years after the first biopsies. The renal amyloid prognostic score did not improve in patient 1, and progressed in patients 2 and 3. The renal amyloid grade progressed in patient 2.

**CONCLUSIONS:** This is the first series demonstrating progression of renal tissue damage after the improvement of proteinuria with anti-IL 1 in AID-associated amyloidosis. Anti-IL1 drugs are important to prevent further amyloid accumulation; however, new treatment strategies are needed to target the amyloid deposits.

DOI: 10.1007/s00467-015-3249-5

PMID: 26563115 [Indexed for MEDLINE]

1435. Nefrologia. 2016 May-Jun;36(3):331-2. doi: 10.1016/j.nefro.2015.07.010. Epub 2015 Nov 11.

Complete remission of nephrotic syndrome in a woman with renal amyloidosis due to familial mediterranean fever.

[Article in English, Spanish]

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DOI: 10.1016/j.nefro.2015.07.010

PMID: 26560399 [Indexed for MEDLINE]

1436. Medicine (Baltimore). 2015 Nov;94(45):e1818. doi: 10.1097/MD.0000000000001818.

Paradoxical Autoinflammatory Skin Reaction to Tumor Necrosis Factor Alpha

# Blockers Manifesting as Amicrobial Pustulosis of the Folds in Patients With Inflammatory Bowel Diseases.

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The therapy of inflammatory bowel disease, particularly with tumor necrosis factor (TNF) blockers, may be associated with a number of cutaneous adverse effects, including psoriasis-like, eczema-like, and lichenoid eruptions. Other rare skin complications are neutrophilic dermatoses such as amicrobial pustulosis of the folds (APF), which is a chronic relapsing pustular disorder classified in this spectrum. The authors analyzed clinical, histopathologic, and cytokine expression profiles of 3 inflammatory bowel disease patients with APF triggered by adalimumab (patient 1) and infliximab (patients 2 and 3). All 3 patients presented with sterile pustules involving the cutaneous folds, genital regions, and scalp 6 months after starting adalimumab (patient 1) and 9 months after starting infliximab (patients 2 and 3). Histology was characterized by epidermal spongiform pustules with a dermal neutrophilic and lymphocytic infiltrate. Tumor necrosis factor blocker withdrawal associated with topical and systemic corticosteroids induced complete remission of APF in all 3 patients. The expressions of interleukin (IL)-1 beta and its receptors as well as TNF alpha and its receptors were significantly higher in APF than in controls. Also IL-17, leukocyte selectin, and chemokines, such as IL-8, [C-X-C motif] chemokine ligand 1/2/3 (C = cysteine, X = any amino acid), [C-X-C motif] chemokine ligand 16 (C = cysteine, X = any amino acid), and RANTES (regulated on activation, normal T cell expressed and secreted) were significantly overexpressed. Finally, the authors found significant overexpression of both metalloproteinases 2/9 and their inhibitors 1/2. The observation of 3 patients with APF following anti-TNF therapy expands not only the clinical context of APF but also the spectrum of anti-TNF side effects. Overexpression of cytokines/chemokines and molecules amplifying the inflammatory network supports the view that APF is autoinflammatory in origin.

DOI: 10.1097/MD.0000000000001818

PMCID: PMC4912246

1437. Autoimmun Rev. 2016 Feb;15(2):184-90. doi: 10.1016/j.autrev.2015.11.002. Epub 2015 Nov 7.

Impact of a multidisciplinary approach in enteropathic spondyloarthritis patients.

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Spondyloarthritis (SpA) and inflammatory bowel disease (IBD) are chronic autoinflammatory diseases that partially share the genetic predisposition and the unchecked inflammatory response linking the gut to the joints. The coexistence of both conditions in patients and the increased cross-risk ratios between SpA and IBD strongly suggest a shared pathophysiology. The prevalence of Enteropathic-related Spondyloarthritis (ESpA) in IBD patients shows a wide variation and may be underestimated. It is well accepted that the management of joint pain requires rheumatological expertise in conjunction with gastroenterologist assessment. In this view, we aimed at assessing, in a prospective study performed in a combined Gastro-Intestinal and Rheumatologic "GI-Rhe" clinic: (1) the prevalence of ESpA and other rheumatologic diseases in IBD patients with joint pain; (2) the features of the ESpA population; and (3) the diagnostic delay and the potential impact of the combined assessment. From November 2012 to December 2014, IBD patients with joint pain referring to a dedicated rheumatologist by the IBD-dedicated gastroenterologist were enrolled. Clinical and biochemical evaluations, joint involvement and disease activity assessment, diagnostic delay, and treatment were recorded. IBD patients (n=269)

with joint pain were jointly assessed in the "GI-Rhe" Unit. A diagnosis of ESpA was made in 50.5% of IBD patients with joint pain. ESpA patients showed a peripheral involvement in 53% of cases, axial in 20.6% and peripheral and axial in 26.4% of cases. ESpA patients had a higher prevalence of other autoimmune extra-intestinal manifestations and received more anti-TNF treatment compared with IBD patients. A mean diagnostic delay of 5.2 years was revealed in ESpA patients. Patients with joint disease onset in the 2002-2012 decade had reduced diagnostic delay compared with those with onset in the 1980-1990 and 1991-2001 decades. Diagnostic delay was further reduced for patients with joint onset in the last two years in conjunction with the establishment of the GI-Rhe clinic. Multidisciplinary approach improved management of rheumatic disorders in IBD patients allowing a more comprehensive care.

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DOI: 10.1016/j.autrev.2015.11.002

PMID: 26554932 [Indexed for MEDLINE]

1438. *Pediatr Rheumatol Online J.* 2015 Nov 10;13(1):45. doi: 10.1186/s12969-015-0044-6.

Intestinal malrotation as a misdiagnosis of pediatric colchicine resistant familial Mediterranean fever.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is a disorder characterized by recurrent attacks of fever and serosal inflammation, particularly abdominal pain. Other disease processes, including medical and surgical emergencies, may mimic FMF, especially in atypical cases.

**CASE PRESENTATION:** We present a case of an adolescent male, referred to us with a diagnosis of colchicine resistant FMF, ultimately diagnosed with intestinal malrotation and recurrent volvulus.

CONCLUSIONS: In atypical presentations of FMF with potential "red flags", a thorough patient history is extremely important and should result in prompt referral for the appropriate diagnostic tests.

DOI: 10.1186/s12969-015-0044-6

PMCID: PMC4641426

PMID: 26554556 [Indexed for MEDLINE]

1439. Cell Mol Immunol. 2016 Mar;13(2):148-59. doi: 10.1038/cmi.2015.95. Epub 2015 Nov 9.

Molecular mechanisms regulating NLRP3 inflammasome activation.

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Inflammasomes are multi-protein signaling complexes that trigger the activation of inflammatory caspases and the maturation of interleukin-1 $\beta$ . Among various inflammasome complexes, the NLRP3 inflammasome is best characterized and has been linked with various human autoinflammatory and autoimmune diseases. Thus, the NLRP3 inflammasome may be a promising target for anti-inflammatory therapies. In this review, we summarize the current understanding of the mechanisms by which the NLRP3 inflammasome is activated in the cytosol. We also describe the binding partners of NLRP3 inflammasome complexes activating or inhibiting the inflammasome assembly. Our knowledge of the mechanisms regulating NLRP3 inflammasome signaling and how these influence inflammatory responses offers further insight into potential therapeutic strategies to treat inflammatory diseases associated with dysregulation of the NLRP3 inflammasome.

DOI: 10.1038/cmi.2015.95

PMCID: PMC4786634

PMID: 26549800 [Indexed for MEDLINE]

1440. Presse Med. 2015 Dec;44(12 Pt 1):1266-75. doi: 10.1016/j.lpm.2015.09.012. Epub 2015 Nov 6.

[Recurrent fevers in childhood].

[Article in French]

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Recurrent fevers are defined as multiple stereotypical febrile episodes separated by spontaneous symptom-free intervals and occurring for months and years. Hereditary recurrent fevers are rare prototype Mendelian diseases due to inherited mutations in genes encoding partners of the innate immunity. Recurrent episodes of fever plus acute features of inflammation starting during childhood with family history are the main clues for suspecting HRF. Their common associated complication is AA amyloidosis. The diagnosis is made on clinical grounds but the genetic diagnosis may contribute in most cases of monogenic hereditary recurrent fevers. Recurrent fevers must be distinguished from intermittent fevers, mostly infectious, characterized by variation in associated symptoms from episode-to-episode and without periodicity.

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DOI: 10.1016/j.lpm.2015.09.012

PMID: 26549686 [Indexed for MEDLINE]



1441. Med Arch. 2015 Aug;69(4):269-70. doi: 10.5455/medarh.2015.69.269-270. Epub 2015 Aug 4.

Patient with FMF and Triple MEFV Gene Mutations.

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**INTRODUCTION:** Familial Mediterranean fever (FMF) is the most common auto-inflammatory disease with monogenic (MEFV- gene) inherited pattern. It mainly affects ethnic groups living along the eastern Mediterranean Sea: Turks, Sephardic Jews, Armenians, and Arabs [1]. Today FMF is not rare disease in other Mediterranean ethnicities, such as Greeks, Italians, and Iranians.

**CASE REPORT:** Here we report a child with complex allele mutations E148Q/V726A/R761H, whilst, whose mother showed E148Q/V726A and his father had R761H/wt in analysis. The severity of the disease and genotype-phenotype correlation of patient showed no significant differences with his mother and other patients with the same two mutations, V726A/R761H, E148Q/V726A, and E148Q/R761H.

**CONCLUSION:** This type of mutation is the first report of triple mutations in FMF patients with no specific phenotype correlation.

DOI: 10.5455/medarh.2015.69.269-270

PMCID: PMC4610602

PMID: 26543317 [Indexed for MEDLINE]

1442. Value Health. 2015 Nov;18(7):A676. doi: 10.1016/j.jval.2015.09.2002. Epub 2015 Oct 20.

The Rheumatologist's Perspective In Diagnostic Course and Management of Familial Mediterranean Fever.

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DOI: 10.1016/j.jval.2015.09.2002

PMID: 26533793

1443. Value Health. 2015 Nov;18(7):A666. doi: 10.1016/j.jval.2015.09.2427. Epub 2015 Oct 20.

Cost of Familial Mediterranean Fever (Fmf) Disease In Turkey.

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DOI: 10.1016/j.jval.2015.09.2427

PMID: 26533737

1444. Pediatr Rheumatol Online J. 2015 Nov 4;13(1):43. doi: 10.1186/s12969-015-0041-9.

Early detection of sensorineural hearing loss in Muckle-Wells-syndrome.

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**BACKGROUND:** Muckle-Wells-syndrome (MWS) is an autoinflammatory disease characterized by systemic and organ-specific inflammation due to excessive interleukin (IL)-1 release. Inner ear inflammation results in irreversible sensorineural hearing loss, if untreated. Early recognition and therapy may prevent deafness. The aims of the study were to characterize the spectrum of

hearing loss, optimize the otologic assessment for early disease and determine responsiveness to anti-IL-1-therapy regarding hearing.

**METHODS:** A single center prospective cohort study of children and adults with MWS was performed. Standardized clinical, laboratory and otologic assessments including standard pure tone audiometry, additional high tone thresholds, vestibular organ testing, tinnitus evaluation and functional disability classes were determined serially. Pure-tone-average models were developed and evaluated. Risk factors for hearing loss and the impact of anti-IL-1 treatment were determined.

**RESULTS:** A total of 23 patients with genetically confirmed MWS were included, of whom 63 % were females; 52 % were children. At baseline all patients had active MWS; 91 % reported clinically impaired hearing with 74 % having an abnormal standard assessment (0.5-4 kHz). In contrast, high frequency pure tone averages (HF-PTA) were abnormal in all symptomatic patients including those with early hearing loss (sensitivity 100 %). Females were at highest risk for hearing loss even after adjustment for age ( $p = 0.008$ ). Treatment with IL-1 blockade resulted in improved or stable hearing in 91 % of patients.

**CONCLUSIONS:** Early inner ear inflammation in MWS primarily affects the high frequencies, beyond the range of standard otologic assessment tools. The HF-PTA is a sensitive tool to detect imminent hearing loss and monitor treatment response.

DOI: 10.1186/s12969-015-0041-9

PMCID: PMC4632838

PMID: 26531310 [Indexed for MEDLINE]

1445. Rinsho Byori. 2015 May;63(5):598-604.

[Diagnosis and Clinical Examination of Autoinflammatory Syndrome].

[Article in Japanese]

Ida H.

Autoinflammatory syndrome is characterized by: 1) episodes of seemingly unprovoked inflammation, 2) the absence of a high titer of autoantibodies or auto-reactive T cells, and 3) an inborn error of innate immunity. In this decade, many autoinflammatory syndromes have been reported in Japan, and so many Japanese

physicians have become aware of this syndrome. Monogenic autoinflammatory syndromes present with excessive systemic inflammation including fever, rashes, arthritis, and organ-specific inflammation and are caused by defects in single genes encoding proteins that regulate innate inflammatory pathways. The main monogenic autoinflammatory syndromes are familial Mediterranean fever (FMF), TNF receptor-associated periodic syndrome (TRAPS), mevalonate kinase deficiency (MKD), cryopyrin-associated periodic syndrome (CAPS), Blau syndrome, and pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome. We diagnosed these syndromes as clinical manifestations and performed genetic screening. Many serum cytokines are elevated in patients with autoinflammatory syndrome, but this is not disease-specific. The pathogeneses of many autoinflammatory syndromes are known to be related to inflammasomes, which are multiprotein complexes that serve as a platform for caspase 1 activation and interleukin-1 $\beta$  (IL-1 $\beta$ ) and IL-18 maturation. Especially, NLRP3 inflammasomes may play a crucial role in the initiation and progression of FMF and CAPS. In the future, we hope to discover new clinical examinations which can provide evidence of inflammasome activation independent of genetic screening. In this issue, I introduce autoinflammatory syndromes and discuss the diagnosis and clinical examination of these syndromes.

PMID: 26524899 [Indexed for MEDLINE]

1446. J Clin Invest. 2015 Nov 2;125(11):4196-211. doi: 10.1172/JCI81260. Epub 2015 Oct 20.

Additive loss-of-function proteasome subunit mutations in CANDLE/PRAAS patients promote type I IFN production.

Brehm A, Liu Y, Sheikh A, Marrero B, Omoyinmi E, Zhou Q, Montealegre G, Biancotto A, Reinhardt A, Almeida de Jesus A, Pelletier M, Tsai WL, Remmers EF, Kardava L, Hill S, Kim H, Lachmann HJ, Megarbane A, Chae JJ, Brady J, Castillo RD, Brown D, Casano AV, Gao L, Chapelle D, Huang Y, Stone D, Chen Y, Sotzny F, Lee CC, Kastner DL, Torrelo A, Zlotogorski A, Moir S, Gadina M, McCoy P, Wesley R, Rother KI, Hildebrand PW, Brogan P, Krüger E, Aksentijevich I, Goldbach-Mansky R.

Erratum in

J Clin Invest. 2016 Feb;126(2):795. Rother, Kristina [corrected to Rother, Kristina I].

Autosomal recessive mutations in proteasome subunit  $\beta$  8 (PSMB8), which encodes the inducible proteasome subunit  $\beta$ 5i, cause the immune-dysregulatory disease chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE), which is classified as a proteasome-associated autoinflammatory syndrome (PRAAS). Here, we identified 8 mutations in 4 proteasome genes, PSMA3 (encodes  $\alpha$ 7), PSMB4 (encodes  $\beta$ 7), PSMB9 (encodes  $\beta$ 1i), and proteasome maturation protein (POMP), that have not been previously associated with disease and 1 mutation in PSMB8 that has not been previously reported. One patient was compound heterozygous for PSMB4 mutations, 6 patients from 4 families were heterozygous for a missense mutation in 1 inducible proteasome subunit and a mutation in a constitutive proteasome subunit, and 1 patient was heterozygous for a POMP mutation, thus establishing a digenic and autosomal dominant inheritance pattern of PRAAS. Function evaluation revealed that these mutations variably affect transcription, protein expression, protein folding, proteasome assembly, and, ultimately, proteasome activity. Moreover, defects in proteasome formation and function were recapitulated by siRNA-mediated knockdown of the respective subunits in primary fibroblasts from healthy individuals. Patient-isolated hematopoietic and nonhematopoietic cells exhibited a strong IFN gene-expression signature, irrespective of genotype. Additionally, chemical proteasome inhibition or progressive depletion of proteasome subunit gene transcription with siRNA induced transcription of type I IFN genes in healthy control cells. Our results provide further insight into CANDLE genetics and link global proteasome dysfunction to increased type I IFN production.

DOI: 10.1172/JCI81260

PMCID: PMC4639987

PMID: 26524591 [Indexed for MEDLINE]

1447. Immun Ageing. 2015 Oct 31;12:19. doi: 10.1186/s12979-015-0047-7. eCollection 2015.

NLR family pyrin domain containing 3 (NLRP3) inflammasome gene polymorphism rs7512998 (C>T) predicts aging-related increase of blood pressure, the TAMRISK study.

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**BACKGROUND:** The activation of NLR family pyrin domain containing 3 (NLRP3) inflammasome by cellular stress leads to activation of the inflammasome, and NLRP3 gene polymorphisms have been associated with autoinflammatory diseases. Inflammasomes have also been implicated in the initiation or progression of metabolic disorders such as atherosclerosis, type 2 diabetes and obesity. The association of NLRP3 genetic variant rs7512998 with blood pressure and hypertension was studied in a 50-year-old Finnish cohort with a subpopulation who had available data on blood pressure measurements also at the age of 45 years.

**RESULTS:** NLRP3 gene polymorphism rs7512998 C-allele was associated with higher systolic ( $p = 0.006$ ) and diastolic ( $p = 0.011$ ) blood pressure compared to the TT-genotype carriers in 50-year-old subjects. In addition, by analysis of variance for repeated measures between ages of 45- and 50 years there was a significant time by genotype interaction; blood pressure increased more in subjects with the C-allele both in systolic ( $p = 0.035$ ) and diastolic ( $p = 0.012$ ) values. However, no association with diagnosed hypertension was found.

**CONCLUSION:** We report for the first time that NLRP3 gene polymorphism rs7512998 was associated with systolic and diastolic blood pressure in 50-year-old subjects. In addition, an effect of this variation upon blood pressure was seen in these same subjects in a 5-year follow-up from a 45-year-old cohort to 50 years of age.

DOI: 10.1186/s12979-015-0047-7

PMCID: PMC4628348

PMID: 26523150

1448. Arch Rheumatol. 2015 Nov 3;31(1):87-90. doi: 10.5606/ArchRheumatol.2016.5671. eCollection 2016 Mar.

Coexistence of Familial Mediterranean Fever With Ankylosing Spondylitis and Sjogren's Syndrome: A Rare Occurrence.

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Familial Mediterranean fever is an autosomal recessive disease characterized by recurrent episodes of fever, peritonitis, synovitis, pleuritis, and erysipelas-like skin lesions. Sjogren's syndrome is a chronic autoimmune disorder characterized by dry eyes, dry mouth, and musculoskeletal involvement. Ankylosing spondylitis is an autoinflammatory rheumatic disease which affects mainly the axial skeleton. To our knowledge, coexistence of familial Mediterranean fever with ankylosing spondylitis and Sjogren's syndrome has not been reported previously in the literature. In this article, we report an unusual case of three autoinflammatory diseases in one patient.

DOI: 10.5606/ArchRheumatol.2016.5671

PMCID: PMC5827872

PMID: 29900978

Conflict of interest statement: Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

1449. Arch Rheumatol. 2015 Nov 3;31(2):112-120. doi: 10.5606/ArchRheumatol.2016.5628. eCollection 2016 Jun.

Glutathione-S-Transferase Variants are not Associated With Increased Carotid Intima-Media Thickness in Turkish Familial Mediterranean Fever Patients.

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**Objectives:** This study aims to evaluate the carotid intima-media thickness (CIMT) in patients diagnosed with Familial Mediterranean fever (FMF) and investigate whether there is a relationship between glutathione-S-transferase (GST) gene polymorphisms and CIMT.

**Patients and methods:** Sixty FMF patients (17 males, 43 females; mean age:  $31.43 \pm 11.36$  years; range 18 to 45 years) and 60 healthy controls (22 males, 38 females; mean age:  $29.8 \pm 5.82$  years; range 18 to 40 years) were enrolled in this study. Polymerase chain reaction-restriction fragment length polymorphism methods were carried out to assess GST polymorphisms. CIMT was measured by carotid ultrasonography. Biochemical parameters were also evaluated using biochemical methods.

**Results:** Right and left CIMT of FMF patients were statistically significantly higher than that of control group (CIMT right  $p=0.001$  and CIMT left:  $p=0.033$ ). There was no significant association in terms of GST polymorphisms between FMF and control groups. No significant association was observed between GST polymorphisms and CIMT. Low density lipoprotein, erythrocyte sedimentation rate, and fibrinogen levels were significantly higher in the patient group ( $p<0.05$ ). The difference between groups was not significant in terms of other biochemical parameters ( $p>0.05$ ).

**Conclusion:** Although no significant association was observed between GST polymorphisms and CIMT in FMF patients and controls, CIMT was statistically significantly higher in FMF patients compared to controls.

DOI: 10.5606/ArchRheumatol.2016.5628

PMCID: PMC5827825

PMID: 29900931

**Conflict of interest statement:** Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

1450. Clin Exp Rheumatol. 2015 Nov-Dec;33(6):947-8. Epub 2015 Oct 30.

Efficacy and safety of abatacept in a patient with rheumatoid arthritis and concomitant *Staphylococcus aureus* osteomyelitis.

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PMID: 26517199 [Indexed for MEDLINE]

1451. BMJ Case Rep. 2015 Oct 29;2015. pii: bcr2015210513. doi: 10.1136/bcr-2015-210513.

Anti-interleukin 6 receptor therapy for hyper-IgD syndrome.

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Hyper-IgD syndrome (HIDS) is a rare, severe hereditary autoinflammatory disease characterised by periodic fevers, elevated serum IgD levels and a wide range of symptoms. Although a few randomised controlled trials have been performed in this disorder, there are no straightforward treatment protocols and none of the potential therapies are registered for this indication. We report a case of a young woman with severe HIDS who failed numerous therapies. Eventually, rational treatment with a monoclonal anti-interleukin 6 receptor antibody was initiated.

This therapy resulted in an impressive clinical improvement and reduction in the number of hospital admissions per year. This case report underlines the difficulty of finding a suitable treatment for rare, severe inflammatory diseases. Furthermore, we show that treating patients with targeted therapies may result in clinical benefit for the patient, as well as simultaneously teach us more about the pathophysiology of these rare, relatively understudied diseases.

2015 BMJ Publishing Group Ltd.

DOI: 10.1136/bcr-2015-210513

PMCID: PMC4636692

PMID: 26516243 [Indexed for MEDLINE]

1452. Mol Biol (Mosk). 2015 Sep-Oct;49(5):826-31. doi: 10.7868/S002689841505002X.

[Influence of M680I and M694V mutations on pyrin's domain B30.2 tertiary structure and its complex formation ability with caspase-1].

[Article in Russian]

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The M680I and M694V mutations located in the B30.2 pyrin domain are responsible for the manifestation of the most common forms of Familial Mediterranean fever. It is well known that a malfunction of the pyrin-caspase-1 complex is the main cause of inflammation in FMF. The purpose of this study was to identify possible changes in the tertiary structure of mutated B30.2 domain and to determine their potential consequences in the formation of the pyrin-caspase-1 complex. Using computer modeling, it was found that the above mutations change the tertiary structure of B30.2 domain, causing shifts of binding sites and altering the energy of interaction between B30.2 and caspase-1.

DOI: 10.7868/S002689841505002X

PMID: 26510601 [Indexed for MEDLINE]

1453. Turk J Gastroenterol. 2015 Nov;26(6):487-91. doi: 10.5152/tjg.2015.0223. Epub 2015 Oct 26.

Serum matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 expression in patients with familial Mediterranean fever.

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**BACKGROUND/AIMS:** Serum matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1) are well-known inflammatory biomarkers, with a diagnostic potential for various diseases. The aim of the present study was to determine the potential diagnostic applications of serum MMP-9 and TIMP-1 concentrations in patients with familial Mediterranean fever (FMF).

**MATERIALS AND METHODS:** A total of 66 male FMF patients and 40 age-matched healthy subjects were included in this research. TIMP-1 and MMP-9 levels with conventional inflammation markers were determined. Pearson correlation analysis was used to determine the correlation between the characteristics of patients and the laboratory data.

**RESULTS:** In patients with FMF, serum MMP-9 levels and MMP-9/TIMP-1 ratios were found to be significantly elevated in both acute episode and asymptomatic periods ( $p=0.0001$  and  $p=0.0001$ , respectively). There was no significant difference between TIMP-1 levels. A significant negative correlation between patients' current age and TIMP-1 level in patients with acute episodes was detected ( $p=0.0008$ ,  $r=-0.52$ ). Moreover, a moderate negative correlation was noticed between erythrocyte sedimentation rate and TIMP-1 level in patients with acute episodes ( $p=0.01$ ,  $r=-0.39$ ). Additionally, a moderate negative correlation was found between the duration of colchicine use and MMP-9 and TIMP-1 levels during the attack period ( $p=0.04$ ,  $r=-0.36$  and  $p=0.02$ ,  $r=-0.39$ , respectively).

**CONCLUSION:** Our findings demonstrate that a significant MMP-9/TIMP-1 imbalance exists in patients with FMF, which reflects an ongoing inflammation in both FMF

periods. Thus, the increased MMP-9 levels observed in FMF patients could rationalize therapeutic targeting to MMPs.

DOI: 10.5152/tjg.2015.0223

PMID: 26510088 [Indexed for MEDLINE]

1454. Turk J Gastroenterol. 2015 Nov;26(6):461-7. doi: 10.5152/tjg.2015.0015. Epub 2015 Oct 26.

Rare disorders can be an underlying cause of cyclic vomiting: Familial Mediterranean fever, Helicobacter pylori gastritis, and cavernous transformation of the portal vein.

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**BACKGROUND/AIMS:** Considering the etiology of cyclic vomiting syndrome (CVS) in childhood, a variety of underlying organic causes has been clearly identified in the literature. The aim of this study was to emphasize that endoscopic evaluation in the first step may help diagnosis and treatment in patients with CVS, unlike the CVS-related "North American Society for Pediatric Gastroenterology, Hepatology and Nutrition" (NASPGHAN) consensus statement in 2008.

**MATERIALS AND METHODS:** The medical files of patients with vomiting complaints admitted to our tertiary center between the years 2007 and 2012 were analyzed retrospectively. Patients were identified according to the International Classification of Diseases (ICD) codes at their initial presentation, including vomiting.

**RESULTS:** A total of 815 patients with vomiting complaints were evaluated. Of the 379 patients who presented with vomiting only, 336 patients were already being followed for chronic vomiting. Cyclic vomiting was detected in 31 out of 336 patients.

**CONCLUSION:** In our series, familial Mediterranean fever (FMF), cavernous transformation of the portal vein, and Helicobacter pylori (HP) gastritis presented with CVS for the first time in the pediatric age group. We emphasize that endoscopic evaluation in patients with CVS should be performed as the first

step for appropriate diagnosis and treatment.

DOI: 10.5152/tjg.2015.0015

PMID: 26510083 [Indexed for MEDLINE]

1455. Cornea. 2016 Jan;35(1):77-80. doi: 10.1097/ICO.0000000000000662.

Association Between Keratoconus and Familial Mediterranean Fever in Turkey.

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**PURPOSE:** To evaluate the association between familial Mediterranean fever (FMF) and keratoconus (KC).

**METHODS:** This retrospective case-control study was performed to compare the prevalence of KC in patients with FMF with the corresponding prevalence in control patients without FMF referred to Genetic Diagnostic Center at Diskapi Yildirim Beyazit Training and Research Hospital from June 2012 to June 2015. We included all 100 patients with FMF. Each FMF-affected patient was matched to 3 controls.

**RESULTS:** None of the patients in the control group (0%, 0/300) had KC, whereas 4 of 100 patients with FMF (4%) had KC ( $P < 0.004$ ). Three of 33 patients with a homozygous mutation (9.1%) (M694V/M694V in 2 cases and M680I/M680I in 1 case) and 1 of the 46 patients with a compound heterozygous mutation (2.2%) (M694V/M680I) had KC, whereas none of the 21 patients with a heterozygous mutation (0%) had KC. All patients with KC were women, and mean age was 40.8 years (range, 30-51). Although 1 of the 4 patients with KC had hypertension and type 2 diabetes mellitus, the other 3 patients did not have any systemic illness except FMF. When we compared the prevalence of KC in patients with FMF (4%) with the highest prevalence of KC reported in the literature (0.2%), FMF was a predisposing factor to develop KC [odds ratio: 18.1 (95% CI: 11.9-27.5)] especially in patients with

a homozygous mutation [odds ratio: 43.4 (95% CI: 28.6-65.7)].

CONCLUSIONS: Mediterranean fever (MEFV) gene mutations, particularly in homozygous mutations of the MEFV gene, may be a predisposing factor in the development of KC.

DOI: 10.1097/ICO.0000000000000662

PMID: 26509767 [Indexed for MEDLINE]

1456. RMD Open. 2015 Jul 20;1(1):e000097. doi: 10.1136/rmdopen-2015-000097. eCollection 2015.

Autoinflammatory granulomatous diseases: from Blau syndrome and early-onset sarcoidosis to NOD2-mediated disease and Crohn's disease.

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The recent identification of genetic mutations leading to dysfunction of inflammatory and apoptotic pathways, has allowed to characterise a group of diseases, recognised as monogenic autoinflammatory syndromes. Among those, Blau syndrome (BS) and early-onset sarcoidosis (EOS) have been identified as familial and sporadic phenotypes of the same non-caseating granulomatous form. Both the diseases are caused by mutations in the CARD15/NOD2 gene, encoding the cytosolic NOD2 protein, one of the key molecules in the regulation of innate immunity. Clinical onset is typically located in the first years of life and phenotype is characterised by simultaneous or less articular, cutaneous and ocular non-caseating granulomatous inflammation, which can be variably associated with a heterogeneous systemic spectrum. The CARD15/NOD2 gene has also been identified as one of the genes linked to susceptibility to Crohn's disease (CD), a common

polygenic inflammatory granulomatous bowel disease. The heightened nuclear factor- $\kappa$ B activity, found in the intestinal tissue of patients affected by CD, has probably a genetic cause related to several CARD15/NOD2 polymorphisms. Other substitutions in the CARD15/NOD2 gene have also been found in a recently described disorder, called NOD2-associated autoinflammatory disease, which shares several clinical characteristics with BS and EOS. This review attempts to describe these diseases on the basis of the most recent evidences. We described genetic and clinical aspects, mainly focusing on BS and EOS, the most representative diseases of autoinflammatory granulomatous diseases, with the ultimate purpose to expand their knowledge.

DOI: 10.1136/rmdopen-2015-000097

PMCID: PMC4612691

PMID: 26509073

1457. An Pediatr (Barc). 2016 Jul;85(1):18-25. doi: 10.1016/j.anpedi.2015.08.010. Epub 2015 Oct 23.

[Non-bacterial chronic osteomyelitis: Experience in a tertiary hospital].

[Article in Spanish]

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**INTRODUCTION:** Non-bacterial chronic osteomyelitis (NBCO) is an autoinflammatory disease that presents with recurrent bouts of bone inflammation in the absence of microbiological isolation. It is a diagnosis of exclusion. Its treatment was



classically based on the use of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, although nowadays bisphosphonates or anti-tumour necrosis factor- $\alpha$  (anti-TNF) drugs are frequently used with good results. The objective of the study is to describe our experience in the diagnosis and treatment of patients with NBCO.

**PATIENTS AND METHODS:** Retrospective chart review of patients with NBCO followed up in a tertiary centre between 2008 and 2015.

**RESULTS:** A total of 7 patients with NBCO were recorded. Four were female and the median age was 10 years (IQR 2). The most common complaint was pain that interfered with sleep in 5 of the patients. Six patients had multifocal lesions at diagnosis. Bone biopsy demonstrated neutrophilic or lymphocytic infiltration and sclerosis in 6 patients. Four patients received antibiotics and NSAIDs without clinical response. Five received a short course of prednisone with an adequate control of symptoms, but only one of them maintained remission after corticosteroid suspension. Five patients received bisphosphonates with disease remission in 3 of them. The other 2 showed an inadequate response to pamidronate and were started on anti-TNF therapy (etanercept, infliximab or adalimumab), remaining asymptomatic at present.

**CONCLUSIONS:** Our series, although limited, confirms the effectiveness and safety of bisphosphonate and anti-TNF therapy for children with NBCO.

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DOI: 10.1016/j.anpedi.2015.08.010

PMID: 26506888 [Indexed for MEDLINE]

1458. Arthritis Rheumatol. 2016 Apr;68(4):1026-38. doi: 10.1002/art.39481.

The Role of Follicular Helper T Cell Molecules and Environmental Influences in Autoantibody Production and Progression to Inflammatory Arthritis in Mice.

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**OBJECTIVE:** Antibody-mediated autoimmunity involves cognate interactions between self-reactive T cells and B cells during germinal center (GC) reactions. The aim of this study was to determine the role of essential follicular helper T (Tfh) cell molecules (CXCR5, signaling lymphocytic activation molecule-associated protein) on autoreactive CD4<sup>+</sup> cells and the role of certain environmental influences that may determine GC-driven autoantibody production and arthritis development.

**METHODS:** We transferred self-reactive CD4<sup>+</sup> cells from KRN-Tg mice into recipient mice, which induced autoantibodies and autoimmune arthritis. This model allowed manipulation of environmental effects, such as inflammation, and use of transferred cells that were genetically deficient in important Tfh cell-associated molecules.

**RESULTS:** A deficiency of signaling lymphocytic activation molecule-associated protein (SAP) in CD4<sup>+</sup> cells from KRN-Tg mice completely protected against arthritis, indicating that stable T cell-B cell interactions are required for GC formation, autoantibody production, and arthritis induction. In contrast, a CXCR5 deficiency in CD4<sup>+</sup> cells from KRN-Tg mice still induced disease when these cells were transferred into wild-type mice, suggesting that T cell help for B cells could rely on other migration mechanisms. However, various manipulations influenced this system, including elimination of bystander effects through use of CD28(-/-) recipient mice (reduced disease) or use of inflammation-inducing Freund's complete adjuvant (progression to arthritis). We also examined the capacity of preexisting GCs with a nonautoimmune specificity to co-opt autoimmune T cells and observed no evidence for any influence.

**CONCLUSION:** In addition to the quality and quantity of cognate CD4<sup>+</sup> cell help, external factors such as inflammation and noncognate CD4<sup>+</sup> cell bystander activation trigger autoimmunity by shaping events within autoimmune GC responses. SAP is an essential molecule for autoimmune antibody production, whereas the importance of CXCR5 varies depending on the circumstances.

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DOI: 10.1002/art.39481

1459. Medicine (Baltimore). 2015 Oct;94(42):e1858. doi: 10.1097/MD.0000000000001858.

Putative Role of Serum Amyloid-A and Proinflammatory Cytokines as Biomarkers for Behcet's Disease.

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Behcet's disease (BD) is a multisystemic disorder of unknown etiology characterized by relapsing oral-genital ulcers, uveitis, and involvement of vascular, gastrointestinal, neurological, and musculoskeletal system. Although disease pathogenesis is still unclear, both innate and adaptive immunity have shown to play a pivotal role, and multiple proinflammatory cytokines seem to be involved in different pathogenic pathways that eventually lead to tissue damage. The aims of our study were to evaluate serum cytokines levels of IL-8, IL-18, IFN- $\alpha$ 2a, IL-6, IFN- $\gamma$ , CXCL10, CXCL11, CXCL9, and SAA levels in patients with BD, in comparison to healthy controls (HC), and to correlate their levels to disease activity. We included 78 serum samples obtained from 58 BD patients and analyzed a set of proinflammatory cytokines including IL-8, IL-18, IFN- $\alpha$ 2a, IL-6, IFN- $\gamma$ , CXCL10, CXCL11, and CXCL9 by multiplex bead analysis as well as SAA by enzyme-linked immunosorbent assay. Compared to HC, BD patients showed elevated cytokine levels of IL-8, IL-18, IFN- $\alpha$ 2a, and IL-6, and low levels of CXCL11. BD patients with SAA serum levels >20 mg/L showed higher levels of proinflammatory markers than HC or group with SAA  $\leq$ 20 mg/L. IL-18, IFN- $\alpha$ 2a, and IL-6 were higher in BD group with SAA >20 mg/L than HC, while IL-8 and CXCL9 levels were higher than in patients with SAA  $\leq$ 20 mg/L and HC. Active BD patients with SAA >20 mg/L exhibited elevated levels of inflammatory mediators, suggesting that may exist a relationship between SAA and proinflammatory cytokines in the intricate scenario

of BD pathogenesis.

DOI: 10.1097/MD.0000000000001858

PMCID: PMC4620803

PMID: 26496336 [Indexed for MEDLINE]

1460. Medicine (Baltimore). 2015 Oct;94(42):e1528. doi: 10.1097/MD.0000000000001528.

Proinflammatory Cytokines and Antiskin Autoantibodies in Patients With Inherited Epidermolysis Bullosa.

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Epidermolysis bullosa (EB) is a rare disorder characterized by inherited skin adhesion defects with abnormal disruption of the epidermal-dermal junction in response to mechanical trauma. Our aim was to investigate a set of cytokine levels in serum samples from patients suffering from epidermolysis bullosa simplex (EBS), dystrophic epidermolysis bullosa (DEB), and healthy controls (HCs), exploring their potential correlations with antiskin autoantibody titers and disease activity. Forty patients afferent to the Dermatological Ward of Bari City Hospital and 9 HCs were enrolled and subdivided according to the dystrophic (DEB) and simplex forms (EBS). We found a significant increase in interleukin (IL)-1 $\beta$  plasmatic levels of DEB (P = 0.0224) and EBS (P = 0.0465) patients compared to HCs; IL-6 levels were significantly higher in DEB than in EBS

patients ( $P = 0.0004$ ) or HCs ( $P = 0.0474$ ); IL-2 levels were significantly increased in DEB compared with EBS ( $P = 0.0428$ ). Plasmatic tumor necrosis factor- $\beta$  and interferon- $\gamma$  were higher in DEB patients than in HCs ( $P = 0.0448$  and  $0.0229$ ). Conversely, tumor necrosis factor- $\alpha$  was significantly decreased in DEB ( $P = 0.0034$ ). IL-5 correlated with anti-BP180 ( $r = -0.5018$ ,  $P = 0.0338$ ), anti-BP230 ( $r = -0.6097$ ,  $P = 0.0122$ ), and anticollagen VII ( $r = -0.5166$ ,  $P = 0.0405$ ) autoantibodies; interferon- $\gamma$  correlated with anti-BP180 ( $r = 0.9633$ ,  $P < 0.0001$ ), anti-BP230 ( $r = 0.9071$ ,  $P < 0.0001$ ), and anticollagen VII ( $r = 0.8619$ ,  $P = 0.0045$ ) autoantibodies. Score of disease severity was significantly correlated with IL-6 ( $r = 0.6941$ ,  $P = 0.029$ ) and IL-12 ( $r = 0.5503$ ,  $P = 0.0272$ ). The present study supports that EB might be considered a systemic inflammatory disease rather than a skin-limited disorder; clinical disease activity scores could be also integrated by laboratory data such as IL-6 and IL-12 dosage; biotherapies targeting specific cytokine networks probably represent a way to go in the future.

DOI: 10.1097/MD.0000000000001528

PMCID: PMC4620762

PMID: 26496255 [Indexed for MEDLINE]

1461. Clin Rev Allergy Immunol. 2015 Dec;49(3):263-70. doi: 10.1007/s12016-015-8518-3.

Ocular Involvement in Systemic Autoimmune Diseases.

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Eye involvement represents a common finding in patients with systemic autoimmune diseases, particularly rheumatoid arthritis, Sjogren syndrome, seronegative spondyloarthropathy, and antineutrophil cytoplasmic antibody (ANCA)-associated

vasculitis. The eye is a privileged immune site but commensal bacteria are found on the ocular surface. The eye injury may be inflammatory, vascular or infectious, as well as iatrogenic, as in the case of hydroxychloroquine, chloroquine, corticosteroids, and bisphosphonates. Manifestations may affect different components of the eye, with episcleritis involving the episclera, a thin layer of tissue covering the sclera; scleritis being an inflammation of the sclera potentially leading to blindness; keratitis, referring to corneal inflammation frequently associated with scleritis; and uveitis as the inflammation of the uvea, including the iris, ciliary body, and choroid, subdivided into anterior, posterior, or panuveitis. As blindness may result from the eye involvement, clinicians should be aware of the possible manifestations and their management also independent of the ophthalmologist opinion as the therapeutic approach generally points to the underlying diseases. In some cases, the eye involvement may have a diagnostic implication, as for episcleritis in rheumatoid arthritis, or acute anterior uveitis in seronegative spondyloarthritis. Nonetheless, some conditions lack specificity, as in the case of dry eye which affects nearly 30 % of the general population. The aim of this review is to elucidate to non-ophthalmologists the major ocular complications of rheumatic diseases and their specific management and treatment options.

DOI: 10.1007/s12016-015-8518-3

PMID: 26494481 [Indexed for MEDLINE]

1462. Postgrad Med J. 2015 Dec;91(1082):665-9. doi: 10.1136/postgradmedj-2015-133554. Epub 2015 Oct 21.

Pyrexia of unknown origin 90 years on: a paradigm of modern clinical medicine.

Brown M.

In 1925, Sir Thomas Horder, a leading physician of his day, gave a lecture, published in this journal, entitled 'Some cases of pyrexia without physical signs'. The paper highlighted what was already a familiar clinical presentation "which taxes our resources to the utmost". Fast-forward through 90 years of careful clinical description, technological innovation in diagnosis and treatment, emergent infections, novel diagnoses, demographic shifts, and radical changes in the health economy. Sir Thomas would find certain aspects familiar, and others revolutionary, in the differential diagnosis and management of the

21st century patient with pyrexia of unknown origin (PUO). Within high-income settings, the proportion of cases due to infection has declined, albeit unevenly. The era of untreated HIV, and the consequences of iatrogenic intervention and immunosuppression, led to Durack and Street's subclassification of the condition in the early 1990 s into classic, nosocomial, neutropenic and HIV-associated PUO. Shifts towards ambulatory care have driven a change in the definition of many diseases. An era of observant clinicians, who lent their names to eponymous syndromes, followed by meticulous serological, genetic and clinicopathological correlation, generated a battery of diagnoses that, along with malignancy, form a large proportion of diagnoses in more recent clinical care. In the current era, universal access to cross-sectional imaging and an infinite array of laboratory tests has undermined the attention paid to history and examination. In some areas of the clinical assessment, such as assessing the fever pattern, this shift is supported by research evidence. The issues that need to be addressed in the next 90 years of technological innovation, information sharing and health service transformation are likely to include: transcriptomic approaches to diagnosis; the place of positron emission tomography (PET) in the diagnostic pathway; the optimal management of high ferritin states; and the most cost-effective diagnostic environment, in the face of this era of specialisation and fragmentation of care. In the meantime, this review covers some important early 21st century lessons to be shared in avoiding diagnostic pitfalls and choosing empirical therapy.

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DOI: 10.1136/postgradmedj-2015-133554

PMID: 26489766 [Indexed for MEDLINE]

1463. Clin Exp Rheumatol. 2015 Nov-Dec;33(6 Suppl 94):S15-8. Epub 2015 Oct 19.

Familial Mediterranean fever in Armenia in 2015: some interesting lessons.

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PMID: 26487400 [Indexed for MEDLINE]

1464. Int J Rheum Dis. 2017 Nov;20(11):1872. doi: 10.1111/1756-185X.12785. Epub 2015 Oct 21.

A case of familial Mediterranean fever with triple MEFV gene mutations.

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DOI: 10.1111/1756-185X.12785

PMID: 26487349 [Indexed for MEDLINE]

1465. Clin Exp Rheumatol. 2015 Nov-Dec;33(6 Suppl 94):S170. Epub 2015 Oct 20.

Intermediate uveitis associated with familial Mediterranean fever.

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PMID: 26487035 [Indexed for MEDLINE]



1466. Clin Exp Rheumatol. 2015 Nov-Dec;33(6 Suppl 94):S113-6. Epub 2015 Oct 19.

Increased serum concentrations of neutrophil-derived protein S100A12 in heterozygous carriers of MEFV mutations.

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**OBJECTIVES:** To assess subclinical inflammation in heterozygous carriers of Mediterranean fever (MEFV) gene mutations, analysis of classical inflammation markers and S100A12 was performed.

**METHODS:** Exons 2, 3, and 10 of the MEFV gene, C-reactive protein (CRP), serum amyloid A protein (SAA), procalcitonin (PCT), and S100A12 concentrations, erythrocyte sedimentation rate (ESR), and differential blood count were analysed in apparently healthy parents (n=26) of homozygous children with familial Mediterranean fever (FMF). Their general health condition was assessed by a standardised questionnaire. In order to collect data on the disease course, subjects were reevaluated after 5 years by means of telephone interview and/or questionnaire.

**RESULTS:** Twenty-two individuals with one typical mutation in the MEFV gene were included. Mean values (mean±SEM) of classical inflammation markers were within the normal range (ESR of 11.7±1.9 mm/h, SAA 4.7±0.4 mg/l, CRP 0.26±0.04 mg/dl), while PCT was non-detectable in all cases (<0.1 µg/l). Eleven subjects showed elevated S100A12 levels [>140 ng/ml] with a mean concentration of 205±43 ng/ml. Thus, the mean value of S100A12 was 1.5-fold higher than the regular cut-off.

**CONCLUSIONS:** 50% of the heterozygous MEFV mutation carriers exhibited elevated

S100A12 levels, supporting previous observations that S100 molecules are very sensitive biomarkers of subclinical inflammation. Possibly, S100A12 could be a prognostic biomarker to detect individuals at risk of FMF manifestation who might benefit from colchicine therapy.

PMID: 26486615 [Indexed for MEDLINE]

1467. Int J Rheum Dis. 2017 Nov;20(11):1868-1871. doi: 10.1111/1756-185X.12776. Epub 2015 Oct 20.

Tocilizumab is effective in a familial Mediterranean fever patient complicated with histologically proven recurrent fasciitis and myositis.

Umeda M(1)(2), Aramaki T(1), Fujikawa K(3), Iwamoto N(2), Ichinose K(2), Terada K(1), Takeo G(1), Yonemitsu N(1), Ueki Y(1), Migita K(4), Kawakami A(2).

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(4)Clinical Research Center, National Hospital Organization, Nagasaki Medical Center, Nagasaki, Japan.

DOI: 10.1111/1756-185X.12776

PMID: 26481326 [Indexed for MEDLINE]

1468. Rheum Dis Clin North Am. 2015 Nov;41(4):643-63. doi: 10.1016/j.rdc.2015.07.006. Epub 2015 Aug 30.

Etiology and Pathogenesis of Psoriatic Arthritis.

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The current model of psoriatic arthritis implicates both the IL-23/IL-17 axis and the tumor necrosis factor (TNF) pathways in disease pathogenesis. Although specific major histocompatibility complex class I molecules are associated with the psoriatic disease phenotype, no specific antigen or autoantibody has been identified. Instead, an array of genes may code for an autoinflammatory loop, potentially activated by mechanical stress and dysbiosis in the skin or gut. Danger signals released by innate immune cells activate a Th1 and Th17 response that leads to synovitis, enthesitis, axial inflammation, and altered bone homeostasis characterized by pathologic bone resorption and new bone formation.

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DOI: 10.1016/j.rdc.2015.07.006

PMID: 26476224 [Indexed for MEDLINE]

1469. Intern Med. 2015;54(20):2643-6. doi: 10.2169/internalmedicine.54.4937. Epub 2015 Oct 15.

Malignant nephrosclerosis in a patient with familial Mediterranean fever.

Yamanouchi M(1), Ubara Y, Imafuku A, Kawada M, Koki M, Sumida K, Hiramatsu R, Hasegawa E, Hayami N, Suwabe T, Hoshino J, Sawa N, Ohashi K, Fujii T, Matsuda M, Takaichi K.

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A 37-year-old man was admitted to our hospital for an evaluation of renal dysfunction and hypertension. The C-reactive protein level was 6.0 mg/dL, and the serum renin activity was extremely high. A renal biopsy showed malignant nephrosclerosis-like lesions with an onion skin pattern. He had a history of recurrent abdominal pain associated with periodic fevers above 38 degrees that resolved within three days. A MEditerranean FeVer (MEFV) gene analysis revealed

that he was homozygous for the E148Q polymorphism (exon 2) and heterozygous for the L110P polymorphism (exon 2). The present case demonstrates that persistent subclinical inflammation can lead to malignant nephrosclerosis in familial Mediterranean fever patients with this genotype.

DOI: 10.2169/internalmedicine.54.4937

PMID: 26466703 [Indexed for MEDLINE]

1470. Klin Lab Diagn. 2015 Jun;60(6):46-7.

[THE CERTAIN CLINICAL CHARACTERISTICS OF BLOOD IN PATIENTS WITH FAMILY MEDITERRANEAN FEVER OF ARMENIAN POPULATION].

[Article in Russian]

Pepoian AZ, Arutunian N, Grigorian A, Tsaturian VV, Manvelian AM, Dilnian E, Balaian MA, Torok T.

The study was carried out to evaluate erythrocyte sedimentation rate, glucose level, rheumatoid factor and C-reactive protein in blood of patients with periodic peritonitis at the stage of remission. Also, effect of colchicine on activity of lactase was analyzed. It is demonstrated that frequency of increase of levels of erythrocyte sedimentation rate and C-reactive protein during period of remission differed depending on gender while at the same time indicators of rheumatoid factor were within limits of normality in all patients. Despite research literature data establishing effect of colchicine on lactose assimilability, no significant inhibition of lactose activity was established in examined volunteers.

PMID: 26466452 [Indexed for MEDLINE]

1471. Int J Chronic Dis. 2015;2015:152616. doi: 10.1155/2015/152616. Epub 2015 Jul 13.

Mean Platelet Volume and Splenomegaly as Useful Markers of Subclinical Activity in Egyptian Children with Familial Mediterranean Fever: A Cross-Sectional Study.

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**Objective.** To study whether mean platelet volume (MPV) and splenomegaly could be used as subclinical inflammatory markers in children with familial Mediterranean fever (FMF) at the attack-free period. **Patients and Methods.** The study included ninety-seven children with FMF. MPV was carried out within 4 hours of blood sampling according to standard laboratory practice. Splenomegaly was determined by abdominal ultrasound (USG). **Results.** High MPV was detected in 84.45% of our studied patients and was significantly higher in FMF patients with splenomegaly than in patients without splenomegaly. There was a statistically significant correlation between MPV and splenic span ( $P = 0.045$ ). **Conclusion.** Elevated MPV and its significant correlation with splenic span in FMF children during the attack-free periods support the use of MPV and splenomegaly as useful markers of the subclinical inflammation in FMF patients at the attack-free period.

DOI: 10.1155/2015/152616

PMCID: PMC4590932

PMID: 26464867

1472. Rheumatology (Oxford). 2016 Jul;55(7):1153-8. doi: 10.1093/rheumatology/kev378. Epub 2015 Oct 13.

Non-thrombocytopenic purpura in familial Mediterranean fever-comorbidity with Henoch-Schönlein purpura or an additional rare manifestation of familial Mediterranean fever?

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Henoch-Schönlein purpura is a relatively common vasculitis mainly affecting children. It is characterized by purpuric skin rash, abdominal cramping, and haematuria. Skin biopsies taken from Henoch-Schönlein purpura lesions disclose perivascular IgA deposits. FMF is an autoinflammatory disease characterized by recurrent attacks of fever lasting 2-3 days which resolve spontaneously. Typical manifestations of the disease are peritonitis, pleuritis, pericarditis, arthritis and erysipelas-like erythema usually affecting the lower limbs. Over the years many reviews emphasized the clinical impression that Henoch-Schönlein purpura is more common among FMF patients than in healthy control population. In this review we summarize these reports and show that sometimes Henoch-Schönlein purpura associated with FMF differs from typical isolated Henoch-Schönlein purpura, and this is also the case with polyarteritis nodosa and SpA associated with FMF. It is suggested that these clinical manifestations (polyarteritis nodosa, Henoch-Schönlein purpura and SpA) should be considered to be associated with FMF as part of what we call FMF rather than as co-existing additional separate clinical entities.

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DOI: 10.1093/rheumatology/kev378

PMID: 26464521 [Indexed for MEDLINE]

1473. J Crohns Colitis. 2016 Jan;10(1):112-5. doi: 10.1093/ecco-jcc/jjv186. Epub 2015 Oct 13.

Diagnostic and Treatment Options for Severe IBD in Female X-CGD Carriers with Non-random X-inactivation.

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**BACKGROUND AND AIMS:** X-linked chronic granulomatous disease [X-CGD] due to hemizygous mutations in CYBB is characterised by invasive bacterial and fungal infections and granulomatous inflammation. Inflammatory bowel disease [IBD] is an additional or isolated manifestation. Allogeneic haematopoietic stem cell transplantation [alloHSCT] is the standard curative treatment. X-CGD carriers are usually healthy but those with non-random X-chromosome inactivation [XCI] may develop infectious or autoinflammatory manifestations.

**METHODS AND RESULTS:** We report on two female patients with severe treatment-refractory Crohn-like IBD manifesting at age 23 and 8 years, respectively. NADPH-oxidase activity testing and molecular genetics proved X-CGD carrier status with non-random XCI. As in CGD, histopathology from colonic biopsies disclosed pigment-laden macrophages and reduced CD68(+) macrophages. Following submyelo-ablative conditioning, the younger patient was treated with alloHSCT at age 20 years. She came into remission within 3 months after transplantation and shows complete mucosal healing after 16 months off all medications.

**CONCLUSIONS:** We suggest that children and young adults with refractory IBD should mandatorily be tested for CGD. AlloHSCT should be considered as curative therapy in severely diseased female carriers of X-CGD with non-random XCI.

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DOI: 10.1093/ecco-jcc/jjv186

PMID: 26464403 [Indexed for MEDLINE]

1474. Mod Rheumatol. 2018 Mar;28(2):365-368. doi: 10.3109/14397595.2015.1106639. Epub 2015 Nov 20.

Progression of palindromic rheumatism to juvenile idiopathic arthritis in a Japanese girl carrying heterozygous L110P-E148Q substitutions of MEFV gene.

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Palindromic rheumatism (PR), a rare disease in children, is characterized by recurrent arthritis or periartthritis and asymptomatic interval. We report evolution of PR to juvenile idiopathic arthritis in a Japanese girl with heterozygous complex L110P-E148Q allele of MEFV gene. Poor response to colchicine alone suggests that the MEFV substitution could increase the susceptibility to arthritis rather than caused arthritis associated with atypical Familial Mediterranean Fever. Weekly methotrexate is a choice for such cases.

DOI: 10.3109/14397595.2015.1106639

PMID: 26457478 [Indexed for MEDLINE]

1475. Hum Mutat. 2016 Jan;37(1):7-15. doi: 10.1002/humu.22915. Epub 2015 Oct 21.

Mutation Update for COL2A1 Gene Variants Associated with Type II Collagenopathies.

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Mutations in the COL2A1 gene cause a spectrum of rare autosomal-dominant conditions characterized by skeletal dysplasia, short stature, and sensorial defects. An early diagnosis is critical to providing relevant patient care and follow-up, and genetic counseling to affected families. There are no recent exhaustive descriptions of the causal mutations in the literature. Here, we provide a review of COL2A1 mutations extracted from the Leiden Open Variation Database (LOVD) that we updated with data from PubMed and our own patients. Over 700 patients were recorded, harboring 415 different mutations. One-third of the mutations are dominant-negative mutations that affect the glycine residue in the G-X-Y repeats of the alpha 1 chain. These mutations disrupt the collagen triple helix and are common in achondrogenesis type II and hypochondrogenesis. The mutations resulting in a premature stop codon are found in less severe phenotypes such as Stickler syndrome. The p.(Arg275Cys) substitution is found in all patients with COL2A1-associated Czech dysplasia. LOVD-COL2A1 provides support and potential collaborative material for scientific and clinical projects aimed at elucidating phenotype-genotype correlation and differential diagnosis in patients with type II collagenopathies.

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DOI: 10.1002/humu.22915

PMID: 26443184 [Indexed for MEDLINE]

1476. *Pediatr Rheumatol Online J.* 2015 Oct 6;13(1):38. doi: 10.1186/s12969-015-0037-5.

The common NOD2/CARD15 variant P268S in patients with non-infectious uveitis: a cohort study.

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**BACKGROUND:** The etiology of Autoimmune chronic uveitis (ACU) is still unknown; NOD2/CARD15 gene mutations are responsible for the Blau Syndrome and can induce uveitis in animal models.

**PRESENTATION OF THE HYPOTHESIS:** Aim of our study was to assess if NOD2/CARD15 variants have a role in the etiology or in the clinical course of patients with ACU, either idiopathic or associated with other inflammatory diseases.

**TESTING THE HYPOTHESIS:** We consecutively enrolled 25 patients (19 pediatric and 6 adults) affected with ACU. For each patient medical history was reviewed and clinical data were recorded. Allelic and genotypic frequencies of NOD2/CARD15 variations were calculated in patients and matched with those of 25 healthy controls. The statistical analysis was performed. Fifteen patients showed the polymorphism P268S/SNP5 (SNP rs2066842) as heterozygous carriers while two patients were homozygous for the same polymorphism; one patient carried also the variant c647 18-16 TCT on intron 3, not previously reported in the literature.

Statistical analysis for NOD2/CARD15 genotyping showed significant differences between patients and controls for allelic frequencies ( $p = 0.04$ , OR: 4.03, 95 %; CI = 1.2-13.5) but not for genotypic frequencies. We could not identify a significant phenotype-genotype correlation.

**IMPLICATIONS OF THE HYPOTHESIS:** In our cohort of Italian patients, the NOD2/CARD15 common variant P268S/SNP5 could potentially be significantly associated with ACU.

DOI: 10.1186/s12969-015-0037-5

PMCID: PMC4595328

PMID: 26438151 [Indexed for MEDLINE]

1477. Trends Immunol. 2015 Oct;36(10):578-604. doi: 10.1016/j.it.2015.08.007.

The Regulation of Immunological Processes by Peripheral Neurons in Homeostasis and Disease.

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The nervous system and the immune system are the principal sensory interfaces between the internal and external environment. They are responsible for recognizing, integrating, and responding to varied stimuli, and have the capacity to form memories of these encounters leading to learned or 'adaptive' future responses. We review current understanding of the cross-regulation between these systems. The autonomic and somatosensory nervous systems regulate both the development and deployment of immune cells, with broad functions that impact on hematopoiesis as well as on priming, migration, and cytokine production. In turn, specific immune cell subsets contribute to homeostatic neural circuits such as those controlling metabolism, hypertension, and the inflammatory reflex. We examine the contribution of the somatosensory system to autoimmune, autoinflammatory, allergic, and infectious processes in barrier tissues and, in this context, discuss opportunities for therapeutic manipulation of neuro-immune interactions.

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DOI: 10.1016/j.it.2015.08.007

PMCID: PMC4592743

PMID: 26431937 [Indexed for MEDLINE]

1478. Clin Rev Allergy Immunol. 2017 Feb;52(1):34-44. doi: 10.1007/s12016-015-8512-9.

Idiopathic Inflammatory Myopathies: an Update on Classification and Treatment

with Special Focus on Juvenile Forms.

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Juvenile inflammatory myopathies represent a heterogeneous group of rare and potentially fatal disorders of unknown aetiology, characterised by inflammation and proximal and symmetric muscle weakness. Beyond many similarities, specific clinical, laboratoristic and histopathologic features underlie different subsets with distinguishing demographic, prognostic and therapeutic peculiarities. Over time, several forms of inflammatory idiopathic myopathies have been described, including macrophagic myofascitis, immune-mediated necrotizing myopathy and the spectrum of amyopathic dermatomyositis that include hypomyopathic dermatomyositis, inclusion body myositis and cancer-associated myositis occurring almost exclusively in adults. However, juvenile dermatomyositis is the most frequent in childhood, whereas polymyositis is relatively more frequent in adults. The aetiology is nowadays widely unclear; however, current theories contemplate a combination of environmental triggers, immune dysfunction and specific tissue responses involving muscle, skin and small vessels endothelium in genetically susceptible individuals. Myositis-specific autoantibodies, found almost exclusively in patients with myositis and myositis-associated autoantibodies, detectable both among patients with myositis and in subjects suffering from other autoimmune diseases, have an important clinical role because of their relation to specific clinical features, response to therapy and prognosis. The gold standard treatment for juvenile dermatomyositis is represented by corticosteroids, along with adjunctive steroid-sparing

immunosuppressive therapies, which are used to counteract disease activity, prevent mortality, and reduce long-term disability. Further treatment approach such as biologic agents and autologous stem cell transplantation are emerging during the last years, in particular in patients difficult to treat and with poor prognosis. Therefore, a highly medical specialised approach is required for diagnosis and management of these conditions. This review comprehensively examines juvenile inflammatory myopathies focusing on clinical and laboratory classifications as well as on the current treatment approaches, referring in particular on biologic agents and latest therapeutic opportunities.

DOI: 10.1007/s12016-015-8512-9

PMID: 26429707 [Indexed for MEDLINE]

1479. Hum Immunol. 2016 May;77(5):375-81. doi: 10.1016/j.humimm.2015.09.050. Epub 2015 Sep 30.

Association analysis of class II cytokine and receptor genes in vitiligo patients.

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The loss of melanocytes in vitiligo is mainly attributed to defective autoimmune mechanisms and lately autoinflammatory mediators have become more emphasized. Among these, a number of class II cytokines and their receptors have displayed altered expression patterns in vitiligo. Thus, we selected 30 SNPs from the regions of respective genes to be genotyped in Estonian case-control sample (109 and 328 individuals, respectively). For more precise analyses, patients were divided into subgroups based on vitiligo progression activity, age of onset, sex, occurrence of vitiligo among relatives, extent of depigmented areas, appearance of Köbner's phenomenon, existence of halo nevi, occurrence of spontaneous repigmentation, and amount of thyroid peroxidase antibodies. No associations appeared in whole vitiligo group. In subgroups, several allelic and haplotype associations were found. The strongest involved SNPs rs12301088 (near IL26 gene), that was associated with familial vitiligo and existence of halo nevi, and rs2257167 (IFNAR1 gene), that was associated with female vitiligo. Additionally, haplotypes consisting of rs12301088 and rs12321603 alleles (IL26-IL22 genes), that were associated with familial vitiligo and existence of halo nevi. In conclusion, several genetic associations with vitiligo subphenotypes were revealed and functional explanations to these remain to be determined in respective studies.

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DOI: 10.1016/j.humimm.2015.09.050

PMID: 26429320 [Indexed for MEDLINE]

1480. Diagn Pathol. 2015 Jul 16;10:104. doi: 10.1186/s13000-015-0344-7.

Diffuse and multifocal nephrogenic adenoma with Familial Mediterranean Fever: a case report with molecular study.

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Nephrogenic adenoma, also referred to nephrogenic metaplasia, is a benign proliferative lesion of urothelium, usually associated with chronic physical stimuli or inflammation. Familial Mediterranean fever is an inherited autosomal recessive disease characterized by recurrent short episodes of fever. The site of mutation is found in MEFV gene which controls inflammatory responses. We have experienced a case of nephrogenic adenoma in a 16-year-old girl with Familial Mediterranean Fever, showing proliferative lesions diffusely in the urinary bladder and multifocally in the other parts of urinary tract. These lesions disappeared after colchicine treatment. We searched for MEFV gene mutation using the specimen from the resected urinary bladder and detected heterozygous mutation of E148Q. There is a possibility that control of inflammation caused by the surgery for vesicoureteral reflux in the local site didn't work well on the background of heterozygous mutation of MEFV gene, and as a result, nephrogenic adenoma appeared. This is the first report of a combination of two rare diseases. We have to be aware that nephrogenic adenoma can occur in association with Familial Mediterranean Fever, and the former condition should be taken into consideration when rendering a correct pathological diagnosis.

PMID: 26428868 [Indexed for MEDLINE]

1481. Pediatr Rheumatol Online J. 2015;13 Suppl 1:O1-P211. Epub 2015 Sep 28.

8th International Congress of Familial Mediterranean Fever and Systemic Autoinflammatory Diseases.

[No authors listed]

PMCID: PMC4597419

PMID: 26424586

1482. Int J Rheumatol. 2015;2015:912137. doi: 10.1155/2015/912137. Epub 2015 Aug 27.

Familial Mediterranean Fever in Iran: A Report from FMF Registration Center.

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Background. Familial Mediterranean fever (FMF) is a periodic AR autoinflammatory disorder. This comprehensive study describes FMF in Iran as a country near Mediterranean area. Materials and Methods. From the country FMF registration center 403 patients according to Tel-Hashomer criteria enrolled this study, 239 patients had MEFV gene mutations analyses. Data, if needed, was analyzed by SPSS v20. Results. 175 patients (43.4%) were female and 228 patients (56.6%) were male. The mean age was 21.3 years. Abdominal pain was in 93.3% patients and 88.1% had fever. Abdominal pain was the main complaint of patients in (49.6%). The mean interval between attacks was  $36.5 \pm 29.6$  days and the mean duration of every episodes was  $43.3 \pm 34.5$  hours. 15.1% of patients had positive family history and 12.7% had previous surgery; in 52.3% of patients delay in diagnosis was more than three years. 12 common MEFV gene mutations were analyzed, 21.33% were without mutations, 39.7% had compound heterozygote, 25.52% showed heterozygous, and



13.38% showed homozygous results. The most common compound genotype was M694V-V726A (% 10.46) and in alleles M694V (% 20.9) and V726A (% 12.7) were the most frequent mutations, respectively. Conclusion. M694V was the most common mutation, and the most common compound genotype was M694V-V726A. Our genotype results are similar to Arabs and in some way to Armenians, erysipelas-like skin lesions are not common in this area, and clinical criteria are the preferred methods in diagnosis of FMF.

DOI: 10.1155/2015/912137

PMCID: PMC4564791

PMID: 26413094

1483. Nefrologia. 2016;36(1):63-6. doi: 10.1016/j.nefro.2015.06.026. Epub 2015 Sep 26.

Anakinra induces complete remission of nephrotic syndrome in a patient with familial mediterranean fever and amyloidosis.

[Article in English, Spanish]

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Renal amyloidosis is one of the most severe complications of familial Mediterranean fever (FMF). Colchicine has reduced the incidence of this complication, which now only appears in untreated, under-treated and resistant patients, but it is usually ineffective in patients with advanced amyloidosis. Here we report a patient with FMF and biopsy-proven amyloidosis who presented with nephrotic syndrome despite colchicine treatment. Anakinra (an interleukin-1 $\beta$

inhibitor) was started and a dramatic complete remission of nephrotic syndrome was observed in the following months. Anakinra can be an effective treatment for FMF patients with severe secondary amyloidosis.

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DOI: 10.1016/j.nefro.2015.06.026

PMID: 26409501 [Indexed for MEDLINE]

1484. Clin Rheumatol. 2016 Jul;35(7):1841-7. doi: 10.1007/s10067-015-3078-8. Epub 2015 Sep 23.

Relationship between periodontal destruction and gene mutations in patients with familial Mediterranean fever.

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Recent studies have shown that genetic factors involved in the host responses might determine the disease severity for both familial Mediterranean fever (FMF) and periodontitis. The present study aimed to investigate the relationship of FMF with periodontitis and to search for the potential association between periodontitis and MEFV gene missense variations in patients with FMF. The study consisted of 97 FMF patients and 34 healthy volunteers. FMF patients were classified according to the kind of MEFV gene mutation: (1) patients with homozygous M694V gene mutation, (2) patients with heterozygous M694V gene

mutation, and (3) patients with MEFV gene different mutations. Gingival Index (GI), Plaque Index (PI), probing pocket depth (PD), and clinical attachment level (CAL) were measured in all participants. The results of multivariate logistic regression showed a highly significant association between homozygous M694V gene mutation and periodontitis in FMF patients ( $p < 0.05$ ). After adjusting for potential confounders (smoking, body weight, age, and gender), FMF patients with homozygous M694V gene mutation were 3.51 (1.08-11.45) times more likely to present periodontitis than the other FMF patients. These results indicate that the presence of homozygous M694V gene mutation seems to increase the risk for periodontitis in FMF patients.

DOI: 10.1007/s10067-015-3078-8

PMID: 26400644 [Indexed for MEDLINE]

1485. Clin Exp Rheumatol. 2015 Nov-Dec;33(6 Suppl 94):S19-23. Epub 2015 Sep 24.

The carrier rate and spectrum of MEFV gene mutations in central and southeastern European populations.

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**OBJECTIVES:** Familial Mediterranean fever (FMF) is an autosomal-recessive disorder caused by mutations in MEFV gene. Eastern Mediterranean populations have the highest number of carriers, whereas western Mediterranean populations are less frequently affected. The aim of this study was to determine the carrier rate and spectrum of MEFV gene mutations in apparently healthy populations and in suspected FMF patients from central and southeastern European (CSEE) countries.

**METHODS:** We screened 507 apparently healthy persons from 5 CSEE countries. Exons 2 and 10 of the MEFV gene were PCR amplified and subsequently sequenced with ABI prism310 genetic analyser. Six most common mutations in the MEFV gene were tested: V726A, K695R, M694V, M694I, M680I in exon 10, and E148Q in exon 2. In suspected FMF patients we screened all MEFV exons in selected cases.

**RESULTS:** The overall carrier frequency of all MEFV mutations was higher than expected (9.3%). In the whole cohort we did not find any apparently healthy persons with two mutations. Heterozygous mutations were found in apparently healthy subjects from different CSEE countries as follows: Macedonia 16%, Serbia 11%, Bosnia and Herzegovina 8%, Slovenia 6% and Hungary 5%. The most common mutation in healthy controls was K695R, appearing in 40% of mutated alleles. The most common mutation in suspected FMF patients was M694V, followed by K695R.

**CONCLUSIONS:** We found a higher than expected carrier rate of MEFV gene mutations in populations from CSEE countries. It is interesting to note that 40% of detected carriers carry the K695R mutation.

PMID: 26399837 [Indexed for MEDLINE]

1486. Clin Exp Rheumatol. 2015 Nov-Dec;33(6 Suppl 94):S156-62. Epub 2015 Sep 22.

Development of a medication adherence scale for familial Mediterranean fever (MASIF) in a cohort of Turkish children.

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**OBJECTIVES:** To develop and assess the validity and reliability of an adherence scale concerning medical treatment in paediatric FMF patients.

**METHODS:** The Medication Adherence Scale in FMF Patients (MASIF) is a 18-item

questionnaire that evaluates adherence to medication in four domains. Validation of the instrument was accomplished in paediatric FMF patients (aged 2-18 years) under medication at least for 6 months. The first step was to build up the scale through qualitative approach (with interviews using semi-structured questions).

Validation analyses included assessment of feasibility, face and content validity; construct validity, internal consistency and test-retest reliability.

**RESULTS:** One hundred and fifty patients with FMF were enrolled in the study. The mean age of the patients was  $11.11 \pm 4.02$  years and 48.7% of them were male. The MASIF was found to be feasible and valid for both face and content. It correlated with the Morisky Medication Adherence Scale as a gold standard thereby demonstrating good construct validity ( $r=0.515$ ,  $p<0.001$ ). Assessment of content validity identified four subscales. The internal consistency, Cronbach's alpha was 0.728. There was a positive and significant correlation between test and retest scores ( $r=0.843$ ;  $p<0.001$ ). Also, a significant correlation between parents' and children's reports ( $r=0.781$ ,  $p<0.001$ ).

**CONCLUSIONS:** Based on these results, the use of this scale to assess and follow up the adherence to treatment in paediatric FMF patients under medical treatment is recommended.

PMID: 26393894 [Indexed for MEDLINE]

1487. Cell Rep. 2015 Sep 29;12(12):1986-96. doi: 10.1016/j.celrep.2015.08.046. Epub 2015 Sep 17.

Inhibition of Super-Enhancer Activity in Autoinflammatory Site-Derived T Cells Reduces Disease-Associated Gene Expression.

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The underlying molecular mechanisms for many autoimmune diseases are poorly understood. Juvenile idiopathic arthritis (JIA) is an exceptionally well-suited model for studying autoimmune diseases due to its early onset and the possibility to analyze cells derived from the site of inflammation. Epigenetic profiling, utilizing primary JIA patient-derived cells, can contribute to the understanding of autoimmune diseases. With H3K27ac chromatin immunoprecipitation, we identified a disease-specific, inflammation-associated, typical enhancer and super-enhancer signature in JIA patient synovial-fluid-derived CD4(+) memory/effector T cells. RNA sequencing of autoinflammatory site-derived patient T cells revealed that BET inhibition, utilizing JQ1, inhibited immune-related super-enhancers and preferentially reduced disease-associated gene expression, including cytokine-related processes. Altogether, these results demonstrate the potential use of enhancer profiling to identify disease mediators and provide evidence for BET inhibition as a possible therapeutic approach for the treatment of autoimmune diseases.

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DOI: 10.1016/j.celrep.2015.08.046

PMID: 26387944 [Indexed for MEDLINE]

1488. Ann Rheum Dis. 2016 Aug;75(8):1550-7. doi: 10.1136/annrheumdis-2015-207701. Epub 2015 Sep 17.

Next-generation sequencing and its initial applications for molecular diagnosis of systemic auto-inflammatory diseases.

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**OBJECTIVES:** Systemic auto-inflammatory disorders (SAIDs) are a heterogeneous group of monogenic diseases sharing a primary dysfunction of the innate immune system. More than 50% of patients with SAID does not show any mutation at gene(s) tested because of lack of precise clinical classification criteria and/or



incomplete gene screening. To improve the molecular diagnosis and genotype interpretation of SAIDs, we undertook the development of a next-generation sequencing (NGS)-based protocol designed to simultaneous screening of 10 genes. METHODS: Fifty patients with SAID, already genotyped for the respective causative gene(s), were massively sequenced for the coding portions of MEFV, MVK, TNFRSF1A, NLRP3, NLRP12, NOD2, PSTPIP1, IL1RN, LPIN2 and PSMB8. Three different bioinformatic pipelines (Ion Reporter, CLC Bio Genomics Workbench, GATK-based in-house workflow) were compared.

RESULTS: Once resulting variants were compared with the expected mutation list, no workflow turned out to be able to detect all the 79 variants known in the 50 DNAs. Additional variants were also detected, validated by Sanger sequencing and compared to assess true and false positive detection rates of the three workflows. Finally, the overall clinical picture of 34 patients was re-evaluated in the light of the new mutations found.

CONCLUSIONS: The present gene panel has resulted suitable for molecular diagnosis of SAIDs. Moreover, genotype-phenotype correlation has confirmed that the interpretation of NGS data in patients with an undefined inflammatory phenotype is remarkably difficult, thus supporting the need of evidence-based and validated clinical criteria to be used concurrently with the genetic analysis for the final diagnosis and classification of patients with SAIDs.

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DOI: 10.1136/annrheumdis-2015-207701

PMID: 26386126 [Indexed for MEDLINE]

1489. Clin Rheumatol. 2016 Jun;35(6):1603-7. doi: 10.1007/s10067-015-3077-9. Epub 2015 Sep 18.

The effect of colchicine and disease severity on physical growth in children with familial Mediterranean fever.

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This study aimed to investigate the effects of colchicine on growth parameters in familial Mediterranean fever (FMF) patients. Fifty-one (29 girls, 22 boys) FMF patients were enrolled in the study. All of the patients were in the prepubertal stage and had not received colchicine treatment before the study. Anthropometric measurements, demographic features, clinical findings at diagnosis and during periods of attacks of FMF, disease activity, frequency of exacerbations, colchicine dosage, and weight and height measurements were recorded at an interval of 6 months. Height, weight, and body mass index standard deviation scores and Z-scores were calculated. The mean height standard deviation score (HSDS) was significantly increased from  $-0.64 \pm 1.20$  to  $-0.26 \pm 1.07$  ( $p < 0.001$ ), the mean weight standard deviation score (WSDS) was significantly increased from  $-0.60 \pm 1.03$  to  $-0.45 \pm 0.98$  ( $p = 0.008$ ), and the mean body mass index standard deviation score was decreased from  $-0.33 \pm 1.06$  to  $-0.47 \pm 0.98$  ( $p = 0.128$ ) at 1 year after colchicine treatment compared with before initiation of treatment. In patients who had no FMF attacks during colchicine treatment, height and weight were significantly increased at 1 year (HSDS:  $p < 0.001$  WSDS:  $p = 0.002$ ), but in patients who had recurrent attacks, height and weight did not change (HSDS:  $p = 0.051$ , WSDS:  $p = 0.816$ ). Even when subclinical inflammation is present, preventing attacks of FMF with colchicine allows growth to continue. However, suppression of subclinical inflammation and control of attacks of FMF are required for weight gain.

DOI: 10.1007/s10067-015-3077-9

PMID: 26384820 [Indexed for MEDLINE]

1490. J Eur Acad Dermatol Venereol. 2016 Mar;30(3):404-12. doi: 10.1111/jdv.13303. Epub 2015 Sep 15.

The role of cytokine deficiencies and cytokine autoantibodies in clinical dermatology.

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Cytokines are small, secreted proteins that are essential for promoting and maintaining a normal immune response. Upregulation of cytokines frequently occurs in autoimmune and inflammatory diseases. Conversely, several immunodeficiency, autoimmune and autoinflammatory disorders are known to occur due to a downregulation or absence of cytokines. Here, we review the diagnosis and clinical management of cytokine deficiency syndromes in dermatology. We will review the biology of cytokines, and the current approved indications for recombinant cytokines and anticytokine antibodies. We will also review the role of cytokine deficiencies and cytokine autoantibodies in immunodeficiency syndromes, as well as in autoimmune disorders. Finally, we will examine autoinflammatory disorders due to cytokine deficiencies.

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DOI: 10.1111/jdv.13303

PMID: 26372900 [Indexed for MEDLINE]

1491. Int J Mol Sci. 2015 Sep 7;16(9):21277-93. doi: 10.3390/ijms160921277.

To Extinguish the Fire from Outside the Cell or to Shutdown the Gas Valve Inside?  
Novel Trends in Anti-Inflammatory Therapies.

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Cytokines are the most important soluble mediators of inflammation. Rare pediatric diseases provided exemplar conditions to study the anti-inflammatory efficacy of new generation therapies (biologics/biopharmaceuticals) selectively targeting single cytokines. Monoclonal antibodies and recombinant proteins have revolutionized anti-inflammatory therapies in the last two decades, allowing the specific targeting of single cytokines. They are very effective in extinguishing inflammation from outside the cell, even with the risk of an excessive and prolonged immunosuppression. Small molecules can enter the cell and shutdown the valve of inflammation by directly targeting signal proteins involved in cytokine release or in response to cytokines. They are orally-administrable drugs whose dosage can be easily adjusted to obtain the desired anti-inflammatory effect. This could make these drugs more suitable for a wide range of diseases as stroke, gout, or neurological impairment, where inflammatory activation plays a pivotal role as trigger. Autoinflammatory diseases, which have previously put anti-cytokine proteins in the limelight, can again provide a valuable model to measure the real potential of small inhibitors as anti-inflammatory agents.

DOI: 10.3390/ijms160921277

PMCID: PMC4613252

PMID: 26370962 [Indexed for MEDLINE]

1492. Rheumatology (Oxford). 2016 Feb;55(2):343-6. doi: 10.1093/rheumatology/kev315. Epub 2015 Sep 13.

Different disease subtypes with distinct clinical expression in familial Mediterranean fever: results of a cluster analysis.

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Comment in

Rheumatology (Oxford). 2016 Jun;55(6):1147.

Rheumatology (Oxford). 2016 Jun;55(6):1147-8.

**OBJECTIVE:** The aim of this study was to evaluate whether there are clinical subgroups that may have different prognoses among FMF patients.

**METHODS:** The cumulative clinical features of a large group of FMF patients [1168 patients, 593 (50.8%) male, mean age 35.3 years (s.d. 12.4)] were studied. To analyse our data and identify groups of FMF patients with similar clinical characteristics, a two-step cluster analysis using log-likelihood distance measures was performed. For clustering the FMF patients, we evaluated the following variables: gender, current age, age at symptom onset, age at diagnosis, presence of major clinical features, variables related with therapy and family history for FMF, renal failure and carriage of M694V.

**RESULTS:** Three distinct groups of FMF patients were identified. Cluster 1 was characterized by a high prevalence of arthritis, pleuritis, erysipelas-like erythema (ELE) and febrile myalgia. The dosage of colchicine and the frequency of amyloidosis were lower in cluster 1. Patients in cluster 2 had an earlier age of disease onset and diagnosis. M694V carriage and amyloidosis prevalence were the highest in cluster 2. This group of patients was using the highest dose of colchicine. Patients in cluster 3 had the lowest prevalence of arthritis, ELE and febrile myalgia. The frequencies of M694V carriage and amyloidosis were lower in cluster 3 than the overall FMF patients. Non-response to colchicine was also slightly lower in cluster 3.

**CONCLUSION:** Patients with FMF can be clustered into distinct patterns of clinical and genetic manifestations and these patterns may have different prognostic

significance.

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DOI: 10.1093/rheumatology/kev315

PMID: 26370398 [Indexed for MEDLINE]

1493. Minerva Pediatr. 2017 Feb;69(1):50-58. doi: 10.23736/S0026-4946.16.04216-X. Epub 2015 Sep 10.

Final diagnosis of children and adolescents with musculoskeletal complaints.

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**BACKGROUND:** Musculoskeletal complaints (MSCs) are one of the leading causes of outpatient admissions. However, analytical and epidemiological data are limited. The aim of this study is to identify the etiology of MSCs (excluding acute traumatic conditions) in children and adolescents, and to identify clues for the differential diagnosis.

**METHODS:** Children and adolescents presenting with musculoskeletal pain, swelling

or limitation of movement were enrolled in a prospective design. Demographic, clinical and laboratory features were recorded.

**RESULTS:** Four hundred and twenty-two children (48.2% female) with a mean age of  $7.90 \pm 3.95$  years were enrolled. Etiology was identified in 97.2% of the cases: non-inflammatory and mechanical conditions (NIMC; 42.2%), rheumatic diseases (RD; 31%), infection-related disorders (IRD; 21.6%) and malignancy (M; 2.4%). NIMC was characterized by longer duration of complaints, a higher rate of non-articular complaints, a lower rate of joint involvement and limping and lower levels of leukocytes, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The prevalence of RD was higher in the age group of >12 years; younger age was associated with higher prevalence of IRD. Small-joint involvement was highest in the RD group. Median ESR in RD and M groups was higher; compared to the other groups; the frequency of patients with  $ESR \geq 60$  mm/hr was higher in the M group; compared to the RD group. In the RD group familial Mediterranean fever (9.7%), juvenile idiopathic arthritis (8.3%) and Henoch-Schönlein purpura (5.7%) were the leading causes of MSCs.

**CONCLUSIONS:** RD accounted for one-third of the etiologies for MSCs. Age, duration of complaints, pattern of joint involvement and acute phase reactants are practical tools that may guide the pediatrician for diagnosis.

DOI: 10.23736/S0026-4946.16.04216-X

PMID: 26365744 [Indexed for MEDLINE]

1494. *Pediatr Allergy Immunol.* 2016 Feb;27(1):78-82. doi: 10.1111/pai.12490. Epub 2015 Oct 20.

Could familial Mediterranean fever gene mutations be related to PFAPA syndrome?

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**BACKGROUND:** The cause and pathophysiology of PFAPA syndrome is unknown. The aim of this study was to determine all MEFV gene variants relevant to familial Mediterranean fever in children with PFAPA syndrome.

**METHODS:** All MEFV gene variants were analyzed in patients with PFAPA syndrome. All patients were evaluated using the Gaslini scoring system. Serum immunoglobulin levels were also determined upon admission.

**RESULTS:** We evaluated 64 patients with PFAPA syndrome. The median age at diagnosis was 37.5 (min-max: 6-96) months, and the percentage of male patients was 55.0%. The Gaslini diagnostic score for periodic fever was high in 81.0% of the patients. An MEFV gene mutation was found in 42 (66.0%) children. Mostly, heterozygous or compound heterozygous variants of the MEFV gene were found. Two patients were homozygous for R202Q. MEFV gene mutations were not detected in 22 (34.0%) patients. No significant differences in clinical or laboratory findings were observed between the two groups ( $p > 0.05$ ), and there were no significant differences in period and duration of the fever episodes ( $p > 0.05$ ). The fever of all 47 patients (100.0%) who received prednisolone during the episodes decreased within hours and did not recur. Eighteen of the patients using prednisolone underwent prophylaxis with colchicine, and the fever episodes of 9/18 (50.0%) patients using colchicine decreased within months.

**CONCLUSIONS:** Most patients presenting with PFAPA syndrome have heterozygous MEFV gene mutations. Whether carrying a heterozygous MEFV gene is the primary cause of this syndrome requires further investigation.

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DOI: 10.1111/pai.12490

PMID: 26360812 [Indexed for MEDLINE]

1495. Mediators Inflamm. 2015;2015:570418. doi: 10.1155/2015/570418. Epub 2015 Aug 18.

Basic Characteristics of Adults with Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenopathy Syndrome in Comparison with the Typical Pediatric Expression of Disease.

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Autoinflammatory diseases are caused by inflammasome dysregulation leading to overproduction of proinflammatory cytokines and a pathological delay in the inflammation switching off. The progress of cellular biology has partially clarified pathogenic mechanisms behind monogenic autoinflammatory diseases, whereas little is known about the polygenic ones. Although the genetic susceptibility of periodic fever, aphthous stomatitis, pharyngitis, and adenopathy (PFAPA) syndrome is still obscure, the presence of overlapping symptoms with monogenic periodic fevers, the recurrence in family members, the important role played by dysregulated interleukin- (IL-)  $1\beta$  secretion during flares, the overexpression of inflammasome-associated genes during attacks, and, last but not least, the therapeutic efficacy of IL- $1\beta$  blockade strongly indicate a potential genetic involvement in its pathogenesis, probably linked with environmental factors. PFAPA syndrome has a typical inception in the pediatric age, but a delayed onset during adulthood has been described as well. Treatments required as well as effectiveness of tonsillectomy remain controversial, even if the disease seems to have a self-limited course mostly in children. The purpose of this review is to provide an overview of this complex polygenic/multifactorial autoinflammatory disorder in which the innate immune system undoubtedly plays a basic role.

DOI: 10.1155/2015/570418

PMCID: PMC4556059

PMID: 26357457 [Indexed for MEDLINE]

1496. Clin Rheumatol. 2015 Dec;34(12):2001-10. doi: 10.1007/s10067-015-3068-x. Epub 2015 Sep 10.

Enthesal involvement in systemic disorders.

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The objective of this study is to review the data on enthesal involvement in systemic disorders. A Pubmed search utilizing the indexing terms "enthesitis" and "enthesitis" was conducted and the data pertinent to the aim of the review was extracted and organized in accordance with the preplanned structure of the manuscript. A number of cadaver-based studies, as well as studies using ultrasonography and magnetic resonance imaging, have detailed new distinct aspects of entheses physiology and pathology in a variety of rheumatic and non-rheumatic systemic disorders. Major progress has been done in characterization of separate components of the entheses organ, imaging of entheses, elaboration of the role and features of enthesal disease in spondyloarthropathies, juvenile idiopathic arthritis, osteoarthritis, familial Mediterranean fever, hyperuricemia, and other systemic conditions. The knowledge acquired and summarized herein shows that entheses can be affected in various ways in variety of medical disorders with different pathogenesis. Better understanding of the risk factors, mechanisms and natural history of enthesopathies is warranted. The current progress in the understanding of enthesal involvement in systemic disorders represents just the first step in resolving the entheses-related enigmas.

DOI: 10.1007/s10067-015-3068-x

PMID: 26354427 [Indexed for MEDLINE]

1497. Iran J Basic Med Sci. 2015 Jul;18(7):659-63.

FMF Genotype-phenotype correlation in Iranian Azeri Turks: Association between

M694V/R761H mutation and amyloidosis.

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**OBJECTIVES:** Familial Mediterranean fever (FMF), an inherited autosomal recessive disorder, is frequently present among individuals of Mediterranean origin.

Differences in the clinical manifestations of FMF between different ethnic groups have been documented. The aim of the present study was to determine the most common characteristics of FMF and the relationship between clinical findings and the most common mutant alleles of the MEFV gene in an Iranian Azeri Turk population.

**MATERIALS AND METHODS:** We analyzed clinical and genetic data from 415 patients identified as having FMF clinical symptoms and who were referred to the Molecular Genetics Laboratory of Tabriz/Iran over the last 3 years. The mutation type and clinical characteristics were determined for each patient.

**RESULTS:** The following primary clinical characteristics of the patients were observed peritonitis was observed in 378 (93.8%), high-grade fever in 351 (86.88%), arthritis in 215 (54.57%), pleuritis in 207 (53.49%), myalgia in 153 (41.69%), AA amyloidosis in 149 (40.16%), and erysipelas-like erythema in 54 (14.96%) subjects. A positive response to colchicines treatment was noted in 374 (95.1%) patients including 303 patients with two mutated alleles and 71 patients with one identified mutation.

**CONCLUSION:** In contrast to previous studies, there was no significant association between M694V mutation and development of amyloidosis. The M680I/M680I, M680I, M694I, and M694V/R761H genotypes were found to be associated with the development of amyloidosis. These results indicate that physicians need to pay careful attention to patients with asymptomatic or mildly symptomatic FMF with these genotypes.

PMCID: PMC4556758

PMID: 26351556

1498. J Cell Biol. 2015 Sep 14;210(6):973-89.

TRIM-mediated precision autophagy targets cytoplasmic regulators of innate immunity.

Kimura T, Jain A, Choi SW, Mandell MA, Schroder K, Johansen T, Deretic V.

The present paradigms of selective autophagy in mammalian cells cannot fully explain the specificity and selectivity of autophagic degradation. In this paper, we report that a subset of tripartite motif (TRIM) proteins act as specialized receptors for highly specific autophagy (precision autophagy) of key components of the inflammasome and type I interferon response systems. TRIM20 targets the inflammasome components, including NLRP3, NLRP1, and pro-caspase 1, for autophagic degradation, whereas TRIM21 targets IRF3. TRIM20 and TRIM21 directly bind their respective cargo and recruit autophagic machinery to execute degradation. The autophagic function of TRIM20 is affected by mutations associated with familial Mediterranean fever. These findings broaden the concept of TRIMs acting as autophagic receptor regulators executing precision autophagy of specific cytoplasmic targets. In the case of TRIM20 and TRIM21, precision autophagy controls the hub signaling machineries and key factors, inflammasome and type I interferon, directing cardinal innate immunity response systems in humans.

DOI: 10.1083/jcb.201503023

PMCID: PMC4576868

PMID: 26347139 [Indexed for MEDLINE]

1499. Rheumatology (Oxford). 2016 Mar;55(3):403-10. doi: 10.1093/rheumatology/kev337. Epub 2015 Sep 5.

Recent insights into the role of autophagy in the pathogenesis of rheumatoid arthritis.

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Autophagy appears to play a dual role in eukaryotic cells. It manifests cytoprotective effects through the regulation of catabolic processes and the clearance of pathogens; however, a correlation between autophagy and the pathogenesis of autoimmune/autoinflammatory conditions has recently been described. Autophagy has emerged as a mediator in the pathogenesis of RA. Autophagy may regulate apoptosis resistance and hyperplasia in synovial fibroblasts, promote osteoclastogenesis and stimulate osteoclast-mediated bone resorption through the delivery of citrullinated peptides to MHC compartments, which results in the activation of the innate and adaptive immune response, thereby resulting in RA. Given the likely importance of autophagy in the pathogenesis of RA, here we reviewed the detailed mechanisms concerning the pathogenicity of autophagy and autophagy proteins in RA.

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DOI: 10.1093/rheumatology/kev337

PMID: 26342228 [Indexed for MEDLINE]

1500. Rheumatology (Oxford). 2015 Nov;54(11):2118. doi: 10.1093/rheumatology/kev235. Epub 2015 Sep 5.

Comment on: Dysregulated mature IL-1 $\beta$  production in familial Mediterranean fever.

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Comment in  
Rheumatology (Oxford). 2015 Nov;54(11):2119.

Comment on  
Rheumatology (Oxford). 2015 Apr;54(4):660-5.

DOI: 10.1093/rheumatology/kev235  
PMID: 26342224 [Indexed for MEDLINE]

1501. Rheumatology (Oxford). 2015 Nov;54(11):2119. doi: 10.1093/rheumatology/kev333.  
Epub 2015 Sep 5.

Comment on: Dysregulated mature IL-1 $\beta$  production in familial Mediterranean fever:  
reply.

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Comment on  
Rheumatology (Oxford). 2015 Apr;54(4):660-5.  
Rheumatology (Oxford). 2015 Nov;54(11):2118.

DOI: 10.1093/rheumatology/kev333  
PMID: 26342223 [Indexed for MEDLINE]

1502. J Korean Med Sci. 2015 Sep;30(9):1241-5. doi: 10.3346/jkms.2015.30.9.1241. Epub  
2015 Aug 13.

S1000A12, Chitotriosidase, and Resolvin D1 as Potential Biomarkers of Familial  
Mediterranean Fever.

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Familial Mediterranean fever (FMF) is an auto-inflammatory disease characterised by periodic inflammatory attacks. We investigated changes in monocyte-granulocyte derived S10012A and chitotriosidase in both the attack and silent period of FMF for better estimation of inflammation. Endogenous resolvin was determined for utility to restrict inflammation. This study included 29 FMF patients (15 M/14 F) and 30 healthy controls (15 M/15 F). Serum levels of highly sensitive C-reactive protein, serum amiloid A (SAA), S100A12, chitotriosidase, and resolvin D1 were measured. Age, sex, body mass indexes, and lipids were similar between patients and controls. Biomarkers including hs-CRP, SAA, S100A12, chitotriosidase, and resolvin D1 were higher in the attack period of FMF patients compared to controls ( $P < 0.001$ ). When FMF patients in the silent period were compared with their attack period, hs-CRP, SAA, and chitotriosidase were found elevated in the attack period ( $P < 0.001$ ,  $P < 0.001$ , and  $P = 0.02$  respectively). Serum levels of SAA, S100A12, chitotriosidase, and resolvin D1 in the silent period of FMF patients were still found elevated compared to healthy controls, indicating subclinical inflammation ( $P < 0.001$ ,  $P < 0.001$ ,  $P = 0.009$ , and  $P < 0.001$  respectively ). In subgroup analysis, patients with M694V homozygote and heterozygote mutations had higher S10012A and hs-CRP compared to other mutation carriers. Our findings indicate that chitotriosidase and S10012A are useful in diagnosis and detection of subclinical inflammation and/or assessment of disease activity in FMF patients. They could be more informative for inflammation in various disease states compared to hsCRP and SAA. Resolvin D1 is elevated in both the attack and silent periods of FMF. It may be helpful to restrict inflammation.

DOI: 10.3346/jkms.2015.30.9.1241

PMCID: PMC4553669

PMID: 26339162 [Indexed for MEDLINE]

1503. Arthritis Res Ther. 2015 Sep 4;17:243. doi: 10.1186/s13075-015-0765-4.

Efficacy and safety of canakinumab in adolescents and adults with colchicine-resistant familial Mediterranean fever.

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**INTRODUCTION:** This open-label pilot study aimed to investigate the efficacy of canakinumab in colchicine-resistant familial Mediterranean fever (FMF) patients.

**METHOD:** Patients with one or more attacks in a month in the preceding 3 months despite colchicine were eligible to enter a 30-day run-in period. Patients who had an attack during the first run-in period advanced to a second 30-day period. At the first attack, patients started to receive three canakinumab 150 mg subcutaneous injections at 4-week intervals, and were then followed for an additional 2 months. Primary efficacy outcome measure was the proportion of patients with 50 % or more reduction in attack frequency. Secondary outcome



measures included time to next attack following last canakinumab dose and changes in quality of life assessed by SF-36.

**RESULTS:** Thirteen patients were enrolled in the run-in period and 9 advanced to the treatment period. All 9 patients achieved a 50 % or more reduction in attack frequency, and only one patient had an attack during the treatment period.

C-reactive protein and serum amyloid A protein levels remained low throughout the treatment period. Significant improvement was observed in both physical and mental component scores of the Short Form-36 at Day 8. Five patients had an attack during the 2-month follow-up, occurring median 71 (range, 31 to 78) days after the last dose. Adverse events were similar to those observed in the previous canakinumab trials.

**CONCLUSION:** Canakinumab was effective at controlling the attack recurrence in patients with FMF resistant to colchicine. Further investigations are warranted to explore canakinumab's potential in the treatment of patients with colchicine resistant FMF.

**TRIAL REGISTRATION:** ClinicalTrials.gov NCT01088880 . Registered 16 March 2010.

DOI: 10.1186/s13075-015-0765-4

PMCID: PMC4559892

PMID: 26337145 [Indexed for MEDLINE]

1504. Ann Saudi Med. 2015 Mar-Apr;35(2):151-6. doi: 10.5144/0256-4947.2015.151.

The relationship between red cell distribution width and homozygous M694V mutation in familial Mediterranean fever patients.

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**BACKGROUND AND OBJECTIVE:** Familial Mediterranean fever (FMF) is characterized by recurrent and self-limiting attacks with peritonitis, pleuritis, arthritis, and erysipelas-like erythema. We aimed to investigate the red cell distribution width (RDW) level as an inflammatory marker in FMF patients compared with normal subjects.

DESIGN AND SETTINGS: A retrospective study of FMF patients at the Department of Gastroenterology, Cumhuriyet University, between November 2011-February 2013.

METHODS: A total of 249 FMF patients and 131 age- and sex-matched control participants were included in the current study. RDW levels were also analyzed by standard methods. Each patient was given 2 mL of blood sample to obtain genomic DNA.

RESULTS: Statistically significant differences were observed in RDW values between the FMF patients and the control group. Also, RDW levels were higher in the FMF patients with the homozygous M94V mutation compared with those with other mutations. The receiver-operating characteristic curve analysis suggested that the optimum RDW cutoff point for the FMF patients was 13.95, with a sensitivity, specificity, negative predictive value, and positive predictive value of 70%, 64%, 68%, and 66%, respectively (area under the curve: 0.711, 95% confidence interval 0.627-0.795,  $P < .0001$ ).

CONCLUSION: We suggest that RDW may show subclinical inflammation in FMF patients. RDW may be a promising marker in predicting the homozygous M694V mutation in FMF patients.

DOI: 10.5144/0256-4947.2015.151

PMCID: PMC6074134

PMID: 26336022 [Indexed for MEDLINE]

1505. *Pediatr Emerg Care*. 2015 Sep;31(9):652-3. doi: 10.1097/PEC.0000000000000545.

An Insidious Danger in Children With Familial Mediterranean Fever: Colchicine Intoxication.

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Colchicine is an anti-inflammatory drug, which has been used for the treatment of familial Mediterranean fever for several decades with narrow therapeutic-toxicity window. Colchicine poisoning is rare but frequently a life-threatening emergency condition in pediatric practice. It may occur by excessive ingestion of colchicine tablets accidentally or intentionally. Herein, we report a suicide

attempt with colchicine in a 12-year-old girl who had been followed up with the diagnosis of familial Mediterranean fever. She was admitted to our emergency department with gastrointestinal complaints and subsequently died because of the rapidly deteriorating metabolic and hemodynamic conditions.

DOI: 10.1097/PEC.0000000000000545

PMID: 26335230 [Indexed for MEDLINE]

1506. J Dermatol. 2016 Mar;43(3):314-7. doi: 10.1111/1346-8138.13068. Epub 2015 Sep 1.

Psoriasis-like lesions in a patient with familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is a rare hereditary autoinflammatory disorder that is caused by pyrin gene mutation associated with aberrance of the interleukin (IL)-1 $\beta$  pathway and characterized by recurrent, self-limiting attacks of fever and other inflammatory symptoms. We report a case of FMF with annular erythema and psoriasis-like lesions, the latter of which demonstrated parakeratosis with neutrophil microabscesses and mild inflammatory mononuclear cell infiltration in the upper dermis. Immunofluorescence staining showed IL-17-positive T-cells. Skin eruption with neutrophil migration in the epidermis may be provoked by T-helper 17 cell activation through the abnormal IL-1 $\beta$  cascade in FMF.

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DOI: 10.1111/1346-8138.13068

PMID: 26332735 [Indexed for MEDLINE]

1507. J Pediatr Adolesc Gynecol. 2015 Dec;28(6):e193-5. doi: 10.1016/j.jpag.2015.06.005. Epub 2015 Jun 14.

Familial Mediterranean Fever: An Unusual Case Presentation.

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**BACKGROUND:** Familial Mediterranean Fever is a heritable illness typically characterized by recurrent fevers and serositis. Triggers of this illness include many things, such as cold or stress.

**CASE:** This case describes a teenager who initially presented to the gynecologist office because of recurrent fevers with menses. Because she only had symptoms with menses, was healthy between attacks, and met the Livneh criteria, treatment with colchicine and combined oral contraceptive pills was initiated, with improvement of her symptoms.

**SUMMARY AND CONCLUSION:** There are multiple etiologies for febrile illness during menses, and one should consider familial Mediterranean fever as a possible cause of cyclic fevers.

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DOI: 10.1016/j.jpag.2015.06.005

PMID: 26324575 [Indexed for MEDLINE]

1508. Clin Dermatol. 2015 Sep-Oct;33(5):531-7. doi: 10.1016/j.clindermatol.2015.05.004. Epub 2015 May 27.

Seronegative reactive spondyloarthritis and the skin.

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Spondyloarthritis represent a group of conditions affecting the axial and peripheral musculoskeletal apparatus and are often associated with psoriasis, infections, and inflammatory bowel diseases. Other diseases included in this category are psoriatic arthritis, ankylosing spondylitis, and enteropathic arthritis. Reactive arthritis is an elusive spondyloarthritis, commonly occurring 1 to 3 weeks after a digestive or a genitourinary tract infection, in which microorganisms do not infect the joint directly. Reactive arthritis is classically characterized by large-joint arthritis, urethritis in men and cervicitis in women, and eye inflammation (usually conjunctivitis or uveitis) but encompasses numerous other symptoms and signs, including manifestations of dermatologic interest such as keratoderma blenorrhagicum and circinate balanitis. The diagnosis of reactive arthritis is clinical, and the infectious agent cannot always be identified due to disease latency after the infection. Most cases are self-limiting, but reactive arthritis may become chronic in 30% of cases. Treatment options include anti-inflammatory drugs, steroids, and sulfasalazine; biologic agents, such as tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) blockers, have been recently used, but there are only a few randomized clinical trials on the treatment of reactive arthritis. The effectiveness of antimicrobials needs further evaluation.

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DOI: 10.1016/j.clindermatol.2015.05.004

1509. Clin Dermatol. 2015 Sep-Oct;33(5):520-6. doi: 10.1016/j.clindermatol.2015.05.002. Epub 2015 May 27.

Cutaneous manifestations of systemic autoinflammatory disorders.

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Rare systemic autoinflammatory diseases (sAIDs) are driven by cytokine-mediated uncontrolled inflammation that results from activation of innate immune pathways. sAIDs present with recurrent fever episodes, fatigue, musculoskeletal symptoms, gastrointestinal, neurologic, and skin manifestations. They include hereditary monogenic and acquired multifactorial disorders, show a significant morbidity and usually persist for life. Due to the limited awareness of sAIDs, they are often associated with a considerable delay in diagnosis. Within the last decade, the use of cytokine-neutralizing therapies has been shown to improve the clinical symptoms of many patients with different sAIDs. Because skin involvement, such as urticarial, pustular, or ulcerative eruptions, is common in a variety of autoinflammatory disorders, dermatologists should be aware of the most important diseases and their skin phenotypes. This review gives an overview on prototype sAIDs with focus on cutaneous manifestations, clinical clues, and diagnostic approaches. Effective treatment options, such as anti-interleukin-1-targeted therapies, are discussed.

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DOI: 10.1016/j.clindermatol.2015.05.002

PMID: 26321397 [Indexed for MEDLINE]

1510. Clin Dermatol. 2015 Sep-Oct;33(5):509-11. doi:  
10.1016/j.clindermatol.2015.05.011. Epub 2015 May 27.

The skin as a target organ in multisystemic diseases II.

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Progress in medical science has given a new reading to the claim that the skin could be a mirror of the pathological changes found in the internal organs. The concept that we previously promoted is furthered in this issue; namely that the greatest part of skin diseases are systemic ones. In this issue we focus on another group of diseases with systemic involvement and skin manifestations. We review such inflammatory conditions as lichen planus, autoinflammatory syndromes, and pyoderma gangrenosum focusing on their systemic involvement. We have not missed such classic examples of systemic involvement as scleroderma. In this issue we have included two infectious diseases with multi-organ involvement: Lyme disease and Herpes simplex. In contrast to our previous work, we have also addressed neoplastic diseases - namely mycosis fungoides.

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DOI: 10.1016/j.clindermatol.2015.05.011

PMID: 26321395 [Indexed for MEDLINE]

1511. Clin Exp Rheumatol. 2015 Nov-Dec;33(6):818-23. Epub 2015 Aug 31.

Epidemiology and outcome of adult-onset Still's disease in Northwestern Thrace region in Turkey.

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**OBJECTIVES:** Adult-onset Still's disease (AOSD) is a rare disease that is classified among the multifactorial autoinflammatory disorders. It is characterised by fever, arthritis and, a typical salmon-coloured rash, and is accompanied by fever at nights. Currently, there is limited data on the prevalence of AOSD.

**METHODS:** Patients diagnosed with AOSD at the Department of Rheumatology of Trakya University Medical Faculty, between 2003 to 2014 were reviewed retrospectively.

Patients' clinical features, laboratory measurements, demographics, treatments, follow-up durations, disease courses, outcomes and complications were evaluated.

**RESULTS:** Our study included 42 patients with AOSD of whom, 32 (76.2%) were females and 10 (23.8%) were males (female to male ratio: 3.2). Over the course of the study, the annual incidence of AOSD was 0.62/100,000; and the overall prevalence was 6.77/100,000. The most common findings were fever (97.6%), arthralgia (95.2%), arthritis (76.2%), rash (73.8%) and sore throat (40.5%).

**CONCLUSIONS:** In our hospital-based study on AOSD which is a disease with very limited epidemiological data, the frequency of AOSD was found to be significantly higher than in other series. Female gender was more common in our series; and polycyclic pattern was more common in patients with longer follow-ups.

PMID: 26320744 [Indexed for MEDLINE]

1512. Immunity. 2015 Sep 15;43(3):463-74. doi: 10.1016/j.immuni.2015.07.022. Epub 2015 Aug 25.

Cytosolic Nuclease TREX1 Regulates Oligosaccharyltransferase Activity Independent of Nuclease Activity to Suppress Immune Activation.



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Comment in

Immunity. 2015 Sep 15;43(3):411-3.

TREX1 is an endoplasmic reticulum (ER)-associated negative regulator of innate immunity. TREX1 mutations are associated with autoimmune and autoinflammatory diseases. Biallelic mutations abrogating DNase activity cause autoimmunity by allowing immunogenic self-DNA to accumulate, but it is unknown how dominant frameshift (fs) mutations that encode DNase-active but mislocalized proteins cause disease. We found that the TREX1 C terminus suppressed immune activation by interacting with the ER oligosaccharyltransferase (OST) complex and stabilizing its catalytic integrity. C-terminal truncation of TREX1 by fs mutations dysregulated the OST complex, leading to free glycan release from dolichol carriers, as well as immune activation and autoantibody production. A connection between OST dysregulation and immune disorders was demonstrated in *Trex1*(-/-) mice, TREX1-V235fs patient lymphoblasts, and TREX1-V235fs knock-in mice. Inhibiting OST with aclacinomycin corrects the glycan and immune defects

associated with Trex1 deficiency or fs mutation. This function of the TREX1 C terminus suggests a potential therapeutic option for TREX1-fs mutant-associated diseases.

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DOI: 10.1016/j.immuni.2015.07.022

PMCID: PMC4575271

PMID: 26320659 [Indexed for MEDLINE]

1513. J Mol Neurosci. 2015 Dec;57(4):605-13. doi: 10.1007/s12031-015-0643-1. Epub 2015 Aug 30.

Molecular Mechanisms of the Action of Vitamin A in Th17/Treg Axis in Multiple Sclerosis.

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Multiple sclerosis (MS) is an autoinflammatory disease of the central nervous system (CNS). The immunopathogenesis of this disease involves an impaired balance of T helper (Th) 17 cells and regulatory T (Tregs) cells. MS is an autoinflammatory disease characterized by the degeneration of the CNS. For many years, MS has been considered to be an autoreactive Th1 and Th17 cell-dominated disease. The activity and number of Th17 cells are increased in MS; however, the function and number of Treg cells are reduced. Therefore, in MS, the balance between Th17 cells and Treg cells is impaired. Th17 cells produce

pro-inflammatory cytokines, which play a role in experimental autoimmune encephalomyelitis (EAE) and MS. However, Treg cell-mediated production of cytokines maintains immune homeostasis and can ameliorate the progression of MS. These observations, therefore, confirm the pathogenic and protective role of Th17 and Treg cells, respectively, and highlight the importance of maintaining the balance of both of these cell types. Evidence suggests that vitamin A and its active metabolites (all-trans-retinoic acid and 9-cis-retinoic acid) modulate the imbalance of Th17 and Treg cells through multiple molecular pathways and can be considered as a promising target in the prevention and treatment of MS.

DOI: 10.1007/s12031-015-0643-1

PMID: 26319266 [Indexed for MEDLINE]

1514. Saudi Med J. 2015 Sep;36(9):1126-7. doi: 10.15537/smj.2015.9.12219.

A brief history of familial Mediterranean fever.

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DOI: 10.15537/smj.2015.9.12219

PMCID: PMC4613641

PMID: 26318474 [Indexed for MEDLINE]

1515. Am J Dermatopathol. 2016 Jan;38(1):39-49. doi: 10.1097/DAD.0000000000000390.

Neutrophilic Epitheliotropism is a Histopathological Clue to Neutrophilic Urticarial Dermatositis.

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**BACKGROUND:** Neutrophilic urticarial dermatosis (NUD) comprises a particular autoinflammatory condition within the spectrum of aseptic neutrophilic dermatoses characterized by a distinct urticarial eruption clinically and a neutrophilic dermatosis histopathologically.

**OBJECTIVE:** In this study, we reviewed skin biopsies of lesional skin of patients seen in our outpatient clinic for autoimmune dermatoses and in allergy department from 1982 to 2014 that fulfilled these criteria.

**METHODS:** A total of 77 biopsies from 50 patients were analyzed histopathologically. Included were cases of Schnitzler syndrome, Still disease, systemic lupus erythematosus, Sjögren syndrome, cryopyrin-associated periodic syndrome, primary biliary cirrhosis, inflammatory bowel disease, and those that had signs of systemic inflammation not otherwise specified, that is, fever, arthritis, leukocytosis, and elevated erythrocyte sedimentation rate. A control cohort was defined as including a total of 70 biopsies from 50 patients comprising neutrophilic urticaria (pressure-induced and not pressure-induced), conventional urticaria, lupus erythematosus expressing neutrophils, and exanthematous drug reaction of macular type expressing neutrophils.

**RESULTS:** Skin biopsies of NUD revealed a perivascular and interstitial neutrophilic infiltrate focally extending into the epithelia of epidermis, hair follicles, sebaceous and sweat glands, a feature which we termed neutrophilic epitheliotropism. This neutrophilic epitheliotropism proved to be of high sensitivity (83.1%) and lower specificity (74.3%). The histological findings could be substantiated by immunohistochemical markers for leukocytes (elastase and myeloperoxidase), in particular in cases where neutrophils showed uncharacteristic band-like nuclei.

**CONCLUSIONS:** Neutrophilic epitheliotropism is a new sensitive and specific histopathological clue for NUD, a histopathological reaction pattern within the spectrum of neutrophilic dermatoses that needs to be differentiated from conventional urticaria.

DOI: 10.1097/DAD.0000000000000390

PMID: 26317390 [Indexed for MEDLINE]

[112th Scientific Meeting of the Japanese Society of Internal Medicine:  
Educational Lecture: Diagnosis and Therapy for Autoinflammatory Syndrome].

[Article in Japanese]

Ida H.

PMID: 30160907 [Indexed for MEDLINE]

1517. Expert Rev Clin Immunol. 2015;11(10):1083-92. doi: 10.1586/1744666X.2015.1077702.  
Epub 2015 Aug 27.

Current treatment recommendations and considerations for cryopyrin-associated  
periodic syndrome.

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Cryopyrin-associated periodic syndrome (CAPS) encompasses a spectrum of three  
phenotypes of increasing severity. The syndrome is due to dominant mutations in  
NLRP3, which encodes a key component of the innate immunity that regulates the  
secretion of IL-1 $\beta$ . CAPS manifests as systemic inflammation, which compromises  
quality of life and leads to serious complications and handicap. Anti-IL-1 drugs  
have shown remarkable efficacy in treating CAPS symptoms and have significantly  
changed patients' lives. They have acceptable safety profiles but do have some  
differences. We review three drugs that are currently marketed for CAPS, give  
additional information for the practical use of these drugs, and provide some  
recommendations for management.

DOI: 10.1586/1744666X.2015.1077702

PMID: 26312542 [Indexed for MEDLINE]

1518. Curr Top Microbiol Immunol. 2017;403:1-36. doi: 10.1007/82\_2015\_467.

Prix Fixe: Efferocytosis as a Four-Course Meal.

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During development, stress, infection, or normal homeostasis, billions of cells die on a daily basis, and the responsibility of clearing these cellular corpses lies with the phagocytes of innate immune system. This process, termed efferocytosis, is critical for the prevention of inflammation and autoimmunity, as well as modulation of the adaptive immune response. Defective clearance of dead cells is characteristic of many human autoimmune or autoinflammatory disorders, such as systemic lupus erythematosus (SLE), atherosclerosis, and diabetes. The mechanisms that phagocytes employ to sense, engulf, and process dead cells for an appropriate immune response have been an area of great interest. However, insight into novel mechanisms of programmed cell death, such as necroptosis, has shed light on the fact that while the diner (or phagocyte) is important, the meal itself (the type of dead cell) can play a crucial role in shaping the pursuant immune response.

DOI: 10.1007/82\_2015\_467

PMCID: PMC5587179

PMID: 26305046 [Indexed for MEDLINE]

1519. J Immunol. 2015 Oct 1;195(7):3416-26. doi: 10.4049/jimmunol.1401494. Epub 2015 Aug 24.

PSTPIP2, a Protein Associated with Autoinflammatory Disease, Interacts with Inhibitory Enzymes SHIP1 and Csk.

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Mutations in the adaptor protein PSTPIP2 are the cause of the autoinflammatory disease chronic multifocal osteomyelitis in mice. This disease closely resembles the human disorder chronic recurrent multifocal osteomyelitis, characterized by sterile inflammation of the bones and often associated with inflammation in other organs, such as the skin. The most critical process in the disease's development is the enhanced production of IL-1 $\beta$ . This excessive IL-1 $\beta$  is likely produced by neutrophils. In addition, the increased activity of macrophages, osteoclasts, and megakaryocytes has also been described. However, the molecular mechanism of how PSTPIP2 deficiency results in this phenotype is poorly understood. Part of the PSTPIP2 inhibitory function is mediated by protein tyrosine phosphatases from the proline-, glutamic acid-, serine- and threonine-rich (PEST) family, which are known to interact with the central part of this protein, but other regions of PSTPIP2 not required for PEST-family phosphatase binding were also shown to be indispensable for PSTPIP2 function. In this article, we show that PSTPIP2 binds the inhibitory enzymes Csk and SHIP1. The interaction with SHIP1 is of particular importance because it binds to the critical tyrosine residues at the C terminus of PSTPIP2, which is known to be crucial for its PEST-phosphatase-independent inhibitory effects in different cellular systems. We demonstrate that in neutrophils this region is important for the PSTPIP2-mediated suppression of IL-1 $\beta$  processing and that SHIP1 inhibition results in the enhancement of this processing. We also describe deregulated neutrophil response to multiple activators, including silica, Ab aggregates, and LPS, which is suggestive of a rather generalized hypersensitivity of these cells to various external stimulants.

DOI: 10.4049/jimmunol.1401494

PMID: 26304991 [Indexed for MEDLINE]

1520. Biochim Biophys Acta. 2015 Nov;1852(11):2494-503. doi: 10.1016/j.bbadis.2015.08.011. Epub 2015 Aug 21.

Activated STING enhances Tregs infiltration in the HPV-related carcinogenesis of tongue squamous cells via the c-jun/CCL22 signal.

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The negative role of the activated stimulator of IFN genes (STING) has been uncovered in autoinflammatory disease and cancer. However, the role of STING in virus-related carcinogenesis is not well known. Herein, HPV(+) tongue squamous cell carcinoma (TSCC) (n=25) and HPV(-) TSCC samples (n=25) were randomly collected and were verified by in situ hybridization (ISH) and p16 immunohistochemistry (IHC) to assess the expression and activated status of STING through IHC. The results showed that the expression of STING was up-regulated during the development of TSCC. Interestingly, although the expression of STING showed no difference between HPV(+/-) TSCC samples, the activated status of STING with dark staining around the nucleus was observed in HPV(+) TSCC samples. The role of activated STING was analyzed in three cell lines by siRNA and indicated



that activated STING had no impact on cell viability or apoptosis but promoted the induction of several immunosuppressive cytokines, e.g., IL-10, IDO and CCL22, which facilitated the infiltration of regulatory T cells (Tregs). Moreover, increased infiltration of Foxp3(+) Tregs along with increased expression of CCL22 was confirmed in HPV(+) TSCC samples. An inhibitor of the MAPK/AP-1 pathway (U0126) and the silencing of c-jun significantly suppressed CCL22 induction and the recruitment of Tregs by activated STING. Furthermore, down-regulated miR-27 was verified in independent fresh TSCC samples (n=50) and eight cell lines, which enhanced STING activation and led to increased CCL22 expression for Tregs recruitment in the TSCC microenvironment. Therefore, our findings provided distinct insight into the side effects of activated STING in HPV-related carcinogenesis.

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DOI: 10.1016/j.bbadis.2015.08.011

PMID: 26303640

1521. Anatol J Cardiol. 2015 Aug;15(8):669-70. doi: 10.5152/akd.2015.15839.

Assessment of left ventricular functions with tissue Doppler, strain, and strain rate echocardiography in patients with familial Mediterranean fever.

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Comment on

Anatol J Cardiol. 2015 Aug;15(8):663-8.

DOI: 10.5152/akd.2015.15839

PMCID: PMC5336869

PMID: 26301348 [Indexed for MEDLINE]

1522. Amyloid. 2015;22(3):207-8. doi: 10.3109/13506129.2015.1068751. Epub 2015 Aug 10.

The rate and significance of type 1/type 2 serum amyloid A protein gene polymorphisms in patients with ankylosing spondylitis and amyloidosis.

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A relationship between the presence of amyloidosis and SAA1 genotype has been shown in recent studies of (principally) familial Mediterranean fever patients. We found that the SAA1 rs12218 polymorphism was significantly more prevalent in ankylosing spondylitis patients with amyloidosis.

DOI: 10.3109/13506129.2015.1068751

PMID: 26300108 [Indexed for MEDLINE]

1523. Autoimmun Rev. 2016 Jan;15(1):9-15. doi: 10.1016/j.autrev.2015.08.008. Epub 2015 Aug 21.

Clinical and genetic characterization of the autoinflammatory diseases diagnosed in an adult reference center.

Hernández-Rodríguez J(1), Ruíz-Ortiz E(2), Tomé A(3), Espinosa G(3), González-Roca E(2), Mensa-Vilaró A(2), Prieto-González S(4), Espígol-Frigolé G(4), Mensa J(5), Cardellach F(6), Grau JM(6), Cid MC(4), Yagüe J(2), Aróstegui JI(2), Cervera R(3).

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**INTRODUCTION:** Autoinflammatory diseases (AID) are usually diagnosed during the pediatric age. However, adult-onset disease or diagnosis during adulthood has been occasionally described.

**OBJECTIVES:** To assess the clinical and genetic characteristics of adult patients diagnosed with an AID in an adult referral center for AID.

**METHODS:** We retrospectively evaluated clinical and genetic features of adult patients ( $\geq 16$  years) diagnosed with an AID or referred after AID diagnosis to the Clinical Unit of AID, at the Department of Autoimmune Diseases, Hospital Clínic of Barcelona, from 2008 to 2014.

**RESULTS:** During the study period, a genetic study for suspected AID was requested to 90 patients at the Department of Autoimmune Diseases. A final diagnosis of monogenic AID was achieved in 17 patients (19% of patients tested). Five additional cases were diagnosed with periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome and 10 patients with AID were referred from other adult departments. Finally, a total of 32 patients with AID

were finally diagnosed or monitored in our Clinical Unit. These included 12 (37.5%) familial Mediterranean fever, 6 (18.8%) tumour necrosis factor-receptor associated periodic syndrome, 8 (25%) cryopirin-associated periodic syndromes (Muckle-Wells syndrome [MWS] or overlap familial cold-associated periodic syndrome/MWS), 1 (3.1%) mevalonate kinase deficiency, and 5 (15.6%) PFAPA. Clinical evidence of disease-onset during childhood and adulthood was observed in 15 (47%) and 17 (53%) patients, respectively. Overall, the final diagnosis was obtained after a delay of a mean of 12 years (range 0-47 years). Compared to children, adult patients with AID in our series presented more frequently with non-severe manifestations and none of them developed amyloidosis during follow-up. Adult patients also carried higher proportion of low-penetrance mutations or polymorphisms and all genetic variants were presented in heterozygosis or as heterozygous compounds.

CONCLUSIONS: Adult disease-onset or delayed diagnosis of AID during adulthood is associated with milder disease phenotypes, and seem to be driven by mild genotypes, with predominant presence of low-penetrance mutations or polymorphisms.

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DOI: 10.1016/j.autrev.2015.08.008

PMID: 26299986 [Indexed for MEDLINE]

1524. Nat Rev Immunol. 2015 Sep 15;15(9):529-44. doi: 10.1038/nri3875. Epub 2015 Aug 21.

Translating nucleic acid-sensing pathways into therapies.

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Nucleic acid sensing by innate receptors initiates immune defences against

viruses and other pathogens. A hallmark of this response is the release of interferons (IFNs), which promote protective immunity by inducing IFN-stimulated genes (ISGs). A similar ISG signature is found in autoinflammatory and autoimmune conditions, indicating that chronic activation of nucleic acid-sensing pathways may contribute to these diseases. Here, we review how nucleic acid-sensing pathways are currently being targeted pharmacologically with both agonists and antagonists. We discuss how an improved understanding of the biology of these pathways is leading to novel therapies for infections, cancer, and autoimmune and autoinflammatory disorders, and how new therapeutics will, in turn, generate a deeper understanding of these complex diseases.

DOI: 10.1038/nri3875

PMID: 26292638 [Indexed for MEDLINE]

1525. MAbs. 2015;7(6):1151-60. doi: 10.1080/19420862.2015.1081323. Epub 2015 Aug 18.

The molecular mode of action and species specificity of canakinumab, a human monoclonal antibody neutralizing IL-1 $\beta$ .

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Interleukin-1 $\beta$  (IL-1 $\beta$ ) plays a key role in autoinflammatory diseases, such as systemic juvenile idiopathic arthritis (sJIA) or cryopyrin-associated periodic syndrome (CAPS). Canakinumab, a human monoclonal anti-IL-1 $\beta$  antibody, was recently approved for human use under the brand name Ilaris®. Canakinumab does not cross-react with IL-1 $\beta$  from mouse, rat, rabbit, or macaques. The crystal structure of the canakinumab Fab bound to human IL-1 $\beta$  was determined in an attempt to rationalize the species specificity. The X-ray analysis reveals a complex surface epitope with an intricate network of well-ordered water molecules at the antibody-antigen interface. The canakinumab paratope is largely pre-organized, as demonstrated by the structure determination of the free Fab. Glu 64 of human IL-1 $\beta$  is a pivotal epitope residue explaining the exquisite species specificity of canakinumab. We identified marmoset as the only non-human primate species that carries Glu 64 in its IL-1 $\beta$  and demonstrates full cross-reactivity of canakinumab, thereby enabling toxicological studies in this

species. As demonstrated by the X-ray structure of the complex with IL-1 $\beta$ , canakinumab binds IL-1 $\beta$  on the opposite side with respect to the IL-1RAcP binding site, and in an approximately orthogonal orientation with respect to IL-1RI. However, the antibody and IL-1RI binding sites slightly overlap and the VH region of canakinumab would sterically interfere with the D1 domain of IL-1RI, as shown by a structural overlay with the IL-1 $\beta$ :IL-1RI complex. Therefore, direct competition with IL-1RI for IL-1 $\beta$  binding is the molecular mechanism of neutralization by canakinumab, which is also confirmed by competition assays with recombinant IL-1RI and IL-1RII.

DOI: 10.1080/19420862.2015.1081323

PMCID: PMC4966334

PMID: 26284424 [Indexed for MEDLINE]

1526. Int J Rheum Dis. 2017 Jan;20(1):103-108. doi: 10.1111/1756-185X.12732. Epub 2015 Aug 18.

Safety profile of biologic agents for Behçet's disease in a multicenter observational cohort study.

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**AIM:** The primary aim of this study was to explore the safety profile of biologic treatments in Behçet's disease (BD), based on their mechanism of action; the secondary aim was to study any potential variation in terms of retention rate according to each single drug.

**METHOD:** We studied a total of 85 treatment regimens with biologic agents from 64 patients. The total follow-up was calculated as 8640 patient-years (anti-tumor necrosis factor [TNF]-alpha 7.020, anti-interleukin [IL]-beta 1.368). Cumulative rates of drug retention were studied using the Kaplan-Meier plot and covariates in the regression model included the mechanism of action of the biologic agent, other concomitant therapies, disease duration, sex, age at start of drug therapy; for each confounding factor hazard ratios (HR) were calculated.

**RESULTS:** The most frequently prescribed biologic treatments were anti-TNF-alpha agents (79%), while anti-IL1-beta was used in the remaining regimens. Concomitant disease-modifying antirheumatic drugs were prescribed in 36% of patients, mainly cyclosporine and methotrexate, while in 35/85 regimens low-dose glucocorticoids were associated. During the follow-up, in all but one regimen the safety profile was free of any adverse events or serious adverse events; we observed only one case of endocarditis, reported during the 10th month of etanercept.

**CONCLUSION:** Data from a large multicenter cohort suggest that anti-TNF-alpha and anti-IL1-beta agents are characterized by an excellent safety profile in BD.

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DOI: 10.1111/1756-185X.12732

PMID: 26284332 [Indexed for MEDLINE]

1527. Nat Rev Rheumatol. 2015 Oct;11(10):567-9. doi: 10.1038/nrrheum.2015.114. Epub 2015 Aug 18.

Autoinflammation. Management of hereditary recurrent fevers--SHARE experience.

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Comment on

Ann Rheum Dis. 2015 Sep;74(9):1636-44.

Although new therapeutic options are available for patients with autoinflammatory diseases, evidence-based treatment guidelines are lacking. An initiative in European paediatric rheumatology aims to develop best-practice recommendations for the management of these rare disorders.

DOI: 10.1038/nrrheum.2015.114

PMID: 26282081 [Indexed for MEDLINE]

1528. Intern Med. 2015;54(16):2069-72. doi: 10.2169/internalmedicine.54.3371. Epub 2015 Aug 15.

A Case Presenting with the Clinical Characteristics of Tumor Necrosis Factor (TNF) Receptor-associated Periodic Syndrome (TRAPS) without TNFRSF1A Mutations Successfully Treated with Tocilizumab.

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A 30-year-old woman had suffered from recurrent and self-limiting fevers since childhood. Although she had no mutations in the exons or introns of the tumor necrosis factor (TNF) receptor superfamily member 1A gene, her clinical characteristics were consistent with those of TNF receptor-associated periodic syndrome (TRAPS). She did not respond to treatment with etanercept, although tocilizumab therapy was successful, subsequently ameliorating her symptoms and



preventing further inflammatory attacks. Interleukin-6 blocking therapy should be considered as a new alternative treatment in patients with TRAPS who do not respond to etanercept.

DOI: 10.2169/internalmedicine.54.3371

PMID: 26278305 [Indexed for MEDLINE]

1529. Autoimmun Rev. 2015 Dec;14(12):1147-53. doi: 10.1016/j.autrev.2015.08.002. Epub 2015 Aug 9.

Inherited anomalies of innate immune receptors in pediatric-onset inflammatory diseases.

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Pattern-recognition receptors (PRRs) can detect various pathogen-associated molecular patterns such as carbohydrates, nucleic acids or bacterial peptides and

play a major role in both innate and adaptive immunity. In physiological conditions, the engagement of PRRs triggers the production of proinflammatory cytokines and promotes pathogen destruction. Inappropriate stimulation or defective regulation of PRR has been recently evidenced in several inherited inflammatory disorders. This new field of childhood-onset inflammatory diseases encompass the so-called type-I interferon-related diseases and autoinflammatory diseases.

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DOI: 10.1016/j.autrev.2015.08.002

PMID: 26269221 [Indexed for MEDLINE]

1530. Indian J Dermatol Venereol Leprol. 2015 Sep-Oct;81(5):518-9. doi: 10.4103/0378-6323.162319.

Unilateral cutaneous vasculitis: An uncommon presentation and a possible explanation.

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DOI: 10.4103/0378-6323.162319

PMID: 26261133 [Indexed for MEDLINE]

1531. Nat Rev Cardiol. 2016 Feb;13(2):99-105. doi: 10.1038/nrcardio.2015.115. Epub 2015 Aug 11.

Recurrent pericarditis: new and emerging therapeutic options.

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Recurrent pericarditis is one of the most common and troublesome complications after an episode of pericarditis, and affects 20-50% of patients treated for pericarditis. In most of these patients, the pericarditis remains idiopathic, although an immune-mediated (either autoimmune or autoinflammatory) pathogenesis is often presumed. The mainstay of therapy for recurrences is aspirin or NSAIDs, with the adjunct of colchicine. Corticosteroids are a second-line option to be considered for specific indications, such as connective tissue disease or pregnancy; contraindications or intolerance to aspirin, NSAIDs, and/or colchicine; or insufficient response to these medications. Furthermore, corticosteroids can be added to NSAIDs and colchicine in patients with persistent symptoms. In patients who do not respond adequately to any of these conventional therapies, alternative treatment options include azathioprine, intravenous human immunoglobulins, and anakinra. An improved understanding of how recurrent pericarditis develops after an initiating event is critical to prevent this complication, and further research is needed into the pathogenesis of recurrences. We discuss the aetiology and diagnosis of recurrent pericarditis, and extensively review the treatment options for this condition.

DOI: 10.1038/nrcardio.2015.115

PMID: 26259934 [Indexed for MEDLINE]

1532. J Immunol Methods. 2015 Nov;426:76-81. doi: 10.1016/j.jim.2015.08.004. Epub 2015 Aug 8.

Reconstituted AIM2 inflammasome in cell-free system.

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Absent in melanoma 2 (AIM2) is an intracellular pattern-recognition receptor, which is a member of the PYHIN protein family, consisting of a PYD domain and an IFN-inducible nuclear localization (HIN) domain. AIM2 is reported to oligomerize with adaptor protein ASC upon sensing bacterial and viral cytosolic DNA in order to form the AIM2 inflammasome, which activates caspase-1 leading to IL-1 $\beta$  secretion. Dysregulation of AIM2 inflammasome is supposed to result in autoinflammatory and autoimmune diseases. Thus, the development of new targeted drugs against AIM2 inflammasome would be important for the treatment of these diseases. However, since AIM2 inflammasome is an intracellular receptor, enforced internalization of both ligands and candidate molecules is necessary for the screening of AIM2-inflammasome-targeted molecules. We developed a reconstituted AIM2 inflammasome in a cell-free system with amplified luminescent proximity homogeneous assay (Alpha). Strong Alpha signal was detected upon incubation with poly-deoxyadenylic-deoxythymidylic acid, poly(dA:dT), whereas no Alpha signal was detected upon incubation with muramyl dipeptide, one of the NLR ligands of Nod2 ligand. The interaction between AIM2 and ASC was disrupted by an anti-human ASC monoclonal antibody, CRID3, a class of diarylsulfonylurea-containing compounds, and glycyrrhizin, a substance found in liquorice root. Thus, the reconstituted AIM2 inflammasome in a cell-free system is useful for screening AIM2-inflammasome-targeted therapeutic molecules.

DOI: 10.1016/j.jim.2015.08.004

PMID: 26259507 [Indexed for MEDLINE]

1533. Clin Nephrol. 2016 Aug;86(2):100-5. doi: 10.5414/CN108343.

Colchicine toxicity in renal patients - Are we paying attention?

Medani S, Wall C.

Colchicine is an approved agent in the management and prophylaxis of gout and familial Mediterranean fever but its therapeutic value is limited by its narrow therapeutic index. Multisystem toxicity is uncommonly reported; and is often associated with renal impairment and/or specific drug interactions. We report two cases of colchicine toxicity marked by severe neuromyopathy in a diabetic with stage 4 chronic kidney disease (CKD) and a renal transplant recipient. Both patients presented with diarrhea, acute on chronic kidney injury and progressive muscle weakness while on colchicine for several weeks or longer. In addition to kidney disease, risk factors for colchicine toxicity included maintenance therapy with simvastatin in the first patient and cyclosporine in the second. Creatine phosphokinase (CPK) was elevated in both cases at presentation and neurophysiologic studies showed a pattern of severe myopathy with axonal sensorimotor neuropathy. The first patient recovered from neurological weakness in a few weeks, but the second patient suffered an extraordinarily protracted and severe neuromuscular disability for a year. The two cases reinforce the need for extra vigilance in prescribing and monitoring colchicine therapy in renal patients with specific attention to drug interactions known to increase the risk of toxicity, thus avoiding such combinations in patients with renal impairment.

DOI: 10.5414/CN108343

PMID: 26249546 [Indexed for MEDLINE]

1534. Mol Genet Genomic Med. 2015 Jul;3(4):272-82. doi: 10.1002/mgg3.140. Epub 2015 Apr 5.

Global epidemiology of Familial Mediterranean fever mutations using population

exome sequences.

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Familial Mediterranean fever (FMF) is an inherited disorder characterized by recurrent episodes of fever accompanied by sterile peritonitis, arthritis, and pleuritis. Many mutations in the MEFV gene have been identified as causing FMF. However, accompanying epidemiological information remains quite scarce except in some Mediterranean countries, and the degree of penetrance has been a subject of controversy. Here, I established a genetic epidemiology of full FMF mutations using two population exome studies. Of 57 mutations associated with FMF, 22 were detected in a total of 9007 individuals from two exome sequences. Exome-based epidemiology revealed the carrier rates of FMF in 28 populations in 19 countries by individual mutation and showed strong population specificity for the MEFV mutations. Unexpectedly high carrier rates suggested that some mutations are benign variants with no pathological significance and highlighted the need for caution in analyzing MEFV mutations. Similar approach could be used to uncover the incomplete or no penetrance of mutations in most inherited disorders.

DOI: 10.1002/mgg3.140

PMCID: PMC4521964

PMID: 26247045

1535. Arthritis Rheumatol. 2015 Nov;67(11):3027-36. doi: 10.1002/art.39292.

Musculoskeletal symptoms in patients with cryopyrin-associated periodic syndromes: a large database study.

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**OBJECTIVE:** To determine the type and frequency of musculoskeletal symptoms at onset and during followup of cryopyrin-associated periodic syndromes (CAPS).

**METHODS:** We retrospectively recorded the articular and muscular symptoms of patients with CAPS followed up in French hospitals. Data were presented as frequencies or the median (range), and patient groups were compared using chi-square test, Fisher's exact test, and Mann-Whitney test.

**RESULTS:** The study included 133 patients (33 children), 20 with familial cold autoinflammatory syndrome, 88 with Muckle-Wells syndrome, 22 with chronic infantile neurologic, cutaneous, articular syndrome, and 3 with unclassified CAPS. The median age was 35 years (range 0-78 years) at the time of the study, 1 year (range 0-41 years) at symptom onset, and 23 years (range 0-58 years) at diagnosis. The disease was sporadic in 17% of the patients. Cutaneous symptoms predominated at onset (77%), followed by articular symptoms (30%). The p.Thr348Met and p.Arg260Trp NLRP3 mutations were significantly associated with the presence and absence of articular symptoms at onset, respectively. During followup, 86% of the patients had musculoskeletal symptoms, 88% had arthralgia, and 58% had arthritis, but only 9% had joint destruction. Tendinopathies occurred in 21.5% of the patients, tender points in 16.5%, and myalgia in 33%. Only 3 patients had typical knee deformities. Radiographs were rarely obtained. Except for bone deformities, osteoarticular symptoms occurred at similar frequencies in the different CAPS phenotypes.

**CONCLUSION:** Joint manifestations were frequent in all CAPS phenotypes. Bone deformities were rare. Musculoskeletal manifestations varied within given families but tended to worsen over time.

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DOI: 10.1002/art.39292

PMID: 26245507 [Indexed for MEDLINE]

1536. Am J Cardiovasc Drugs. 2015 Oct;15(5):295-306. doi: 10.1007/s40256-015-0133-4.

Pharmacotherapeutic considerations for using colchicine to treat idiopathic



pericarditis in the USA.

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The clinical significance of colchicine in the treatment of acute idiopathic (viral) pericarditis (IP) was only elucidated less than a decade ago. Multiple trials have shown the benefit of colchicine in decreasing the rate of recurrence, primarily in the European population. However, the colchicine formulation used in these trials is not available in Western countries such as the USA. In the USA, two formulations are available: the 0.6 mg capsule and the 0.6 mg tablet. As a result, higher doses than administered in the European trials must be utilized to treat IP. However, the use of these dosage forms has never been studied in the treatment of IP. Pharmacokinetic and pharmacodynamic knowledge of colchicine germane to clinicians such as drug disposition and drug-drug or drug-disease interactions have not been extensively reviewed in recent years. Furthermore, the safety of colchicine in the treatment of IP has not been extensively studied, and literature regarding adverse drug events originates from data in patients treated for familial Mediterranean fever and gout. This review will help the clinician understand pharmacotherapeutic considerations and thereby optimize therapy and ensure patient safety when using colchicine to treat IP.

DOI: 10.1007/s40256-015-0133-4

PMID: 26243656 [Indexed for MEDLINE]

1537. Clin Exp Rheumatol. 2015 Nov-Dec;33(6 Suppl 94):S67-71. Epub 2015 Aug 5.

Efficacy and safety of canakinumab in cryopyrin-associated periodic syndromes: results from a Spanish cohort.

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**OBJECTIVES:** Cryopyrin-associated periodic syndromes (CAPS) are dominantly-inherited autoinflammatory diseases. The uncontrolled IL-1 $\beta$  overproduction observed in these patients is the rational basis to treat them with anti-IL-1 drugs. The objective of this study was to evaluate the efficacy and safety of treatment with the long-lasting fully humanised anti-IL-1 $\beta$  monoclonal antibody canakinumab in a Spanish cohort of patients with CAPS.

**METHODS:** Clinical and laboratory data of CAPS patients carrying a heterozygous germline NLRP3 mutation were obtained. The initial treatment scheme with canakinumab was 150 mg/8 weeks administered subcutaneously in adult patients and 2 mg/kg/8 weeks in paediatric patients.

**RESULTS:** Eight unrelated patients were enrolled. Canakinumab was the first anti-IL-1 drug used in three of them; five were already receiving anakinra. The clinical response to the initial canakinumab scheme was positive in all patients, and was quickly observed in the first 24-72 hours. Four required increasing the frequency and/or dose of canakinumab. A limited or no efficacy in those symptoms related to consequence of the deforming arthropathy and neurosensorial deafness was observed. The adverse side effects were restricted to infectious complications in a small percentage of patients. The treatment was well tolerated by all patients, with no reactions at drug site injections.

**CONCLUSIONS:** Canakinumab caused fast and sustained remissions in most clinical and biochemical manifestations in all enrolled patients, with a limited efficacy in the structural lesions. Dose adjustments seem to be necessary for children and/or for patients with the most severe CAPS phenotypes. Treatment was well

tolerated with a low incidence of adverse effects.

PMID: 26243511 [Indexed for MEDLINE]

1538. Nat Rev Rheumatol. 2015 Nov;11(11):670-80. doi: 10.1038/nrrheum.2015.105. Epub 2015 Aug 4.

Redox distress and genetic defects conspire in systemic autoinflammatory diseases.

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Inflammation is initiated by innate immune cell activation after contact with pathogens or tissue injury. An increasing number of observations have suggested that cellular stress, in the absence of infection or evident damage, can also induce inflammation. Thus, inflammation can be triggered by exogenous pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs)-so-called classic inflammation-or by endogenous stress resulting from tissue or cellular dysfunction. External triggers and cellular stress activate the same molecular pathways, possibly explaining why classic and stress-induced inflammation have similar clinical manifestations. In some systemic autoinflammatory diseases (SAIDs), inflammatory cells exhibit reduction-oxidation (redox) distress, having high levels of reactive oxygen species (ROS), which promote proinflammatory cytokine production and contribute to the subversion of mechanisms that self-limit inflammation. Thus, SAIDs can be viewed as a paradigm of stress-related inflammation, being characterized by recurrent flares or chronic inflammation (with no recognizable external triggers) and by a failure to downmodulate this inflammation. Here, we review SAID pathophysiology, focusing on the major cytokines and DAMPs, and on the key roles of redox distress. New therapeutic opportunities to tackle SAIDs by blocking

stress-induced pathways and control the response to stress in patients are also discussed.

DOI: 10.1038/nrrheum.2015.105

PMID: 26241183 [Indexed for MEDLINE]

1539. Ugeskr Laeger. 2015 Jul 20;177(30). pii: V12140756.

[Schnitzler syndrome is a diagnostic challenge].

[Article in Danish]

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Schnitzler syndrome (SS) is a rare autoinflammatory disorder characterized by a chronic urticarial rash and a monoclonal immunoglobulin M gammopathy, accompanied by recurrent fever, lymphadenopathy, arthralgia or arthritis, hepato- or splenomegaly and elevated levels of markers of systemic inflammation. Because patients often present to various specialists with different symptoms the syndrome is often undiagnosed, and it can take years before the correct diagnosis is made. Treatment with interleukin-1 receptor antagonists has a rapid effect on SS.

PMID: 26240044 [Indexed for MEDLINE]

1540. Expert Opin Drug Metab Toxicol. 2015;11(11):1781-94. doi: 10.1517/17425255.2015.1076391. Epub 2015 Aug 4.

Colchicine as an anti-inflammatory and cardioprotective agent.

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**INTRODUCTION:** Colchicine has been successfully used for the treatment of neutrophilic disorders such as familial Mediterranean fever (FMF), Behçet disease (BD) and gout. There is a growing interest in its cardiovascular effects.

**AREAS COVERED:** A MEDLINE/PubMed search for English articles published from January 1972 to June 2015 was completed using the following terms: therapy, pharmacokinetics, efficiency, side effects, toxicity, heart, colchicine, inflammation, FMF, amyloidosis, BD, gout, cardiovascular disorders, pericarditis, arrhythmias, inflammation, neutrophils, platelets.

**EXPERT OPINION:** By targeting neutrophils, endothelial cells and platelets, inhibiting mitosis, vascular hyperplasia and fibrosis, colchicine improves outcomes of pericarditis, myocardial ischemia and coronary interventions. Studies in neutrophilic rheumatic diseases and cardiovascular disorders demonstrated that oral colchicine at doses of 0.5 - 2.5 mg/daily is useful for treating pericarditis, myocardial ischemia and coronary occlusion. In rheumatic and cardiovascular disorders, therapeutic doses of the drug reduce C-reactive protein to levels below 2 mg/L, prevent myocardial damage and preserve normal values of atrial and ventricular impulse generation. One of the drug's frequent side effects is diarrhea, which is treated by diet modification or temporary discontinuation of the therapy. Certain drugs (macrolides, statins), comorbidities and certain genetic factors increase risk of colchicine toxicity.

DOI: 10.1517/17425255.2015.1076391

PMID: 26239119 [Indexed for MEDLINE]

1541. Neurol India. 2015 Jul-Aug;63(4):621-2. doi: 10.4103/0028-3886.162097.

Familial Mediterranean fever with convulsions: A rare association in a child.

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DOI: 10.4103/0028-3886.162097

PMID: 26238909

1542. Z Rheumatol. 2015 Aug;74(6):511-24; quiz 525. doi: 10.1007/s00393-015-1572-7.

[Autoinflammatory syndromes in childhood].

[Article in German]

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Systemic autoinflammatory diseases are a group of hereditary and non-hereditary diseases of the innate immune system, characterized by inflammation with no apparent cause, recurrence at irregular intervals and manifestation on the skin, mucous membranes, joints, bone, gastrointestinal tract, blood vessels and the central nervous system (CNS). Amyloidosis and other possibly severe long-term complications are important. Advances in genetics and molecular biology have improved understanding of the pathogenesis of these diseases, including familial Mediterranean fever, mevalonate kinase deficiency syndrome, tumor necrosis factor receptor-associated periodic syndrome, cryopyrin-associated periodic syndrome and improved others. The vast majority of these diseases are based on activation of the interleukin-1 (IL-1) pathway, so that inhibition of IL-1 provides a therapeutic option. Other syndromes are characterized by a granulomatous inflammation. Newer autoinflammatory diseases, such as chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) and stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI) are, however, driven by interferons.

DOI: 10.1007/s00393-015-1572-7

PMID: 26238708 [Indexed for MEDLINE]

1543. Angiology. 2016 May;67(5):456-60. doi: 10.1177/0003319715595744. Epub 2015 Aug 3.

Ischemia-Modified Albumin and Atherosclerosis in Patients With Familial Mediterranean Fever.

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The constriction of vessels due to atherosclerotic lesions causes hypoxia/ischemia and oxidative changes resulting in transformation of free albumin to ischemia-modified albumin (IMA) in the circulation and increased carotid intima-media thickness (cIMT). We investigated the reliability of IMA increase in evaluating atherosclerosis in patients with familial Mediterranean fever (FMF) compared with cIMT. Patients with FMF (n = 58) diagnosed by the Tel-Hashomer criteria in attack-free period and 38 healthy people were included

in the study. Patient demographics as well as the clinical and laboratory characteristics of the healthy controls and patients with FMF were noted. The IMA levels and cIMT in patients with FMF were  $0.30 \pm 0.09$  absorbance units (ABSUs) and  $1.12 \pm 0.27$  mm, respectively, and in the control group, IMA levels and cIMT were  $0.25 \pm 0.07$  ABSU and  $0.74 \pm 0.26$  mm, respectively. The IMA levels and cIMT were significantly higher in patients with FMF than in controls ( $P = .020$  and  $P < .0001$ , respectively). The IMA values showed positive correlation with cIMT in patients with FMF ( $r = .302, P = .041$ ). Our results reveal that IMA--an oxidative stress marker--may be an indicator of atherosclerosis in patients with FMF. This finding deserves further investigation.

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DOI: 10.1177/0003319715595744

PMID: 26238112 [Indexed for MEDLINE]

1544. Cell Host Microbe. 2015 Aug 12;18(2):157-68. doi: 10.1016/j.chom.2015.07.001. Epub 2015 Jul 30.

STING Activation by Translocation from the ER Is Associated with Infection and Autoinflammatory Disease.

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Comment in



STING is an ER-associated membrane protein that is critical for innate immune sensing of pathogens. STING-mediated activation of the IFN-I pathway through the TBK1/IRF3 signaling axis involves both cyclic-dinucleotide binding and its translocation from the ER to vesicles. However, how these events are coordinated, and the exact mechanism of STING activation, remain poorly understood. Here, we found that the *Shigella* effector protein IpaJ potently inhibits STING signaling by blocking its translocation from the ER to ERGIC, even in the context of dinucleotide binding. Reconstitution using purified components revealed STING translocation as the rate-limiting event in maximal signal transduction. Furthermore, STING mutations associated with autoimmunity in humans were found to cause constitutive ER exit and to activate STING independent of cGAMP binding. Together, these data provide compelling evidence for an ER retention and ERGIC/Golgi-trafficking mechanism of STING regulation that is subverted by bacterial pathogens and is deregulated in human genetic disease.

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DOI: 10.1016/j.chom.2015.07.001

PMCID: PMC4537353

PMID: 26235147 [Indexed for MEDLINE]

1545. Vestn Ross Akad Med Nauk. 2015;(2):169-82.

[Autoimmune Rheumatic Diseases - Problems of Immunopathology and Personalized Treatment].

[Article in Russian]

Nasonov EL, Aleksandrova EN, Novikov AA.

By current standards autoimmunity is a complex pathological process based on a violation of tolerance and, consequently, the pathological immune response against its own tissues components (autoantigens) leading to the development of a wide range of autoimmune diseases in humans. In recent years, multiple immune disorders both acquired and/ or congenital (associated with polymorphisms of genes that regulate immune response) have been transcribed. These disorders occur

at the cellular and humoral levels: thymus, intestines, peripheral blood immune cells, including T and B lymphocytes, macrophages, dendritic cells, Treg-cells (Treg), components of complement system, cytokines and others. The interaction between the development of autoimmune rheumatic (ARD) and autoinflammatory diseases and syndromes is detected; a classification of immune-inflammatory diseases is designed. The article describes the results of our studies on the treatment of ARD using innovative genetically engineered biological agents and on the research of pathogenetic mechanisms and diagnostics of ARD based on immunological and molecular biological diagnostic techniques of a wide range of molecular and cellular biomarkers (autoantibodies, inflammatory acute phase proteins, cytokines, chemokines, markers of activation of the vascular endothelium, the components of the complement system, lymphocyte subpopulations, products of metabolism of bone and cartilage tissue, genetic, epigenetic, transcriptomic markers). The approaches to personalized treatment of ARD are presented.

PMID: 26234089 [Indexed for MEDLINE]

1546. J Rheumatol. 2015 Aug;42(8):1534-5. doi: 10.3899/jrheum.141240.

TNFRSF1A Gene Causing Tumor Necrosis Factor Receptor-associated Periodic Syndrome in 2 Siblings Displaying Variable Disease Severity and Discordant Heterozygosity for an MEFV E148Q Variant.

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DOI: 10.3899/jrheum.141240

PMID: 26233954 [Indexed for MEDLINE]

1547. Int J Pediatr Otorhinolaryngol. 2015 Sep;79(9):1566-70. doi: 10.1016/j.ijporl.2015.07.020. Epub 2015 Jul 23.

Cochlear functions in children with familial Mediterranean fever: any role of the severity of the disease?

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**OBJECTIVES:** The aim of the study was to compare the cochlear functions of children diagnosed with familial Mediterranean fever (FMF) with healthy controls and to determine their cochlear functions according to their disease severity.

**METHODS:** Seventy-three children with FMF and 30 healthy controls were included in the study. All the patients and controls were evaluated by audiologic evaluation, including high-frequency pure-tone audiometry and distortion product otoacoustic emission tests (DPOAE). The disease severity was evaluated by scoring systems adapted from those used by Pras et al. and with severity scoring systems from the Sheba Medical Center.

**RESULTS:** High-frequency pure-tone audiometry and DPOAE levels were normal in both

patients and controls. Significant differences in the hearing levels of FMF patients were not found, according to both adapted severity scoring systems. CONCLUSIONS: Cochlear functions in children with FMF had been evaluated by previous studies, but in our study we evaluated hearing functions according to both controls and disease severity. As a unique study comparing cochlear functions according to severity scores, no significant differences were shown between the groups and controls.

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DOI: 10.1016/j.ijporl.2015.07.020

PMID: 26231741 [Indexed for MEDLINE]

1548. Semin Arthritis Rheum. 2015 Dec;45(3):341-50. doi: 10.1016/j.semarthrit.2015.06.013. Epub 2015 Jun 26.

Colchicine--Update on mechanisms of action and therapeutic uses.

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Comment in

Semin Arthritis Rheum. 2016 Apr;45(5):e15.

Semin Arthritis Rheum. 2016 Jun;45(6):e25.

OBJECTIVES: To review the literature and provide an update on the mechanisms of action and therapeutic uses of oral colchicine in arthritis and inflammatory conditions.

METHODS: We performed PubMed database searches through June 2014 for relevant

studies in the English literature published since the last update of colchicine in 2008. Searches encompassed colchicine mechanisms of action and clinical applications in medical conditions. A total of 381 articles were reviewed.

**RESULTS:** The primary mechanism of action of colchicine is tubulin disruption. This leads to subsequent down regulation of multiple inflammatory pathways and modulation of innate immunity. Newly described mechanisms include various inhibitory effects on macrophages including the inhibition of the NACHT-LRRPYD-containing protein 3 (NALP3) inflammasome, inhibition of pore formation activated by purinergic receptors P2X7 and P2X2, and stimulation of dendritic cell maturation and antigen presentation. Colchicine also has anti-fibrotic activities and various effects on endothelial function. The therapeutic use of colchicine has extended beyond gouty arthritis and familial Mediterranean fever, to osteoarthritis, pericarditis, and atherosclerosis.

**CONCLUSION:** Further understanding of the mechanisms of action underlying the therapeutic efficacy of colchicine will lead to its potential use in a variety of conditions.

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DOI: 10.1016/j.semarthrit.2015.06.013

PMCID: PMC4656054

PMID: 26228647 [Indexed for MEDLINE]

1549. Isr Med Assoc J. 2015 Feb;17(2):93-7.

Interleukin-1: Ariadne's Thread in Autoinflammatory and Autoimmune Disorders.

Cantarini L, Lopalco G, Cattalini M, Vitale A, Galeazzi M, Rigante D.

Autoinflammatory and autoimmune disorders are characterized by chronic activation of the immune system, which leads to systemic self-directed inflammation in genetically predisposed individuals. Mutations in inflammasome-related proteins have been associated with autoinflammatory disorders, and the link between inflammasome and autoimmune disorders is becoming increasingly clear. As researchers learn more about these two areas, other disorders that were once thought to be autoimmune are now being considered autoinflammatory, or as having at least an autoinflammatory component. This review depicts the role of interleukin-1 as "Ariadne's thread" on the path through the labyrinth of

autoinflammatory and autoimmune disorders and emphasizes the blurred boundary between innate and adaptive immune systems.

PMID: 26223084 [Indexed for MEDLINE]

1550. Autophagy. 2016;12(2):245-60. doi: 10.1080/15548627.2015.1071759. Epub 2015 Jul 29.

Modulation of inflammation by autophagy: Consequences for human disease.

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Autophagy and inflammation are 2 fundamental biological processes involved in both physiological and pathological conditions. Through its crucial role in maintaining cellular homeostasis, autophagy is involved in modulation of cell metabolism, cell survival, and host defense. Defective autophagy is associated with pathological conditions such as cancer, autoimmune disease, neurodegenerative disease, and senescence. Inflammation represents a crucial line of defense against microorganisms and other pathogens, and there is increasing evidence that autophagy has important effects on the induction and modulation of the inflammatory reaction; understanding the balance between these 2 processes may point to important possibilities for therapeutic targeting. This review focuses on the crosstalk between autophagy and inflammation as an emerging field with major implications for understanding the host defense on the one hand, and for the pathogenesis and treatment of immune-mediated diseases on the other hand.

DOI: 10.1080/15548627.2015.1071759

PMCID: PMC4836004

1551. Foot Ankle Int. 2015 Dec;36(12):1455-62. doi: 10.1177/1071100715596608. Epub 2015 Jul 28.

# Autoinflammation Around AES Total Ankle Replacement Implants.

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**BACKGROUND:** Failure of total ankle replacement (TAR) can be characterized by early peri-implant osteolysis even in the presence of very modest numbers of wear particles. The hypothesis of the study was that this reaction is in part mediated by autoinflammatory responses mediated via damage-associated molecular patterns (DAMPs, danger signals) and pattern-recognizing danger signal receptors (PRRs).

**METHODS:** Peri-implant tissue and control samples from 10 patients with AES implants were immunostained for hypoxia inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ), activated caspase-3, high-mobility group box 1 (HMGB1), receptor for advanced glycation end product (RAGE), and toll-like receptors TLR2 and TLR4. Results were evaluated on a 0 to 4 scale (from 0% to >50% stained area).

**RESULTS:** Peri-implant tissue around failed TAR implants had a relatively high mean HIF-1 $\alpha$  score of 3 on a scale, which however was similar in control samples. HMGB1 (a DAMP) was seen to be mobilized from nuclei to cellular cytoplasm, and the active caspase-3(+) cells were increased. All PRRs were increased in revision

samples.

CONCLUSIONS: Increased expression of HMGB1 and other danger signals together with increased PRR-dependent responsiveness could contribute to autoinflammatory peri-implantitis, multilocular cyst formation, and osteolysis in failed TAR implants.

LEVEL OF EVIDENCE: Level IV, case series.

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DOI: 10.1177/1071100715596608

PMID: 26219907 [Indexed for MEDLINE]

1552. J Leukoc Biol. 2015 Dec;98(6):983-94. doi: 10.1189/jlb.3VMA0315-078R. Epub 2015 Jul 27.

Intravenous immunoglobulin skews macrophages to an anti-inflammatory, IL-10-producing activation state.

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Intravenous Ig is used to treat autoimmune or autoinflammatory disorders, but the mechanism by which it exerts its immunosuppressive activity is not understood completely. To examine the impact of intravenous Ig on macrophages, we compared cytokine production by LPS-activated macrophages in the presence and absence of intravenous Ig. Intravenous Ig treatment induced robust production of IL-10 in response to LPS, relative to LPS stimulation alone, and reduced production of proinflammatory cytokines. This anti-inflammatory, intravenous Ig-induced activation was sustained for 24 h but could only be induced if intravenous Ig were provided within 1 h of LPS stimulation. Intravenous Ig activation led to enhanced and prolonged activation of MAPKs, Erk1/2, p38, and Erk5, and inhibition of each reduced intravenous Ig-induced IL-10 production and suppression of IL-12/23p40. IL-10 production occurred rapidly in response to intravenous Ig + LPS and was sufficient to reduce proinflammatory IL-12/23p40 production in response to LPS. IL-10 induction and reduced IL-12/23p40 production were transcriptionally regulated. IL-10 played a direct role in reducing proinflammatory cytokine production by macrophages treated with intravenous Ig + LPS, as macrophages from mice deficient in the IL-10R  $\beta$  chain or in IL-10 were compromised in their ability to reduce proinflammatory cytokine production. Finally, intraperitoneal injection of intravenous Ig or intravenous Ig + LPS into mice activated macrophages to produce high levels of IL-10 during subsequent or concurrent LPS challenge, respectively. These findings identify IL-10 as a key anti-inflammatory mediator produced by intravenous Ig-treated macrophages and provide insight into a novel mechanism by which intravenous Ig may dampen down inflammatory responses in patients with autoimmune or autoinflammatory diseases.

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DOI: 10.1189/jlb.3VMA0315-078R

PMID: 26216934 [Indexed for MEDLINE]

1553. Rheumatol Int. 2016 Jan;36(1):25-31. doi: 10.1007/s00296-015-3329-7. Epub 2015 Jul 28.

The report of sequence analysis on familial Mediterranean fever gene (MEFV) in South-eastern Mediterranean region (Kahramanmaraş) of Turkey.

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Familial Mediterranean fever (FMF) is defined as an inherited and autosomal recessive disease. Many researches have been done about this subject, and we believe that it should be necessary to focus on phenotype-genotype correlation, especially novel mutation types. We aim to announce the results of FMF sequence analysis in Kahramanmaras/Turkey. The number of participants is 380 males and 451 females who clinically diagnosed as FMF subjects of different age groups. Genomic sequences of exons 2 and 10 and in some cases exon 3 of the MEFV gene were scanned for mutations by sequence analyzer. The most common mutation identified in 230 (57.07 %) patients is heterozygous. The frequencies of mutation types in heterozygous subjects are R202Q (39.13 %), E148Q (18.70 %), M680I (16.52 %), M694V (13.91 %), and V726A (4.78 %), respectively. The most striking point among the compound heterozygous subjects is R202Q/M694V mutation type found at the highest rate (32 subjects). Fever and peritonitis are the most frequent signs of

homozygous M694V and combine heterozygous mutations. Interestingly, the rate of homozygous mutation types (M694V/M694V+ R202Q/R202Q) is 96.70 % among all compound homozygous mutation types. The most frequent rate of homozygous patients is M680I mutation types (68.42 % in all homozygous mutation types). Two novel mutations were found in this study: N206K (p.Asn206Lys) and S208T (p.Ser208Tyr). Our findings in this study on the FMF sequence analysis are different from the results obtained from the other regions of Turkey.

DOI: 10.1007/s00296-015-3329-7

PMID: 26215181 [Indexed for MEDLINE]

1554. Rheumatol Int. 2015 Nov;35(11):1937-41. doi: 10.1007/s00296-015-3325-y. Epub 2015 Jul 26.

Colchicine-clarithromycin-induced rhabdomyolysis in Familial Mediterranean Fever patients under treatment for Helicobacter pylori.

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Chronic administration of colchicine remains a mainstay of therapy for patients

with Familial Mediterranean Fever (FMF). As this medication is a strong CYP3A4 inhibitor, it has the potential to interact with many routinely used medications. One such medication is clarithromycin, itself a strong inhibitor of the same enzyme, and a typical choice for triple therapy eradication of *H. pylori*. Various sequelae of colchicine-clarithromycin interaction have been documented and can be expected by prescribing physicians, with rhabdomyolysis, though rare, being among the most serious. Review of cases from a tertiary academic medical center and full PubMed/MEDLINE literature review. Despite the prevalence of diseases treated with clarithromycin and the expected drug interaction with colchicine, only two cases in the literature document clinical rhabdomyolysis due to colchicine-clarithromycin interaction. In neither case, however, were patients undergoing treatment for FMF. Herein, we describe the first two cases in the literature of clinical rhabdomyolysis in FMF patients under colchicine therapy after administration of clarithromycin as part of therapy treating *H. pylori* infection.

DOI: 10.1007/s00296-015-3325-y

PMID: 26210999 [Indexed for MEDLINE]

1555. Rheumatology (Oxford). 2015 Dec;54(12):2134-44. doi: 10.1093/rheumatology/kev269. Epub 2015 Jul 23.

Treating rheumatological diseases and co-morbidities with interleukin-1 blocking therapies.

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The inflammatory cytokines IL-1 $\alpha$  and IL-1 $\beta$  orchestrate local and systemic inflammatory responses underlying a broad spectrum of diseases. Three agents for reducing IL-1 activities are currently available. Anakinra is a recombinant form

of the naturally occurring IL-1 receptor antagonist. Anakinra binds to the IL-1 receptor and prevents the activity of IL-1 $\alpha$  and IL-1 $\beta$ . The soluble decoy receptor rilonacept and the neutralizing mAb canakinumab block IL-1 $\beta$ . A mAb directed against the IL-1 receptor and a neutralizing anti-human IL-1 $\alpha$  are in clinical trials. The availability of therapies specifically targeting IL-1 unveiled the pathological role of IL-1-mediated inflammation in a broadening list of diseases. Conditions effectively treated with agents blocking IL-1 range from classic rheumatic diseases, such as RA and gout, to autoinflammatory syndromes, such as systemic JIA and FMF. However, IL-1 antagonism is also effective against highly prevalent inflammatory diseases, namely cardiovascular diseases and type 2 diabetes, conditions that are frequently encountered as co-morbidities in patients with rheumatic diseases. Thereby, IL-1 inhibition has the potential to lift the burden of disease for patients with rheumatic conditions, but also to provide clinical benefits beyond the efficacy on osteoarticular manifestations.

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DOI: 10.1093/rheumatology/kev269

PMCID: PMC5009422

PMID: 26209330 [Indexed for MEDLINE]

1556. Clin Exp Immunol. 2015 Dec;182(3):251-60. doi: 10.1111/cei.12687. Epub 2015 Sep 17.

Proinsulin multi-peptide immunotherapy induces antigen-specific regulatory T cells and limits autoimmunity in a humanized model.

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Peptide immunotherapy (PIT) is a targeted therapeutic approach, involving administration of disease-associated peptides, with the aim of restoring antigen-specific immunological tolerance without generalized immunosuppression. In type 1 diabetes, proinsulin is a primary antigen targeted by the autoimmune response, and is therefore a strong candidate for exploitation via PIT in this setting. To elucidate the optimal conditions for proinsulin-based PIT and explore mechanisms of action, we developed a preclinical model of proinsulin autoimmunity in a humanized HLA-DRB1\*0401 transgenic HLA-DR4 Tg mouse. Once proinsulin-specific tolerance is broken, HLA-DR4 Tg mice develop autoinflammatory responses, including proinsulin-specific T cell proliferation, interferon (IFN)- $\gamma$  and autoantibody production. These are preventable and quenchable by pre- and post-induction treatment, respectively, using intradermal proinsulin-PIT injections. Intradermal proinsulin-PIT enhances proliferation of regulatory [forkhead box protein 3 (FoxP3(+))CD25(high)] CD4 T cells, including those capable of proinsulin-specific regulation, suggesting this as its main mode of action. In contrast, peptide delivered intradermally on the surface of vitamin D3-modulated (tolerogenic) dendritic cells, controls autoimmunity in association with proinsulin-specific IL-10 production, but no change in regulatory CD4 T cells. These studies define a humanized, translational model for in vivo optimization of PIT to control autoimmunity in type 1 diabetes and indicate that dominant mechanisms of action differ according to mode of peptide delivery.

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DOI: 10.1111/cei.12687

PMCID: PMC4636887

PMID: 26206289 [Indexed for MEDLINE]

1557. Eur J Immunol. 2015 Oct;45(10):2937-44. doi: 10.1002/eji.201545769. Epub 2015 Aug 17.

Tumour necrosis factor receptor I blockade shows that TNF-dependent and TNF-independent mechanisms synergise in TNF receptor associated periodic syndrome.

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TNF receptor associated periodic syndrome (TRAPS) is an autoinflammatory disease involving recurrent episodes of fever and inflammation. It is associated with autosomal dominant mutations in TNF receptor superfamily 1A gene localised to exons encoding the ectodomain of the p55 TNF receptor, TNF receptor-1 (TNFR1). The aim of this study was to investigate the role of cell surface TNFR1 in TRAPS, and the contribution of TNF-dependent and TNF-independent mechanisms to the production of cytokines. HEK-293 and SK-HEP-1 cell lines were stably transfected with WT or TRAPS-associated variants of human TNF receptor superfamily 1A gene. An anti-TNFR1 single domain antibody (dAb), and an anti-TNFR1 mAb, bound to cell surface WT and variant TNFR1s. In HEK-293 cells transfected with death domain-inactivated (R347A) TNFR1, and in SK-HEP-1 cells transfected with normal (full-length) TNFR1, cytokine production stimulated in the absence of exogenous TNF by the presence of certain TNFR1 variants was not inhibited by the anti-TNFR1 dAb. In SK-Hep-1 cells, specific TRAPS mutations increased the level of cytokine response to TNF, compared to WT, and this augmented cytokine production was suppressed by the anti-TNFR1 dAb. Thus, TRAPS-associated variants of TNFR1 enhance cytokine production by a TNF-independent mechanism and by sensitising cells to a TNF-dependent stimulation. The TNF-dependent mechanism requires cell surface expression of TNFR1, as this is blocked by TNFR1-specific dAb.

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DOI: 10.1002/eji.201545769

PMID: 26202849 [Indexed for MEDLINE]

1558. Int J Rheum Dis. 2017 Aug;20(8):1050-1051. doi: 10.1111/1756-185X.12722. Epub 2015 Jul 22.

Canakinumab efficacy in refractory adult-onset PFAPA syndrome.

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DOI: 10.1111/1756-185X.12722

PMID: 26200174 [Indexed for MEDLINE]

1559. J Leukoc Biol. 2016 Jan;99(1):79-86. doi: 10.1189/jlb.3MR0415-159R. Epub 2015 Jul 21.

Redox stress unbalances the inflammatory cytokine network: role in autoinflammatory patients and healthy subjects.

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The cell stress and redox responses are increasingly acknowledged as factors contributing to the generation and development of the inflammatory response. Several inflammation-inducing stressors have been identified, inside and outside of the cell. Furthermore, many hereditary diseases associate with inflammation and oxidative stress, suggesting a role for mutated proteins as stressors. The nucleotide-binding oligomerization domain, leucine-rich repeat-containing family, pyrin domain-containing 3 (NLRP3) inflammasome is an important node at the crossroad between redox response and inflammation. Remarkably, monocytes from patients with mutations in the NLRP3 gene undergo oxidative stress after stimulation with minute amounts of TLR agonists, resulting in unbalanced



production of IL-1 $\beta$  and regulatory cytokines. Similar alterations in cytokine production are found in healthy monocytes upon TLR overstimulation. This mini-review summarizes recent progress in this field, discusses the molecular mechanisms underlying the loss of control of the cytokine network following oxidative stress, and proposes new therapeutic opportunities.

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DOI: 10.1189/jlb.3MR0415-159R

PMCID: PMC4673480

PMID: 26199031 [Indexed for MEDLINE]

1560. Arthritis Res Ther. 2015 Jul 22;17:187. doi: 10.1186/s13075-015-0696-0.

The role of interleukin-1 beta in the pathophysiology of Schnitzler's syndrome.

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**INTRODUCTION:** Schnitzler's syndrome (SchS) is a disabling autoinflammatory disorder, characterized by a chronic urticarial rash, an M-protein, arthralgia, and other signs of systemic inflammation. Anti-interleukin-1 (IL-1) beta antibodies are highly effective, but the pathophysiology is still largely unknown. Here we studied the effect of in-vivo IL-1 inhibition on serum markers of inflammation and cellular immune responses.

**METHODS:** Eight patients with SchS received monthly subcutaneous (s.c.) injections with 150 mg canakinumab for six months. Blood was drawn for measurement of serum markers of inflammation (12 times per patient) and for functional and phenotypic analysis of both freshly isolated and toll-like receptor (TLR)-ligand-stimulated peripheral blood mononuclear cells (PBMCs) (five times per patient). All data were compared to results of healthy controls.

**RESULTS:** IL-6 levels in serum and in lysates of freshly isolated PBMCs and serum

myeloid-related protein (MRP8)/14 and S100A12 levels correlated with disease activity. In vitro, LPS stimulation resulted in higher IL-6 and IL-1 beta production in PBMCs from symptomatic SchS patients compared to healthy controls, whereas patient cells were relatively hyporesponsive to poly:IC and Pam3Cys. The mRNA microarray of PBMCs showed distinct transcriptomes for controls, symptomatic patients and anti-IL-1-treated patients. Numbers of T- and B-cell subsets as well as M-protein concentrations were not affected by IL-1 inhibition. Free light chain levels were elevated in 4 out of 8 patients.

**CONCLUSIONS:** In conclusion, patient PBMCs are hyperresponsive to LPS, and clinical efficacy of IL-1 beta inhibition in patients with SchS is associated with in-vivo and ex-vivo suppression of inflammation. Interestingly, patient PBMCs showed divergent responses to TLR2/6, TLR3 and TLR4 ligands. Our data underscore that IL-1 beta plays a pivotal role in SchS.

DOI: 10.1186/s13075-015-0696-0

PMCID: PMC4511239

PMID: 26198339 [Indexed for MEDLINE]

1561. Curr Opin Rheumatol. 2015 Sep;27(5):511-9. doi: 10.1097/BOR.0000000000000207.

Newly recognized Mendelian disorders with rheumatic manifestations.

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**PURPOSE OF REVIEW:** We review newly discovered monogenic immune-dysregulatory disorders that were reported in Pubmed over the last year.

**RECENT FINDINGS:** Fourteen novel monogenic immune-dysregulatory disorders that present with innate and acquired/adaptive immune dysregulation and inflammatory clinical phenotypes were identified. These include autosomal-dominant gain-of function mutations in viral innate immune sensors or their adaptors,

TMEM173/STING IFIH1/MDA5 and DDX58/RIG-I that cause complex clinical syndromes distinct from IL-1-mediated diseases and present with a chronic type I interferon (IFN Type I) signature in peripheral blood. Gain-of-function mutations in NLRC4

add a novel inflammasome disorder associated with predisposition to macrophage-activation syndrome and highly elevated IL-18 levels. Mutations in ADA2, TRNT1 and COPA, AP1S3, and TNFRSF11A cause complex syndromes; loss-of-function mutations in enzymes and molecules are linked to the generation of 'cellular stress' and the release of inflammatory mediators that likely cause the inflammatory disease manifestations. A monogenic form of systemic-onset juvenile idiopathic arthritis is caused by homozygous mutations in LACC1. Lastly, mutations in PRKDC (recessive), STAT3, CTLA4, and PIK3R1 (all dominant) lead to impaired central and peripheral T-cell tolerance and present with variable disease manifestations of immunodeficiency and immune dysregulation/autoimmunity. SUMMARY: A number of novel monogenic diseases that present with innate and/or acquired immune dysregulation reveal novel immune pathways that cause human inflammatory diseases and suggest potential novel targets for treatment.

DOI: 10.1097/BOR.0000000000000207

PMCID: PMC4565793

PMID: 26196376 [Indexed for MEDLINE]

1562. Cytokine. 2015 Nov;76(1):25-37. doi: 10.1016/j.cyto.2015.06.017. Epub 2015 Jul 13.

The interleukin (IL)-1 cytokine family--Balance between agonists and antagonists in inflammatory diseases.

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The interleukin (IL)-1 family of cytokines comprises 11 members, including 7 pro-inflammatory agonists (IL-1 $\alpha$ , IL-1 $\beta$ , IL-18, IL-33, IL-36 $\alpha$ , IL-36 $\beta$ , IL-36 $\gamma$ ) and 4 defined or putative antagonists (IL-1R antagonist (IL-1Ra), IL-36Ra, IL-37, and IL-38) exerting anti-inflammatory activities. Except for IL-1Ra, IL-1 cytokines do not possess a leader sequence and are secreted via an unconventional

pathway. In addition, IL-1 $\beta$  and IL-18 are produced as biologically inert pro-peptides that require cleavage by caspase-1 in their N-terminal region to generate active proteins. N-terminal processing is also required for full activity of IL-36 cytokines. The IL-1 receptor (IL-1R) family comprises 10 members and includes cytokine-specific receptors, co-receptors and inhibitory receptors. The signaling IL-1Rs share a common structure with three extracellular immunoglobulin (Ig) domains and an intracellular Toll-like/IL-1R (TIR) domain. IL-1 cytokines bind to their specific receptor, which leads to the recruitment of a co-receptor and intracellular signaling. IL-1 cytokines induce potent inflammatory responses and their activity is tightly controlled at the level of production, protein processing and maturation, receptor binding and post-receptor signaling by naturally occurring inhibitors. Some of these inhibitors are IL-1 family antagonists, while others are IL-1R family members acting as membrane-bound or soluble decoy receptors. An imbalance between agonist and antagonist levels can lead to exaggerated inflammatory responses. Several genetic modifications or mutations associated with dysregulated IL-1 activity and autoinflammatory disorders were identified in mouse models and in patients. These findings paved the road to the successful use of IL-1 inhibitors in diseases that were previously considered as untreatable.

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DOI: 10.1016/j.cyto.2015.06.017

PMID: 26185894 [Indexed for MEDLINE]

1563. Mediators Inflamm. 2015;2015:451675. doi: 10.1155/2015/451675. Epub 2015 Jun 22.

Mucocutaneous Involvement in Behçet's Disease: How Systemic Treatment Has Changed in the Last Decades and Future Perspectives.

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Behçet's disease (BD) is a multisystemic disorder of unknown etiology characterized by the "triple symptom complex" consisting of recurrent oral aphthosis, genital ulcers, and chronic relapsing bilateral uveitis. Recurrent mucocutaneous lesions are generally considered the hallmark of the disease, being the most common symptoms presenting at the onset of disease. Although the improvement of knowledge about the pathogenetic mechanism added important changes in the treatment management of BD clinical manifestations, thus avoiding the appearance of serious life-threatening complications which are disease related, the mucocutaneous lesions are still the most nagging clinical manifestations to be treated. In this work we reviewed the current state of knowledge regarding the therapeutic approaches for mucocutaneous lesions of BD mainly based on controlled studies to provide a rational framework for selecting the appropriate therapy for treating these troublesome features of the disease.

DOI: 10.1155/2015/451675

PMCID: PMC4491584

PMID: 26185360 [Indexed for MEDLINE]

1564. Int J Mol Sci. 2015 Jul 15;16(7):16067-84. doi: 10.3390/ijms160716067.

Mevalonate Pathway Blockade, Mitochondrial Dysfunction and Autophagy: A Possible Link.

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The mevalonate pathway, crucial for cholesterol synthesis, plays a key role in multiple cellular processes. Deregulation of this pathway is also correlated with

diminished protein prenylation, an important post-translational modification necessary to localize certain proteins, such as small GTPases, to membranes. Mevalonate pathway blockade has been linked to mitochondrial dysfunction: especially involving lower mitochondrial membrane potential and increased release of pro-apoptotic factors in cytosol. Furthermore a severe reduction of protein prenylation has also been associated with defective autophagy, possibly causing inflammasome activation and subsequent cell death. So, it is tempting to hypothesize a mechanism in which defective autophagy fails to remove damaged mitochondria, resulting in increased cell death. This mechanism could play a significant role in Mevalonate Kinase Deficiency, an autoinflammatory disease characterized by a defect in Mevalonate Kinase, a key enzyme of the mevalonate pathway. Patients carrying mutations in the MVK gene, encoding this enzyme, show increased inflammation and lower protein prenylation levels. This review aims at analysing the correlation between mevalonate pathway defects, mitochondrial dysfunction and defective autophagy, as well as inflammation, using Mevalonate Kinase Deficiency as a model to clarify the current pathogenetic hypothesis as the basis of the disease.

DOI: 10.3390/ijms160716067

PMCID: PMC4519939

PMID: 26184189 [Indexed for MEDLINE]

1565. Cell Biol Int. 2015 Dec;39(12):1384-94. doi: 10.1002/cbin.10514. Epub 2015 Aug 14.

Pyrin-PSTPIP1 colocalises at the leading edge during cell migration.

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A set of mutations in the MEiterranean FeVer (MEFV) gene causes familial Mediterranean fever (FMF), the most common auto-inflammatory disease. The gene encodes a protein named pyrin, which appears to play an important role in

inflammatory pathways. Furthermore, pyrin, which is expressed in neutrophils, has been reported to interact with proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1) and actin proteins. However, the relations between pyrin and PSTPIP1 during the cell migration have not yet been elucidated. In the present study, we constructed a cell migration assay method using HL-60 cells.

Pyrin-PSTPIP1 interactions were analysed by immunofluorescence staining in control, differentiated and differentiated-stimulated HL-60 cells. In stimulated cells, pyrin-polymerised actin, PSTPIP1-polymerised actin and pyrin-PSTPIP1 were found to be colocalised. Pyrin has been shown to be colocalised with actin and PSTPIP1 at the leading edge of the migrating cell. For the first time, PSTPIP1 was found to interact with dynamic actin and pyrin at the site of polarisation.

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DOI: 10.1002/cbin.10514

PMID: 26179737 [Indexed for MEDLINE]

1566. PLoS One. 2015 Jul 15;10(7):e0132704. doi: 10.1371/journal.pone.0132704. eCollection 2015.

Association between MEFV Mutations M694V and M680I and Behçet's Disease: A Meta-Analysis.

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**OBJECTIVE:** Several studies have identified an association between Behçet's disease (BD) and mutations in the Mediterranean fever (MEFV) gene, which was originally linked to the autosomal recessive disease, Familial Mediterranean fever. However, no consensus has been reached. Here, a meta-analysis was conducted on published data to comprehensively evaluate this relationship.

**METHODS:** Literature searches were performed in Pubmed, Embase, the Web of



Science, and HuGE Navigator databases, in order to identify studies pertaining to the association between MEFV mutations and BD. Two investigators independently extracted and evaluated the data from eligible studies. The association between MEFV mutations (M694V, M680I, and E148Q) and BD was estimated overall by the odds ratio (OR) and 95% confidence intervals (95% CI). Further analysis was conducted with STATA 12.0 software (Stata Corp.; College Station, TX).

RESULTS: Eligible studies (n=8) included genotyping data obtained from 2538 BD patients and 2792 healthy controls. Of the three mutations, M694V (pooled OR: 2.60, 95% CI: 2.02-3.34) and M680I (pooled OR: 1.74, 95% CI: 1.23-2.46) were found to be associated with BD in the overall analysis. The third mutation, E148Q, however, was not found to be linked with BD (pooled OR: 1.26, 95% CI: 0.69-2.31). Subgroup analysis furthermore revealed that M694V and M680I were risk loci for BD specifically in Turkish patients.

CONCLUSIONS: The meta-analysis confirmed that MEFV mutations M694V and M680I were associated with BD. Additional studies from other ethnic populations and functional experiments are necessary to determine the extent to which the MEFV gene underlies the development of BD.

DOI: 10.1371/journal.pone.0132704

PMCID: PMC4503748

PMID: 26176758 [Indexed for MEDLINE]

1567. Transfusion. 2015 Jul;55 Suppl 2:S86-9. doi: 10.1111/trf.13158.

Do immune complexes play a role in hemolytic sequelae of intravenous immune globulin?

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Intravenous immune globulin (IVIG) was developed initially as an immunoglobulin replacement therapy for primary humoral immunodeficiency, but is now widely used in the treatment of autoinflammatory and autoimmune pathologies. In a small number of patients, hemolytic sequelae have been observed after IVIG

administration. The lack of a simple one-to-one correlation between measurable hemagglutinins and hemolysis has led to complicated hypotheses involving coincident necessary variables (e.g., a two-hit hypothesis) and also to the positing of causal factors other than hemagglutinins. One such hypothesis is that immune complexes (ICs) contained within IVIG lead to hemolysis. IVIG-mediated hemolysis was addressed at a recent meeting sponsored by the Food and Drug Administration; the Plasma Protein Therapeutics Association; and the National Heart, Lung, and Blood Institute. The primary literature was reviewed at this meeting followed by detailed discussion. Participants concluded that there is both a theoretical basis by which ICs could contribute to hemolysis after IVIG administration and some published data in support of such a possibility. However, the reported data contain substantial caveats, and the existing evidence does not rise to a level sufficient to either confirm or reject a role for ICs. More detailed and focused human studies will be required to further assess the potential role of ICs in IVIG induced hemolysis. This paper summarizes the relevant literature and expands upon the conclusions of this workshop.

© 2015 AABB.

DOI: 10.1111/trf.13158

PMID: 26174903 [Indexed for MEDLINE]

1568. Semin Arthritis Rheum. 2015 Dec;45(3):357-60. doi: 10.1016/j.semarthrit.2015.05.007. Epub 2015 May 21.

Granulomatous disease associated with NOD2 sequence variants and familial camptodactyly: An intermediate form of NOD2-associated diseases?

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**OBJECTIVE:** Nucleotide-binding oligomerization domain-containing protein-2 (NOD2)-associated diseases may be a spectrum of disease. We report two families who exhibited an intermediate form of Blau syndrome and NOD2-associated autoinflammatory disease (NAID).

**METHODS:** We identified two families with granulomatous disease. The clinical phenotypes and genotypes of these two families were reviewed and analyzed.

**RESULTS:** The proband in family 1 was a white 57-year-old woman, with camptodactyly (age 6 years), inflammatory polyarthritis and dermatitis (age of 30 years), and cough, dyspnea, dry eyes, parotid gland enlargement, and fever. A computerized tomography showed mediastinal lymphadenopathy without hilar involvement, and a mediastinal lymph node biopsy revealed non-caseating granuloma. Pedigree analysis suggested autosomal dominant inheritance, and genetic testing identified a NOD2 sequence variant IVS8(+158). The proband in family 2 was a white 50-year-old woman with inflammatory polyarthritis and periarticular subcutaneous nodules. Skin biopsy showed non-necrotizing granuloma. There was a family history of camptodactyly, and genetic testing identified a NOD2 sequence variant R703C.

**CONCLUSIONS:** Both probands had granulomatous disease and autosomal dominant phenotype of familial camptodactyly coupled with the presence of the NOD2 sequence variants, IVS8(+158), and R703C. Granulomatous disease associated with NOD2 variants may be an intermediate form between Blau syndrome and NAID.

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DOI: 10.1016/j.semarthrit.2015.05.007

PMID: 26164256 [Indexed for MEDLINE]

1569. Comput Math Methods Med. 2015;2015:893507. doi: 10.1155/2015/893507. Epub 2015 May 28.

Unified Modeling of Familial Mediterranean Fever and Cryopyrin Associated Periodic Syndromes.

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Familial mediterranean fever (FMF) and Cryopyrin associated periodic syndromes (CAPS) are two prototypical hereditary autoinflammatory diseases, characterized by recurrent episodes of fever and inflammation as a result of mutations in MEFV and NLRP3 genes encoding Pyrin and Cryopyrin proteins, respectively. Pyrin and Cryopyrin play key roles in the multiprotein inflammasome complex assembly, which regulates activity of an enzyme, Caspase 1, and its target cytokine, IL-1 $\beta$ . Overproduction of IL-1 $\beta$  by Caspase 1 is the main cause of episodic fever and inflammatory findings in FMF and CAPS. We present a unifying dynamical model for FMF and CAPS in the form of coupled nonlinear ordinary differential equations. The model is composed of two subsystems, which capture the interactions and dynamics of the key molecular players and the insults on the immune system. One of the subsystems, which contains a coupled positive-negative feedback motif, captures the dynamics of inflammation formation and regulation. We perform a comprehensive bifurcation analysis of the model and show that it exhibits three modes, capturing the Healthy, FMF, and CAPS cases. The mutations in Pyrin and Cryopyrin are reflected in the values of three parameters in the model. We present extensive simulation results for the model that match clinical observations.

DOI: 10.1155/2015/893507

PMCID: PMC4464681

PMID: 26161132 [Indexed for MEDLINE]

1570. J Immunol. 2015 Aug 15;195(4):1705-12. doi: 10.4049/jimmunol.1501168. Epub 2015 Jul 8.

IL-1 Receptor Antagonist Chimeric Protein: Context-Specific and Inflammation-Restricted Activation.

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Both IL-1 $\alpha$  and IL-1 $\beta$  are highly inflammatory cytokines mediating a wide spectrum of diseases. A recombinant form of the naturally occurring IL-1R antagonist (IL-1Ra), which blocks IL-1R1, is broadly used to treat autoimmune and autoinflammatory diseases; however, blocking IL-1 increases the risk of infection. In this study, we describe the development of a novel form of recombinant IL-1Ra, termed chimeric IL-1Ra. This molecule is a fusion of the N-terminal peptide of IL-1 $\beta$  and IL-1Ra, resulting in inactive IL-1Ra. Because the IL-1 $\beta$  N-terminal peptide contains several protease sites clustered around the caspase-1 site, local proteases at sites of inflammation can cleave chimeric IL-1Ra and turn IL-1Ra active. We demonstrate that chimeric IL-1Ra reduces IL-1-mediated inflammation in vitro and in vivo. This unique approach limits IL-1 receptor blockade to sites of inflammation, while sparing a multitude of desired IL-1-related activities, including host defense against infections and IL-1-mediated repair.

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DOI: 10.4049/jimmunol.1501168

PMID: 26157171 [Indexed for MEDLINE]

## Efficacy and safety profile of anti-interleukin-1 treatment in Behçet's disease: a multicenter retrospective study.

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Growing data have provided encouraging results on the use of interleukin (IL)-1 inhibitors in Behçet's disease (BD). This study was aimed at reporting the largest experience with anti-IL-1 agents in BD patients. We evaluated 30 BD patients receiving treatment with anti-IL-1 agents. The primary aims of the study were to evaluate the efficacy of anakinra (ANA) and canakinumab (CAN) in a cohort of BD. The secondary aims were to evaluate the overall safety profile of the treatments, explore the timing of response to therapy and any adjustment of

dosage and frequency of drugs studied, and investigate predictive factors of response to therapy. The frequency of first line therapy was 90 % with ANA and 10 % with CAN. The overall number of subjects in complete remission after 12 months of therapy with anti-IL-1 drugs was 13: 6 maintained the initial therapy regimen, 1 maintained the same initial anti-IL-1 drug with further therapeutic adjustments, and the remaining 6 shifted from ANA to CAN. Among them, 3 used CAN for at least 12 months without therapeutic adjustments, 1 had therapeutic adjustments, and 3 had an overall history of a 12-month complete remission. Adverse events (AEs) were reported in 15 % patients who received ANA, represented in all cases by local cutaneous reactions, while no AE were observed in patients who received CAN; we did not observe any serious AEs (SAEs) during the follow-up period. Our data have confirmed that the use of anti-IL-1 $\beta$  drugs is efficacious and safe with an overall acceptable retention on treatment.

DOI: 10.1007/s10067-015-3004-0

PMID: 26156661 [Indexed for MEDLINE]

1572. Cent Eur J Immunol. 2015;40(1):115-6. doi: 10.5114/ceji.2015.50843. Epub 2015 Apr 22.

Coexistence of hereditary angioedema in a case of familial Mediterranean fever with partial response to colchicine.

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Hereditary angioedema (HAE) is a very rare and potentially life-threatening genetic disease characterised by episodes of edema in various parts of the body, including the extremities, face, and airway. The disease is usually associated with attacks of abdominal pain. On the other hand, familial Mediterranean fever (FMF) is an inherited condition characterised by recurrent episodes of painful inflammation in the abdomen, chest, or joints. In this report, we present a child with FMF and undiagnosed HAE, which made him a partial responder to colchicine treatment. Consequently, HAE must be considered in differential diagnosis of cases in which a partial response is obtained from FMF treatment, particularly in

countries where FMF is frequently encountered, because early diagnosis of HAE can facilitate prevention of life-threatening complications, such as upper airway obstruction. To our knowledge, our patient is the first patient reported in the literature with the diagnosis of HAE and FMF together.

DOI: 10.5114/ceji.2015.50843

PMCID: PMC4472549

PMID: 26155193

1573. Acta Gastroenterol Belg. 2015 Jun;78(2):240-3.

A case of chronic recurrent multifocal osteomyelitis associated with crohn's disease.

van Ommen C, Dehoorne J, De Baets F, Vande Velde S, Van Winckel M, Van Biervliet S.

Chronic recurrent multifocal osteomyelitis (CRMO) is an autoinflammatory bone disease of unknown etiology, most commonly affecting the metaphysis of long bones, especially the tibia, femur and clavicle. The clinical spectrum varies from self-limited uni-or multi-focal lesions to chronic recurrent courses.

Diagnosis is based on clinical, radiologic and pathological findings, is probably underdiagnosed due to poor recognition of the disease. A dysregulated innate immunity causes immune cell infiltration of the bones with subsequent osteoclast activation leading to sterile bone lesions. The molecular pathophyiology is still incompletely understood but association with other auto-inflammatory diseases such as inflammatory bowel disease (IBD), psoriasis, Wegener's disease, arthritis and synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome is interesting. CRMO can precede the symptoms of the associated disease by several years. The bone remodeling caused by CRMO can cause permanent disability. We report the case of a 10-year-old boy with CRMO in association with Crohn's disease.

© Acta Gastro-Enterologica Belgica.

PMID: 26151695 [Indexed for MEDLINE]



1574. Ann Dermatol Venereol. 2015 Nov;142(11):722-3. doi: 10.1016/j.annder.2015.05.002. Epub 2015 Jul 3.

[A new auto-inflammatory genetic disease associated with cold urticaria: Plaid involving PLCG2 mutation].

[Article in French]

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DOI: 10.1016/j.annder.2015.05.002

PMID: 26149917 [Indexed for MEDLINE]

1575. Mod Rheumatol. 2016;26(1):3-8. doi: 10.3109/14397595.2015.1069459. Epub 2015 Aug 3.

Impact of IL-1 inhibition on fatigue associated with autoinflammatory syndromes.

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Cryopyrin-associated periodic syndromes (CAPS) is a rare group of autoinflammatory disorders that includes familial cold autoinflammatory syndrome or FCAS, Muckle-wells syndrome or MWS, and neonatal-onset multisystem inflammatory disease or NOMID. CAPS is caused by a mutation in the NOD-like receptor family, pyrin domain containing 3 (NLRP3) gene. This ultimately leads to

increased production of interleukin (IL)-1 $\beta$ . IL-1 $\beta$  is a biologically active member of the IL-1 family. It is not only a pro-inflammatory cytokine responsible for features such as fever, rash, and arthritis, but is also a major mediator in the central pathways of fatigue. Fatigue is a major component of CAPS and is associated with severely compromised quality of life. In clinical studies, fatigue was measured using functional assessment of chronic illness therapy-fatigue or FACIT-F and short form-36 or SF-36, physical component score instruments. These questionnaires can also be used to monitor improvement of fatigue following initiation of therapy. IL-1 inhibitors block the IL-1 signaling cascade, thereby preventing systemic inflammation in CAPS. The decrease in systemic inflammation is accompanied by improvement in fatigue.

DOI: 10.3109/14397595.2015.1069459

PMID: 26140469 [Indexed for MEDLINE]

1576. Isr Med Assoc J. 2015 May;17(5):306-9.

Normal Heart Rate Variability in Colchicine-Resistant Familial Mediterranean Fever Patients.

Nussinovitch N, Esev K, Lidar M, Nussinovitch U, Livneh A.

**BACKGROUND:** The relationship between autonomic nervous system (ANS) dysfunction and familial Mediterranean fever (FMF) is controversial. We recently reported normal heart rate variability (HRV), suggestive of normal ANS, in patients with uncomplicated FMF.

**OBJECTIVES:** To evaluate ANS function in colchicine non-responders by using the HRV tool.

**METHODS:** The study group comprised 24 FMF patients suffering from recurrent FMF attacks despite treatment with a maximal colchicine dose. Electrocardiogram was measured under strict conditions and HRV parameters were calculated. Results were compared with age- and gender-matched unaffected controls.

**RESULTS:** No statistically significant difference was found between the groups in any of the HRV parameters: maximal RR, minimal RR and average RR intervals, standard deviation of RR interval, square root of the mean squared differences of successive RR intervals, HRV triangular index, NN50, pNN50, and power spectral analysis parameters.

**CONCLUSIONS:** Although a small difference in HRV parameters in the current study

cannot be entirely excluded, FMF patients in whom colchicine did not provide adequate symptomatic relief and who did not develop amyloidosis appear to have normal HRV parameters suggestive of normal ANS function, compared with healthy adults.

PMID: 26137658 [Indexed for MEDLINE]

1577. EBioMedicine. 2015 Feb 26;2(4):351-5. doi: 10.1016/j.ebiom.2015.02.015. eCollection 2015 Apr.

Reversal of Alopecia Areata Following Treatment With the JAK1/2 Inhibitor Baricitinib.

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**BACKGROUND:** Alopecia areata (AA) is an autoimmune disease resulting in hair loss with devastating psychosocial consequences. Despite its high prevalence, there are no FDA-approved treatments for AA. Prior studies have identified a prominent interferon signature in AA, which signals through JAK molecules.

**METHODS:** A patient with AA was enrolled in a clinical trial to examine the efficacy of baricitinib, a JAK1/2 inhibitor, to treat concomitant CANDLE syndrome. In vivo, preclinical studies were conducted using the C3H/HeJ AA mouse

model to assess the mechanism of clinical improvement by baricitinib.

**FINDINGS:** The patient exhibited a striking improvement of his AA on baricitinib over several months. In vivo studies using the C3H/HeJ mouse model demonstrated a strong correlation between resolution of the interferon signature and clinical improvement during baricitinib treatment.

**INTERPRETATION:** Baricitinib may be an effective treatment for AA and warrants further investigation in clinical trials.

DOI: 10.1016/j.ebiom.2015.02.015

PMCID: PMC4486197

PMID: 26137574 [Indexed for MEDLINE]

1578. J Inflamm (Lond). 2015 Jul 2;12:41. doi: 10.1186/s12950-015-0086-z. eCollection 2015.

Increased expression of the NLRP3 inflammasome components in patients with Behçet's disease.

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**BACKGROUND:** Behçet's disease (BD) is a systemic inflammatory disease with manifestations including recurrent oral and genital ulcerations, and vasculitis involving the skin, mucosa, joints, eyes, veins, arteries, nervous and gastrointestinal systems. BD is seen as a disease at the crossroad between autoimmune and autoinflammatory syndromes, possibly triggered by an aberrant response to infectious stimuli. The relevance of Gram negative bacteria-mediated oral inflammation with the increased expression of NACHT, LRR, and PYD

domains-containing protein 3 (NLRP3), leading to systemic inflammation, prompted us to investigate the expression of NLRP3 inflammasome components and its link with IL-1 $\beta$  hypersecretion.

**FINDINGS:** When peripheral blood mononuclear cells (PBMCs) from 15 active, 15 stable BD patients and 15 healthy volunteers were stimulated, the basal and LPS-induced expressions of NLRP3 inflammasome components were significantly increased at both mRNA and protein levels in BD patients compared to healthy controls. Also, increased expression of NLRP3 and ASC was observed in 25 BD skin lesions compared to 25 erythema nodosum patients. Compatible with this, secretion of IL-1 $\beta$  by PBMCs stimulated with LPS alone or LPS plus ATP was increased in BD compared to healthy controls, which was suppressed by caspase-1 inhibitor.

**CONCLUSION:** Our findings suggest the possible link between increased IL-1 $\beta$  secretion and increased expression of NLRP3 inflammasome components in BD patients with skin manifestations.

DOI: 10.1186/s12950-015-0086-z

PMCID: PMC4487834

PMID: 26136643

1579. PLoS One. 2015 Jul 2;10(7):e0131645. doi: 10.1371/journal.pone.0131645. eCollection 2015.

IL-1 Receptor Antagonist Treatment Aggravates Staphylococcal Septic Arthritis and Sepsis in Mice.

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**BACKGROUND:** Interleukin-1 receptor antagonist (IL-1Ra) is the primary therapy against autoinflammatory syndromes with robust efficacy in reducing systemic inflammation and associated organ injury. However, patients receiving IL-1Ra might be at increased risk of acquiring serious infections.

**AIMS:** To study whether IL-1Ra treatment deteriorates *Staphylococcus aureus* (S. aureus) septic arthritis and sepsis in mice.

**METHOD:** NMRI mice were treated with anakinra (IL-1Ra) daily for 7 days before intravenous inoculation with *S. aureus* strain Newman in both arthritogenic and lethal doses. The clinical course of septic arthritis, histopathological and radiological changes of the joints, as well as the mortality were compared between IL-1Ra treated and control groups.

**RESULTS:** IL-1Ra treated mice developed more frequent and severe clinical septic arthritis. Also, the frequency of polyarthritis was significantly higher in the mice receiving IL-1Ra therapy. In line with the data from clinical arthritis, both histological and radiological signs of septic arthritis were more pronounced in IL-1Ra treated group compared to controls. Importantly, the mortality of IL-1Ra treated mice was significantly higher than PBS treated controls.

**CONCLUSION:** IL-1Ra treatment significantly aggravated *S. aureus* induced septic arthritis and increased the mortality in these mice.

DOI: 10.1371/journal.pone.0131645

PMCID: PMC4489902

PMID: 26135738 [Indexed for MEDLINE]

1580. Intest Res. 2015 Jul;13(3):287-90. doi: 10.5217/ir.2015.13.3.287. Epub 2015 Jun 9.

Familial Mediterranean Fever With Complete Symptomatic Remission During Pregnancy.

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Familial Mediterranean fever (FMF) is an inherited autosomal recessive disorder, ethnically restricted and commonly found among populations surrounding the Mediterranean Sea. FMF is the most prevalent autoinflammatory disease; is characterized by recurrent, self-limited episodes of fever with serositis; and is caused by Mediterranean fever gene (MEFV) mutations on chromosome 16. We describe a case of adult-onset FMF with complete symptomatic remission during pregnancy, without the use of colchicine. A 25-year-old woman had presented with periodic

fever, abdominal pain, and vomiting since she was 21. Her abdominal computed tomography scan showed intestinal nonrotation. She underwent exploratory laparotomy and appendectomy for her symptoms 1 year prior. She had a symptom-free pregnancy period, but abdominal pain and fever recurred after delivery. Mutation analysis of the MEFV gene revealed two point mutations (p.Leu110Pro and p.Glu148Gln). We report an adult female patient with FMF in Korea with complete symptomatic remission during pregnancy.

DOI: 10.5217/ir.2015.13.3.287

PMCID: PMC4479745

PMID: 26131005

1581. Curr Opin Obstet Gynecol. 2015 Aug;27(4):265-70. doi: 10.1097/GCO.0000000000000183.

A link between human papilloma virus vaccination and primary ovarian insufficiency: current analysis.

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**PURPOSE OF REVIEW:** The cause of primary ovarian insufficiency (POI) is multifactorial. Known causes include external factors such as chemotherapy, radiotherapy, exposure to endocrine-disrupting chemicals, infections that lead to a permanent insult to the ovary, autoimmune conditions, and genetic causes. An association between the quadrivalent antihuman papilloma vaccine (HPV4) and POI was recently suggested.

**RECENT FINDINGS:** An increasing number of cases of POI post-HPV4 are being reported. Possible mechanisms for the suspected effect of HPV on female reproductive function are a toxic effect or an autoimmune response. The trigger could be the vaccine immunogen contents or the adjuvants, the latter are used to increase the immune reaction. The adjuvant in HPV4 contains aluminum. Animal models have shown aluminum exposure to inhibit expression of female reproductive

hormones and to induce histologic changes in the ovaries. Specific genetic compositions may be more susceptible to developing an autoinflammatory syndrome after exposure to an environmental factor.

SUMMARY: The mechanisms responsible for POI are not yet fully understood. Although case reports cannot establish causation, awareness of a possible link between HPV4 and POI will help to identify and manage future cases that may arise.

DOI: 10.1097/GCO.0000000000000183

PMID: 26125978 [Indexed for MEDLINE]

1582. Orphanet J Rare Dis. 2015 Jun 30;10:86. doi: 10.1186/s13023-015-0298-6.

Acquired familial Mediterranean fever associated with a somatic MEFV mutation in a patient with JAK2 associated post-polycythemia myelofibrosis.

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**BACKGROUND:** A study was designed to identify the source of fever in a patient with post-polycythemia myelofibrosis, associated with clonal Janus Kinase 2 (JAK2) mutation involving duplication of exon 12. The patient presented with 1-2 day long self-limited periodic episodes of high fever that became more frequent as the hematologic disease progressed.

**METHODS:** After ruling out other causes for recurrent fever, analysis of the pyrin encoding Mediterranean fever gene (MEFV) was carried out by Sanger sequencing in peripheral blood DNA samples obtained 4 years apart, in buccal cells, laser dissected kidney tubular cells, and FACS-sorted CD3-positive or depleted mononucleated blood cells. Hematopoietic cells results were validated by targeted deep sequencing. A Sanger sequence based screen for pathogenic variants of the autoinflammatory genes NLRP3, TNFRSF1A and MVK was also performed.

**RESULTS:** A rare, c.1955G>A, p.Arg652His MEFV gene variant was identified at negligible levels in an early peripheral blood DNA sample, but affected 46 % of

the MEFV alleles and was restricted to JAK2-positive, polymorphonuclear and CD3-depleted mononuclear DNA samples obtained 4 years later, when the patient experienced fever bouts. The patient was also heterozygous for the germ line, non-pathogenic NLRP3 gene variant, p.Q705K. Upon the administration of colchicine, the gold standard treatment for familial Mediterranean fever (FMF), the fever attacks subsided.

**CONCLUSIONS:** This is the first report of non-transmitted, acquired FMF, associated with a JAK2 driven clonal expansion of a somatic MEFV exon 10 mutation. The non-pathogenic germ line NLRP3 p.Q705K mutation possibly played a modifier role on the disease phenotype.

DOI: 10.1186/s13023-015-0298-6

PMCID: PMC4506767

PMID: 26123310 [Indexed for MEDLINE]

1583. Nervenarzt. 2015 Aug;86(8):934-46. doi: 10.1007/s00115-014-4249-6.

[New therapeutic strategies for remyelination in multiple sclerosis].

[Article in German]

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Multiple sclerosis (MS) is characterized by oligodendrocyte death and myelin sheath destruction of the central nervous system (CNS) in response to autoinflammatory processes. Besides demyelination axonal degeneration constitutes the second histopathological hallmark of this disease. A large number of immunomodulatory and targeted immunosuppression treatments have been approved for relapsing remitting (RR) MS where they effectively reduce relapse rates; however, currently no treatment options exist to repair injured axonal tracts or myelin damage that accumulates over time particularly in progressive MS. In light of the growing available therapeutic repertoire of highly potent immunomodulatory medications there is an increasing interest in the development of therapies aimed at neutralizing neurodegenerative damage. Endogenous remyelination processes

occur mainly as a result of oligodendrocyte precursor cell (OPC) activation, recruitment and maturation; however, this repair activity appears to be limited and increasingly fails during disease progression. Based on these observations OPCs are considered as promising targets for the regenerative treatment of all stages of MS. This article presents an overview of approved medications with a suggested role in regeneration, regenerative treatments that are currently being tested in clinical trials, as well as promising future therapeutic approaches derived from basic glial cell research aiming at the promotion of the endogenous repair activity of the brain.

DOI: 10.1007/s00115-014-4249-6

PMID: 26122637 [Indexed for MEDLINE]

1584. Clin Exp Rheumatol. 2015 Nov-Dec;33(6 Suppl 94):S46-53. Epub 2015 Jun 29.

Therapeutic blockade of interleukin-6 by tocilizumab in the management of AA amyloidosis and chronic inflammatory disorders: a case series and review of the literature.

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**OBJECTIVES:** AA amyloidosis is the most serious potential complication of chronic inflammatory disorders. The main aim of treatment is to suppress inflammation thereby inhibiting serum amyloid A protein (SAA), which is the precursor of AA amyloid fibrils, to prevent or halt amyloid deposition. Interleukin (IL)-6 blockade is frequently effective in inflammatory conditions, however, there are few published data on its use in AA amyloidosis or the systemic autoinflammatory diseases (SAIDs) or chronic inflammatory conditions. We assessed clinical and serological responses and adverse events associated with tocilizumab (TCZ) use in 20 adult patients with inflammatory disorders refractory to other treatments, including 70% with AA amyloidosis and four with renal transplants.

**METHODS:** In addition to routine haematology and biochemistry (including SAA)

blood panels, patients with AA amyloidosis underwent SAP scintigraphy to quantify amyloid load. Those with SAIDs underwent genetic analysis to identify mutations/variants in known associated genes. Quality of life (QoL) was surveyed using SF-36v2®.

RESULTS: Whole-cohort median pre-treatment SAA fell from 70 to 4 mg/L within 10 days of the first dose; this response has been maintained over an on-treatment follow-up period of 23 months ( $p < 0.0001$ ). AA amyloid deposits either regressed or remained stable. QoL improved in several domains. Infections were the predominant adverse effect experienced, but none resulted in permanent discontinuation of therapy.

CONCLUSIONS: This small series shows that in patients with treatment-refractory chronic inflammatory conditions TCZ can be effective in suppressing inflammation, and in those with AA amyloidosis, can lead to regression of amyloid deposits. Longer follow-up is required to determine long-term safety and efficacy in these conditions.

PMID: 26120866 [Indexed for MEDLINE]

1585. Transl Res. 2016 Jan;167(1):125-37. doi: 10.1016/j.trsl.2015.06.006. Epub 2015 Jun 11.

Targeting the inflammasome in rheumatic diseases.

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Activation of the inflammasome, a protein complex responsible for many cellular functions, including the activation of the proinflammatory cytokines interleukin (IL)-1 $\beta$  and IL-18, has been identified as a key participant in many rheumatic

diseases including autoimmune, inflammatory, and autoinflammatory syndromes. This review will discuss the recent advances in understanding the role of this complex in various rheumatic diseases. Furthermore, it will focus on available therapies, which directly and indirectly target the inflammasome and its downstream cytokines to quiet inflammation and possibly dampen autoimmune processes.

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DOI: 10.1016/j.trsl.2015.06.006

PMCID: PMC4487391

PMID: 26118952 [Indexed for MEDLINE]

## 1586. RETRACTED ARTICLE

Australas J Dermatol. 2015 Jun 26:e133-e136. doi: 10.1111/ajd.12361. Epub 2015 Jun 26.

An unusual urticarial eruption: Familial cold autoinflammatory syndrome.

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Retraction in

Nguyen R, Robinson A, Nicholls K, Varigos G, Dolianitis C. Aust Dent J. 2015 Sep;60(3):e1.

This is a case of a 26-year-old Caucasian woman with a lifelong history of an episodic urticaria associated with arthralgia, precipitated by exposure to cold. She had no other significant past medical history. She reported several family members with a history of very similar episodic eruptions without definitive diagnoses. An examination showed an urticarial eruption over her limbs with no other systemic findings. A baseline full blood examination, serology and autoimmune screen were normal. A skin biopsy was consistent with urticaria, with dermal oedema and a perivascular infiltrate. Following genetic testing, she was found to be heterozygous for a mutation, p.Ala439Val in the NLRP3 gene, known to

cause familial cold autoinflammatory syndrome (FCAS), which typically presents with urticaria, conjunctivitis and arthralgia, as described in this patient. FCAS is one subtype of a group of conditions known as cryopyrin-associated periodic syndromes (CAPS). CAPS are rare, autosomal dominant inherited conditions with a spectrum of phenotypes, characterised by increased interleukin-1 $\beta$  release with subsequent local and systemic proinflammatory and pyrogenic effects.

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DOI: 10.1111/ajd.12361

PMID: 26115477

1587. PLoS One. 2015 Jun 26;10(6):e0131702. doi: 10.1371/journal.pone.0131702. eCollection 2015.

AIM2 Drives Joint Inflammation in a Self-DNA Triggered Model of Chronic Polyarthritis.

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Erratum in

PLoS One. 2018 Aug 9;13(8):e0202364.

Mice lacking DNase II display a polyarthritis-like disease phenotype that is driven by translocation of self-DNA into the cytoplasm of phagocytic cells, where it is sensed by pattern recognition receptors. While pro-inflammatory gene expression is non-redundantly linked to the presence of STING in these mice, the contribution of the inflammasome pathway has not been explored. To this end, we studied the role of the DNA-sensing inflammasome receptor AIM2 in this self-DNA driven disease model. Arthritis-prone mice lacking AIM2 displayed strongly decreased signs of joint inflammation and associated histopathological findings. This was paralleled with a reduction of caspase-1 activation and pro-inflammatory

cytokine production in diseased joints. Interestingly, systemic signs of inflammation that are associated with the lack of DNase II were not dependent on AIM2. Taken together, these data suggest a tissue-specific role for the AIM2 inflammasome as a sensor for endogenous DNA species in the course of a ligand-dependent autoinflammatory condition.

DOI: 10.1371/journal.pone.0131702

PMCID: PMC4482750

PMID: 26114879 [Indexed for MEDLINE]

1588. Ocul Immunol Inflamm. 2015;23(6):467. doi: 10.3109/09273948.2014.1002569. Epub 2015 Jun 25.

Retinal and Choroidal Thickness in Children with Familial Mediterranean Fever.

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Comment on

Ocul Immunol Inflamm. 2014 Dec;22(6):444-8.

DOI: 10.3109/09273948.2014.1002569

PMID: 26110446 [Indexed for MEDLINE]

1589. Ann Rheum Dis. 2015 Sep;74(9):1636-44. doi: 10.1136/annrheumdis-2015-207546. Epub 2015 Jun 24.

Recommendations for the management of autoinflammatory diseases.

ter Haar NM(1), Oswald M(2), Jeyaratnam J(3), Anton J(4), Barron KS(5), Brogan PA(6), Cantarini L(7), Galeotti C(8), Grateau G(9), Hentgen V(10), Hofer M(11), Kallinich T(12), Kone-Paut I(13), Lachmann HJ(14), Ozdogan H(15), Ozen S(16),

Russo R(17), Simon A(18), Uziel Y(19), Wouters C(20), Feldman BM(21), Vastert SJ(22), Wulffraat NM(22), Benseler SM(23), Frenkel J(3), Gattorno M(24), Kuemmerle-Deschner JB(2).

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Comment in

Nat Rev Rheumatol. 2015 Oct;11(10):567-9.

: Autoinflammatory diseases are characterised by fever and systemic inflammation, with potentially serious complications. Owing to the rarity of these diseases, evidence-based guidelines are lacking. In 2012, the European project Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) was launched to optimise and disseminate regimens for the management of children and young adults with rheumatic diseases, facilitating the clinical practice of paediatricians and (paediatric) rheumatologists. One of the aims of SHARE was to provide evidence-based recommendations for the management of the autoinflammatory diseases cryopyrin-associated periodic syndromes (CAPS), tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) and mevalonate kinase deficiency (MKD). These recommendations were developed using the European League Against Rheumatism standard operating procedure. An expert committee of paediatric and adult rheumatologists was convened. Recommendations derived from the systematic literature review were evaluated by an online survey and subsequently discussed at a consensus meeting using Nominal Group Technique. Recommendations were accepted if more than 80% agreement was reached. In total, four overarching principles, 20 recommendations on therapy and 14 recommendations on monitoring were accepted with  $\geq 80\%$  agreement among the experts. Topics included (but were not limited to) validated disease activity scores, therapy and items to assess in monitoring of a patient. By developing these recommendations, we aim to optimise the management of patients with CAPS, TRAPS and MKD.

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DOI: 10.1136/annrheumdis-2015-207546

PMID: 26109736 [Indexed for MEDLINE]

1590. J Med Case Rep. 2015 Jun 23;9:145. doi: 10.1186/s13256-015-0618-4.

Interleukin-1 receptor antagonist deficiency with a novel mutation; late onset and successful treatment with canakinumab: a case report.

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**INTRODUCTION:** Interleukin-1 receptor antagonist deficiency is a rare autoinflammatory disease involving neonatal onset of pustulosis, periostitis, and sterile osteomyelitis. The underlying genetic abnormality involves a recessive mutation in IL1RN, which encodes interleukin-1 receptor antagonist. In this case report, we describe a case of a 12-year-old Turkish girl who initially was presented at 1 year of age, older than previously reported children with interleukin-1 receptor antagonist deficiency, and with a novel mutation, p.R26X, in ILR1N.

**CASE PRESENTATION:** Our patient developed pustular cutaneous lesions at 1 year of age. At the age of 12 years, she was hospitalized for arthralgia of her knees, elbows, and ankles and arthritis of the left knee, with simultaneous pustular cutaneous lesions. She was admitted to the intensive care unit because of septicemia and respiratory insufficiency during follow-up. A skin biopsy of

hyperpigmented lesions demonstrated neutrophil infiltration in the epidermis and subepidermal pustular dermatosis. Interleukin-1 receptor antagonist deficiency was suspected, and genetic analysis revealed a homozygous mutation (p.R26X) in IL1RN, which led to a diagnosis of interleukin-1 receptor antagonist deficiency. Treatment with canakinumab (recombinant human anti-human interleukin-1 $\beta$  monoclonal antibody) 150 mg subcutaneously once every 6 weeks was initiated. Our patient did not experience further cutaneous lesions or arthritis. Her post-treatment inflammatory markers were normal; she gained weight; and she was able to walk independently.

**CONCLUSIONS:** In this case report, we describe a patient with interleukin-1 receptor antagonist deficiency who responded excellently to canakinumab treatment. We believe more awareness is warranted for interleukin-1 receptor antagonist deficiency in children. It is possible that the mutation in our patient was a founder mutation that may lead to diagnosis of additional cases in Turkey.

DOI: 10.1186/s13256-015-0618-4

PMCID: PMC4495801

PMID: 26100510 [Indexed for MEDLINE]

1591. Front Immunol. 2015 Jun 5;6:291. doi: 10.3389/fimmu.2015.00291. eCollection 2015.

Animal Models of Interferon Signature Positive Lupus.

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Human lupus is strongly associated with a gene expression signature characterized by over-expression of Type I interferon-regulated genes. A strong interferon signature generally is not seen in the standard mouse models of lupus, despite considerable evidence for the involvement of toll-like receptor-driven interferon production. In contrast, pristane-induced lupus exhibits a prominent TLR7-dependent interferon signature. Importantly, genetic disorders with

dysregulated interferon production in both human beings and mice cause severe autoinflammatory diseases but not the typical manifestations of lupus, suggesting that interferon over-production is insufficient to cause systemic lupus erythematosus itself. Single-gene models in mice suggest that lupus-like disease may result from abnormalities in B-cell activation and the clearance of dead cells. Pristane may mimic human systemic lupus erythematosus by causing synergistic abnormalities in interferon production along with defective clearance of apoptotic cells and over-active B-cell signaling.

DOI: 10.3389/fimmu.2015.00291

PMCID: PMC4456949

PMID: 26097482

1592. Am J Dermatopathol. 2015 Jul;37(7):517-22. doi: 10.1097/DAD.0000000000000340.

Histologic and Immunohistochemical Features of the Skin Lesions in CANDLE Syndrome.

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Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome is a newly characterized autoinflammatory disorder, caused by mutations in PSMB8. It is characterized by early-onset fevers, accompanied by a widespread, violaceous, and often annular cutaneous eruption. Although the exact pathogenesis of this syndrome is still obscure, it is

postulated that the inflammatory disease manifestations stem from excess secretion of interferons. Based on preliminary blood cytokine and gene expression studies, the signature seems to come mostly from type I interferons, which are proposed to lead to the recruitment of immature myeloid cells into the dermis and subcutis. In this study, we systematically analyzed skin biopsies from 6 patients with CANDLE syndrome by routine histopathology and immunohistochemistry methods. Skin lesions showed the presence of extensive mixed dermal and subcutaneous inflammatory infiltrate, composed of mononuclear cells, atypical myeloid cells, neutrophils, eosinophils, and some mature lymphocytes. Positive LEADER and myeloperoxidase staining supported the presence of myeloid cells. Positive CD68/PMG1 and CD163 staining confirmed the existence of histiocytes and monocytic macrophages in the inflammatory infiltrate. CD123 staining was positive, demonstrating the presence of plasmacytoid dendritic cells. Uncovering the unique histopathological and immunohistochemical features of CANDLE syndrome provides tools for rapid and specific diagnosis of this disorder and further insight into the pathogenesis of this severe life-threatening condition.

DOI: 10.1097/DAD.0000000000000340

PMCID: PMC4476069

PMID: 26091509 [Indexed for MEDLINE]

1593. J Cardiovasc Med (Hagerstown). 2016 Apr;17(4):256-62. doi: 10.2459/JCM.0000000000000266.

Anakinra: an emerging option for refractory idiopathic recurrent pericarditis: a systematic review of published evidence.

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**AIMS:** Accumulating evidence suggests idiopathic recurrent pericarditis as a disease of probable autoinflammatory origin, and thus anakinra could be of benefit. The goal of this systematic review was to assess the efficacy and safety of anakinra in this context.

**METHODS:** Reports relevant to anakinra administration in patients with idiopathic recurrent pericarditis published up to October 2014 were searched in several databases. All references found, upon initial assessment at title and abstract level for suitability, were consequently retrieved as full reports for further appraisal.

**RESULTS:** Among 12 citations retrieved, nine reports (four case series and five case reports with 34 patients, 20 men, mean age 26.8 years) were assessed. The mean disease duration was 31 months and the number of recurrences 8.2. Anakinra was generally administered as a daily subcutaneous injection of 100 mg or as a mean dose of 1.1 mg/kg/d in weight-adjusted regimens. The mean full-dose duration was 9.2 months. C-reactive protein normalized within 7.1 days, and steroids were withdrawn within 62 days. Dose tapering was adopted in 64.7% of patients, leading to recurrence in 26% of cases. In a 28.3-month follow-up, eight out of 34 patients (23.5%) were disease free without treatment, after having received anakinra for 10.4 months overall. Anakinra was proved well tolerated, with mild local reaction being reported in 44% of patients.

**CONCLUSION:** Anakinra is a highly effective, rapidly acting, well tolerated and steroid-sparing agent. Recurrences after drug discontinuation are a matter of concern. Randomized trials are required to confirm these findings and address the most effective treatment protocol.

DOI: 10.2459/JCM.0000000000000266

PMID: 26090915 [Indexed for MEDLINE]

1594. Arthritis Res Ther. 2015 Jun 17;17:163. doi: 10.1186/s13075-015-0683-5.

Complementary action of granulocyte macrophage colony-stimulating factor and interleukin-17A induces interleukin-23, receptor activator of nuclear factor- $\kappa$ B ligand, and matrix metalloproteinases and drives bone and cartilage pathology in experimental arthritis: rationale for combination therapy in rheumatoid arthritis.

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INTRODUCTION: Type 17 T helper cells and interleukin (IL)-17 play important roles

in the pathogenesis of human and murine arthritis. Although there is a clear link between IL-17 and granulocyte macrophage colony-stimulating factor (GM-CSF) in the inflammatory cascade, details about their interaction in arthritic synovial joints are unclear. In view of the introduction of GM-CSF and IL-17 inhibitors to the clinic, we studied how IL-17 and GM-CSF orchestrate the local production of inflammatory mediators during experimental arthritis.

**METHODS:** To allow detection of additive, complementary or synergistic effects of IL-17 and GM-CSF, we used two opposing experimental approaches: treatment of arthritic mice with neutralising antibodies to IL-17 and GM-CSF and local overexpression of these cytokines in naive synovial joints. Mice were treated for 2 weeks with antibodies against IL-17 and/or GM-CSF after onset of collagen-induced arthritis. Naive mice were injected intraarticularly with adenoviral vectors for IL-17 and/or GM-CSF, resulting in local overexpression. Joint inflammation was monitored by macroscopic scoring, X-rays and histology. Joint washouts, synovial cell and lymph node cultures were analysed for cytokines, chemokines and inflammatory mediators by Luminex analysis, flow cytometry and quantitative polymerase chain reaction.

**RESULTS:** Combined therapeutic anti-IL-17 and anti-GM-CSF ameliorated arthritis progression, and joint damage was dramatically reduced compared with treatment with anti-IL-17 or anti-GM-CSF alone. Anti-IL-17 specifically reduced synovial IL-23 transcription, whereas anti-GM-CSF reduced transcription of matrix metalloproteinases (MMPs) and receptor activator of nuclear factor  $\kappa$ B ligand (RANKL). Overexpression of IL-17 or GM-CSF in naive knee joints elicited extensive inflammatory infiltrate, cartilage damage and bone destruction. Combined overexpression revealed additive and synergistic effects on the production of MMPs, RANKL and IL-23 in the synovium and led to complete destruction of the joint structure within 7 days.

**CONCLUSIONS:** IL-17 and GM-CSF differentially mediate the inflammatory process in arthritic joints and show complementary and local additive effects. Combined blockade in arthritic mice reduced joint damage not only by direct inhibition of IL-17 and GM-CSF but also by indirect inhibition of IL-23 and RANKL. Our results provide a rationale for combination therapy in autoinflammatory conditions, especially for patients who do not fully respond to inhibition of the separate cytokines.

DOI: 10.1186/s13075-015-0683-5

PMCID: PMC4496892

PMID: 26081345 [Indexed for MEDLINE]



1595. Turk Pediatri Ars. 2014 Sep 1;49(3):198-202. doi: 10.5152/tpa.2014.1998. eCollection 2014 Sep.

Association of familial Mediterranean fever in Turkish children with inflammatory bowel disease.

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AIM: Familial Mediterranean fever (FMF) and inflammatory bowel disease (IBD) carry similar clinical and biological properties. Both are characterized with chronic inflammation attacks and neutrophil migration and impaired apoptosis mechanism are present in the areas of damage in both conditions. In our study, we aimed to determine the frequency of association of FMF in patients with IBD, to compare the demographic, clinical, laboratory and treatment response properties in these patients with the ones in other IBD patients and to determine association of FMF especially in treatment-resistant patients.

MATERIAL AND METHODS: Fifty-three patients who were being followed up with a diagnosis of IBD aged between 0 and 18 years were included in the study. The patient group included the patients who were diagnosed with IBD according to clinical, serological, endoscopic and histopathological criteria, who were being followed up and whose therapies were continuing. Genetic analysis in terms of MEFV gene mutations was performed in all patients with a diagnosis of IBD. Acute phase reactants, complete blood count, immunoglobulin levels, stool analysis, "perinuclear anti-neutrophil cytoplasmic antibodies" (pANCA) and "anti-Saccharomyces cerevisiae antibodies" (ASCA) were studied at the time of diagnosis. The diagnosis of FMF was made according to detailed history, physical examination findings, laboratory tests and the results of genetic analyses in terms of MEFV gene mutations in accordance with the criteria defined in 2009.

**RESULTS:** We found that FMF accompanied in 14 (26.4%) of the patients who had a diagnosis of IBD. 3 of these 14 patients in whom FMF accompanied were being followed up with a diagnosis of Crohn disease and 11 were being followed up with a diagnosis of ulcerative colitis. All of these patients had MEFV gene mutation. These mutations included M694V (50%), K695R (21.4%), M680I (14.3%) and R202Q (14.3%) in order of frequency. When the laboratory data were compared between the patients who had a diagnosis of IBD alone and who had a diagnosis of IBD plus FMF, it was observed that the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values were statistically significantly higher in the IBD+FMF group.

**CONCLUSIONS:** FMF is a common condition in the Turkish population and M694V mutation is found most commonly. In our study, this status did not change in cases where FMF accompanied IBD, but K695R mutation was found more frequently compared to FMF alone. We think that it should be kept in mind that other inflammatory conditions including mainly FMF may accompany IBD, if a case of IBD does not have an expected course or is resistant to treatment.

DOI: 10.5152/tpa.2014.1998

PMCID: PMC4462301

PMID: 26078663

1596. Rheumatology (Oxford). 2015 Sep;54(9):1749-51. doi: 10.1093/rheumatology/kev111. Epub 2015 Jun 14.

On-demand treatment with anakinra: a treatment option for selected TRAPS patients.

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DOI: 10.1093/rheumatology/kev111

PMID: 26078218 [Indexed for MEDLINE]

1597. Nat Rev Rheumatol. 2015 Oct;11(10):573-85. doi: 10.1038/nrrheum.2015.79. Epub 2015 Jun 16.

From bench to bedside and back again: translational research in autoinflammation.

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Translational research approaches brought major changes to the understanding and treatment options of autoinflammatory diseases. Patients with common complex multifactorial diseases such as systemic-onset juvenile idiopathic arthritis (sJIA), and particularly those with rare monogenic autoinflammatory diseases such as cryopyrin-associated periodic syndromes (CAPS) or TNF receptor-associated periodic syndrome (TRAPS), benefited from a deeper understanding of the pathophysiological mechanisms and new treatment options emerging from preclinical studies. The study of IL-1 and IL-6 in this context led to novel therapies by forward translation. Conversely, effective treatment of sJIA and TRAPS with IL-1 blockade stimulated reverse translational efforts to study the pathophysiology of these cytokines in autoinflammatory diseases. These translational efforts led to the discovery of biomarkers such as S100 proteins, IL-18 or serum amyloid A, which are components of the inflammatory process, support diagnosis and allow for monitoring of disease activity, helping to predict patient outcomes. The ongoing characterization of autoinflammatory diseases in individual patients has led to classification into heterogeneous subgroups. Further characterization of relevant

subgroups and the design of tailored treatment regimens, as well as the identification of new therapeutic targets and treatment options, are the major future challenges in the field of autoinflammatory diseases, particularly for paediatric rheumatologists.

DOI: 10.1038/nrrheum.2015.79

PMID: 26077920 [Indexed for MEDLINE]

1598. Semin Immunopathol. 2015 Jul;37(4):403-6. doi: 10.1007/s00281-015-0498-0. Epub 2015 Jun 16.

Advances in the genetically complex autoinflammatory diseases.

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Monogenic diseases usually demonstrate Mendelian inheritance and are caused by highly penetrant genetic variants of a single gene. In contrast, genetically complex diseases arise from a combination of multiple genetic and environmental factors. The concept of autoinflammation originally emerged from the identification of individual, activating lesions of the innate immune system as the molecular basis of the hereditary periodic fever syndromes. In addition to these rare, monogenic forms of autoinflammation, genetically complex autoinflammatory diseases like the periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome, chronic recurrent multifocal osteomyelitis (CRMO), Behçet's disease, and systemic arthritis also fulfill the definition of autoinflammatory diseases-namely, the development of apparently unprovoked episodes of inflammation without identifiable exogenous triggers and in the absence of autoimmunity. Interestingly, investigations of these genetically complex autoinflammatory diseases have implicated both innate and adaptive immune abnormalities, blurring the line between autoinflammation and autoimmunity. This reinforces the paradigm of concerted innate and adaptive immune dysfunction leading to genetically complex autoinflammatory phenotypes.

DOI: 10.1007/s00281-015-0498-0  
PMCID: PMC4559483  
PMID: 26077134 [Indexed for MEDLINE]

1599. Orphanet J Rare Dis. 2015 Jun 16;10:76. doi: 10.1186/s13023-015-0295-9.

Chronic myelomonocytic leukemia as a cause of fatal uncontrolled inflammation in familial Mediterranean fever.

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We report on a familial Mediterranean fever (FMF) patient homozygous for p.M694V in the MEFV gene who developed chronic myelomonocytic leukemia (CMML) leading to an uncontrolled and fatal inflammatory syndrome. Plasma levels of IL-6 and IL-18 were found to be very high, as compared to healthy controls and CMML-free FMF patients. Our study unveils the interplay between two different disorders involving the same target cells, suggesting that in myelodysplasia with inflammatory manifestations, mutations in genes causing autoinflammatory syndromes, like MEFV, can be present and thus could be sought. Early chemotherapy with interleukin inhibitors could be proposed in such unusual situations.

DOI: 10.1186/s13023-015-0295-9

PMCID: PMC4485869

PMID: 26076658 [Indexed for MEDLINE]

1600. Hum Immunol. 2015 Jul;76(7):488-95. doi: 10.1016/j.humimm.2015.06.007. Epub 2015 Jun 12.

Dysregulated production of interleukin-1 $\beta$  upon activation of the NLRP3 inflammasome in patients with familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is caused by mutations in pyrin, a protein expressed in innate immune cells that interacts with caspase-1 and other inflammasome components to regulate interleukin (IL)-1 $\beta$  maturation. Since NLRP3 inflammasome represents major source of IL-1 $\beta$ , we studied its protein expression and function in FMF. We isolated peripheral white blood cells (WBCs) from 20 symptoms-free FMF patients and 21 healthy individuals. Intracellular protein expression of NLRP3, caspase-1, IL-1 $\beta$  at baseline and after LPS/ATP sequential treatment for NLRP3 activation was assessed by immunoblotting. Secreted IL-1 $\beta$  was quantified by ELISA. THP-1 cells were transfected with wild-type or mutant pyrin and IL-1 $\beta$  secretion was measured. FMF WBCs exhibited lower NLRP3 and active

caspase-1 protein expression compared to healthy individuals, and LPS/ATP treatment resulted in significantly lower intracellular IL-1 $\beta$  levels in FMF patients. Likewise, LPS/ATP induced caspase-1-dependent IL-1 $\beta$  release at significantly lower amounts in the FMF group (1182 $\pm$ 192 versus 2134 $\pm$ 245pg/mL in controls,  $p=0.004$ ). Consistently, THP-1 cells transfected with FMF-associated M694V mutant pyrin displayed lower LPS/ATP-induced IL-1 $\beta$  compared with wild-type pyrin-transfected cells. FMF WBCs demonstrate reduced NLRP3-mediated IL-1 $\beta$  production. Additional studies are needed to define whether this finding represents a compensatory mechanism to control inflammation or is directly linked to disease pathogenesis.

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DOI: 10.1016/j.humimm.2015.06.007

PMID: 26074413 [Indexed for MEDLINE]

1601. Rheumatology (Oxford). 2015 Oct;54(10):1904-12. doi: 10.1093/rheumatology/kev207. Epub 2015 Jun 11.

NOD2-associated autoinflammatory disease: a large cohort study.

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**OBJECTIVE:** The aims of the study were to characterize the genotype profile of nucleotide-binding oligomerization domain containing 2 (NOD2)-associated autoinflammatory disease (NAID) and to report an extended study of the disease.

**METHODS:** A total of 143 adult patients presented with clinical phenotypes suspicious for NAID and all were genotyped for NOD2 sequence variants. The



genotype frequencies were compared between our cohort and literature reports. These patients were divided into two groups predicated on the presence or absence of NOD2 variants.

**RESULTS:** Of the 143 patients, 67 (47%) carry NOD2 variants; the genotype frequency was significantly higher among our cohort than in the historical healthy controls. Fifty-four of the 67 carriers of NOD2 variants had NAID, which has a genotype profile that is somewhat different from Crohn's disease. All NAID patients were non-Jewish whites and 69% were women. The median age at onset was 33.5 years and the median disease duration at diagnosis was 10.7 years. NAID was sporadic in 93% of cases. Patients typically presented with periodic fever, dermatitis and inflammatory arthritis. As compared with the NOD2 variant-negative patients, the skin disease more typically manifested as erythematous patches or plaques on the trunk. Oligopolyarthritis/-arthralgia was common, with characteristic distal lower extremity swelling. Associated NOD2 variants were primarily IVS8(+158) or compound IVS8(+158) and R702W.

**CONCLUSION:** This study underscores the NOD2 genotype association with NAID, which is a genetically complex multisystem disorder. It differs phenotypically from Crohn's disease with a distinct genotype profile. This disease may be more common than initially thought.

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DOI: 10.1093/rheumatology/kev207  
PMID: 26070941 [Indexed for MEDLINE]

1602. Semin Immunopathol. 2015 Jul;37(4):413-8. doi: 10.1007/s00281-015-0502-8. Epub 2015 Jun 12.

Pathogenesis of Behçet's disease: autoinflammatory features and beyond.

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Behçet's disease (BD) is an inflammatory disorder of unknown aetiology characterised by recurrent attacks affecting the mucocutaneous tissues, eyes, joints, blood vessels, brain and gastrointestinal tract. It is a multifactorial disease classified as a variable vessel vasculitis, and several environmental triggers may induce inflammatory episodes in genetically susceptible individuals. BD has several autoinflammatory features including recurrent self-limited clinical manifestations overlapping with monogenic autoinflammatory disorders, significant host predisposition and abnormally increased inflammatory response, with a robust innate component. Human leukocyte antigen (HLA)-B\*51 is the strongest susceptibility factor described so far affecting the disease risk and typical phenotype. Non-HLA genetic associations such as endoplasmic reticulum aminopeptidase 1 (ERAP1), interleukin 23 receptor (IL23R) and IL10 variations suggest that BD shares susceptibility genes and inflammatory pathways with spondyloarthritis. Although genomewide association studies revealed an increased risk associated with recessively inherited ERAP1 variations in HLA-B\*51 positive patients, it is not clear yet whether certain peptide-HLA allele combinations result in an adaptive response by a self-antigen-directed cytotoxic response or an innate response by modulating an NK cell activity or causing an unfolded protein response. Understanding of major histocompatibility complex (MHC) Class I-driven inflammatory response is expected to provide insights for the development of better treatment and remission-induction options in BD as well as in ankylosing spondylitis (AS) and psoriasis.

DOI: 10.1007/s00281-015-0502-8

PMID: 26068404 [Indexed for MEDLINE]

1603. Ren Fail. 2015 Aug;37(7):1122-5. doi: 10.3109/0886022X.2015.1056064. Epub 2015 Jun 12.

Association between colchicine resistance and vitamin D in familial Mediterranean fever.

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Comment in

Ren Fail. 2016;38(2):340-1.

Although colchicines are the only effective treatment of familial Mediterranean fever (FMF), resistance to colchicines (CR) which is observed in up to 30% of the patients is still a problem. Clinically, resistance to colchicine is defined as three or more attacks within the last 6 months period while using  $\geq 2$  mg/day colchicine. Previous studies have shown decreased vitamin D levels in FMF patients compared with healthy controls. The aim of this study is to evaluate whether vitamin D levels differ between CR and non-CR FMF patients. This study included 64 FMF patients who were being followed in Nephrology Clinic of Samsun Research and Education Hospital for at least 1 year. FMF was diagnosed according to the criteria defined by Livneh et al. Serum 25-hydroxy vitamin D (25-OHD) concentration (ng/mL) was detected in all FMF patients who were not in an acute attack period. From 64 patients 29 were accepted as CR. Mean 25-OHD level was  $9.39 \pm 1.00$  ng/mL in CR patients and  $18.48 \pm 1.09$  ng/mL in colchicine responsive patients ( $p < 0.001$ ). Plasma vitamin D levels were significantly lower in colchicine resistant patients. Vitamin D deficiency may be a factor in etiopathogenesis of CR. Studies in larger patient samples that particularly evaluate the response to vitamin D replacement in CR FMF patients are needed.

DOI: 10.3109/0886022X.2015.1056064

PMID: 26067744 [Indexed for MEDLINE]

1604. Eur J Dermatol. 2015 Jul-Aug;25(4):335-41. doi: 10.1684/ejd.2015.2586.

Histiocytoid Sweet's Syndrome: A localized cutaneous proliferation of macrophages frequently associated with chronic myeloproliferative disease.

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**BACKGROUND:** Histiocytoid Sweet's syndrome was originally described as cutaneous lesions of Sweet's syndrome where the infiltrate is mostly composed of histiocytoid mononuclear cells. The putative cell has been interpreted as an immature neutrophil based on the intense expression of myeloperoxidase.

**METHODS:** To better understand the nature of the infiltrate and potential mechanisms leading to this distinct form of cutaneous inflammatory cell influx, thirteen cases of histiocytoid Sweet's syndrome, encountered in the routine and consult practice of one of the authors, were studied. The clinical features and microscopic findings are summarized.

**RESULTS:** The study comprised eight men and five women aged from 23 to 80. There was a significant association with underlying myeloproliferative disease. In particular, five patients had underlying myelodysplastic syndrome. One patient had unspecified chronic myeloproliferative disorder and another had AML. Two cases were triggered by drug therapy (Cox-2 inhibitors). One patient had familial Mediterranean fever. The eruption was asymptomatic and an aggressive clinical course was not observed in most cases. Skin biopsies were composed of striking angiocentric and interstitial mononuclear cell infiltrates, often accentuated in the deeper dermis and subcutaneous fat. There was marked leukocytoclasia. Neutrophils were sparse or absent. These cells were strongly positive for CD163 and either expressed CD16 or myeloperoxidase. Variable positivity for myeloid dendritic cell markers including CD11c, BDCA-3, TCL1 oncogene, MXA and CD123 was observed.

**CONCLUSION:** The histiocytoid cells of histiocytoid Sweet's syndrome define a novel subset of activated monocytes. This variant of Sweet's syndrome has a significant association with underlying myeloproliferative disease.

DOI: 10.1684/ejd.2015.2586

PMID: 26067166 [Indexed for MEDLINE]

1605. Int J Rheumatol. 2015;2015:380354. doi: 10.1155/2015/380354. Epub 2015 May 12.

Evaluation of Ovarian Reserve with Anti-Müllerian Hormone in Familial Mediterranean Fever.

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**Objective.** To investigate ovarian reserves in attack-free familial Mediterranean fever (AF-FMF) patients at the reproductive age by anti-Müllerian hormone (AMH), antral follicle count (AFC), ovarian volume, and hormonal parameters. **Methods.** Thirty-three AF-FMF patients aging 18-45 years and 34 healthy women were enrolled and FSH, LH, E2, PRL, and AMH levels were measured in the morning blood samples at 2nd-4th days of menstruation by ELISA. Concomitant pelvic ultrasonography was performed to calculate AFC and ovarian volumes. **Results.** In FMF patient group, median AMH levels were statistically significantly lower in the M69V mutation positive group than in the negative ones ( $P = 0.018$ ). There was no statistically significant difference in median AMH levels between E148Q mutation positive patients and the negative ones ( $P = 0.920$ ). There was also no statistically significant difference in median AMH levels between M680I mutation positive patients and the negative ones ( $P = 0.868$ ). No statistically significant difference was observed in median AMH levels between patients who had at least one mutation and those with no mutations ( $P = 0.868$ ). We realized that there was no difference in comparisons between ovarian volumes, number of follicles, and AMH levels ovarian reserves when compared with FMF patients and healthy

individuals. Conclusions. Ovarian reserves of FMF patients were similar to those of healthy subjects according to AMH. However, AMH levels were lower in FMF patients with M694V mutation.

DOI: 10.1155/2015/380354

PMCID: PMC4443760

PMID: 26064124

1606. Semin Immunopathol. 2015 Jul;37(4):429-37. doi: 10.1007/s00281-015-0501-9. Epub 2015 Jun 10.

Regulating against the dysregulation: new treatment options in autoinflammation.

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In autoinflammatory disorders, dysregulation of the innate immune response leads to an excessive cytokine release. The disease course is often characterized by high morbidity and mortality, treatment is mostly difficult and therapeutic options are limited. In most cases, life-long control of ongoing inflammation is necessary in order to improve clinical symptoms and prevent development of damage. Steroids are helpful in many conditions, but the development of serious side effects often limits their long-term use. Other immunosuppressive, steroid-sparing medications are less effective than in the treatment of autoimmune diseases or do not show any effect. So far, anti-IL1 $\alpha$  and/or  $\beta$ -blocking agents as well as an IL-6 receptor-blocking monoclonal antibody and, to a lesser extent, TNF- $\alpha$  blocking agents were applied in autoinflammatory disorders and significantly improved the outcome. Although these progresses were made in the last years, there are still numerous challenges in order to improve drug therapy in autoinflammation. This review summarizes the current state of new drug development and discusses advantages and disadvantages of possible targets.

DOI: 10.1007/s00281-015-0501-9

PMID: 26059720 [Indexed for MEDLINE]

1607. Semin Immunopathol. 2015 Jul;37(4):419-27. doi: 10.1007/s00281-015-0494-4. Epub 2015 Jun 10.

Caspase-1: an integral regulator of innate immunity.

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Caspase-1 is a unique cysteine protease playing central roles in innate immunity. Pathogens, stress, and damage signals induce activation of caspase-1, typically mediated by proximity-induced autoproteolysis in multimeric protein complexes called the inflammasome. Active caspase-1 induces secretion of pro-inflammatory cytokines and mediates pyroptosis, a programmed pro-inflammatory cell death, thereby initiating an immune response finally leading to pathogen clearance. Excessive activation of caspase-1 is the underlying cause for rare diseases such as periodic fever syndromes, and more common disorders, including atherosclerosis, type 2 diabetes, and gout. Beside these well-known pro-inflammatory functions, active caspase-1 also has anti-inflammatory and protective functions contributing to cell survival, reduced inflammatory cytokine signaling, and improved outcomes in mouse models of burn injury or trauma and shock. Furthermore, naturally occurring procaspase-1 variants with reduced or abrogated enzymatic activity mediate enhanced inflammatory signaling and have been associated to autoinflammatory symptoms. Here, we review functions of caspase-1 focusing on anti-inflammatory signaling pathways and discuss the role of enzymatically inactive caspase-1 as disease-promoting factors in autoinflammatory diseases. Moreover, we illustrate differential requirements for autoproteolysis and enzymatic activity in caspase-1 functions.

DOI: 10.1007/s00281-015-0494-4

PMID: 26059719 [Indexed for MEDLINE]

1608. Clin Exp Rheumatol. 2015 Jul-Aug;33(4):449-56. Epub 2015 Jun 8.

Efficacy and safety of off-label use of rituximab in refractory lupus: data from

the Italian Multicentre Registry.

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**OBJECTIVES:** To evaluate the efficacy and safety of rituximab (RTX) in patients with systemic lupus erythematosus (SLE) refractory to standard therapy in the clinical practice setting.

**METHODS:** 145 SLE patients (ACR criteria) were treated with RTX in 11 Italian Centres: 118 with two infusions (1 g), two weeks apart; 27 with 4 infusions (375 mg/m<sup>2</sup>), one week apart, followed in 10 cases by two further doses, after 1 and 2 months. Systemic complete response (CR) was defined as European Consensus Lupus



Activity Measurement (ECLAM) score  $\leq 1$  and partial response (PR) as  $1 < \text{ECLAM} \leq 3$ . Renal CR (RCR) and renal PR (RPR) were defined according to EULAR recommendations for management of lupus nephritis.

**RESULTS:** Data from 134 (92.4%) patients were available. The mean $\pm$ SD follow-up was 27.3 $\pm$ 18.5 months. After the first course of RTX, CR or PR were observed in 85.8% and CR in 45.5% of cases; RCR or RPR in 94.1% and RCR in 30.9% of patients after 12-month follow-up. Disease flares occurred in 35.1% and renal flares in 31.2% of patients during observational period. Among patients retreated, CR or PR were observed in 84.4% and CR in 57.8% of cases. Adverse events, infections, and infusion reactions occurred after first RTX course in 23.8%, 16.4%, and 3.8% of patients and after retreatment in 33.3%, 22.2% and 11.1%, respectively. No severe infusion reactions or deaths occurred.

**CONCLUSIONS:** Data from Italian multicentre RTX Registry confirmed the efficacy and safety of RTX in SLE patients refractory to standard treatment in clinical practice setting.

PMID: 26053285 [Indexed for MEDLINE]

1609. Rheumatol Int. 2015 Nov;35(11):1943-7. doi: 10.1007/s00296-015-3305-2. Epub 2015 Jun 6.

Canakinumab efficacy and long-term tocilizumab administration in tumor necrosis factor receptor-associated periodic syndrome (TRAPS).

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Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is an autosomal dominantly inherited autoinflammatory disease caused by mutations in

the TNFRSF1A gene. Treatment is aimed at preventing acute disease attacks, improving quality of life, and preventing long-term complications such as systemic reactive amyloidosis. Biologic agents have significantly improved TRAPS management. In particular, interleukin 1 (IL-1) inhibition either with the recombinant IL-1 receptor antagonist anakinra or with the human IgG1 anti-IL-1 $\beta$  monoclonal antibody canakinumab has recently shown to induce a prompt and stable disease remission. Conversely, the successful experience with IL-6 inhibition is nowadays limited to a single patient. Anyway, introduction of new treatment options for patients requiring a lifelong therapy is desirable. We describe two TRAPS patients (son and father) successfully treated with canakinumab and tocilizumab, respectively. In particular, we highlight the clinical and laboratory efficacy as well as the good safety profile of tocilizumab during a 42-month follow-up period.

DOI: 10.1007/s00296-015-3305-2

PMID: 26048626 [Indexed for MEDLINE]

1610. Sci Rep. 2015 Jun 4;5:10819. doi: 10.1038/srep10819.

Crystal structure of TRIM20 C-terminal coiled-coil/B30.2 fragment: implications for the recognition of higher order oligomers.

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Many tripartite motif-containing (TRIM) proteins, comprising RING-finger, B-Box, and coiled-coil domains, carry additional B30.2 domains on the C-terminus of the TRIM motif and are considered to be pattern recognition receptors involved in the detection of higher order oligomers (e.g. viral capsid proteins). To investigate the spatial architecture of domains in TRIM proteins we determined the crystal structure of the TRIM20 $\Delta$ 413 fragment at 2.4 Å resolution. This structure comprises the central helical scaffold (CHS) and C-terminal B30.2 domains and reveals an anti-parallel arrangement of CHS domains placing the B-box domains 170 Å apart from each other. Small-angle X-ray scattering confirmed that the linker between CHS and B30.2 domains is flexible in solution. The crystal

structure suggests an interaction between the B30.2 domain and an extended stretch in the CHS domain, which involves residues that are mutated in the inherited disease Familial Mediterranean Fever. Dimerization of B30.2 domains by means of the CHS domain is crucial for TRIM20 to bind pro-IL-1 $\beta$  in vitro. To exemplify how TRIM proteins could be involved in binding higher order oligomers we discuss three possible models for the TRIM5 $\alpha$ /HIV-1 capsid interaction assuming different conformations of B30.2 domains.

DOI: 10.1038/srep10819

PMCID: PMC4455283

PMID: 26043233 [Indexed for MEDLINE]

1611. Front Immunol. 2015 May 18;6:239. doi: 10.3389/fimmu.2015.00239. eCollection 2015.

Accelerated apoptosis of neutrophils in familial mediterranean Fever.

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The causative mutations for familial Mediterranean fever (FMF) are located in the MEFV gene, which encodes pyrin. Pyrin modulates the susceptibility to apoptosis via its PYD domain, but how the mutated versions of pyrin affect apoptotic processes are poorly understood. Spontaneous and induced rates of systemic neutrophil apoptosis as well as the levels of proteins involved in apoptosis were investigated ex vivo in patients with FMF using flow cytometry and RT-qPCR. The freshly collected neutrophils from the patients in FMF remission displayed a significantly larger number of cells spontaneously entering apoptosis compared to control ( $6.27 \pm 2.14$  vs.  $1.69 \pm 0.18\%$ ). This elevated ratio was retained after

24 h incubation of neutrophils in the growth medium ( $32.4 \pm 7.41$  vs.  $7.65 \pm 1.32\%$ ). Correspondingly, the mRNA level for caspase-3 was also significantly increased under these conditions. In response to the inducing agents, the neutrophils from FMF patients also displayed significantly elevated apoptotic rates compared to control. The elevated rates, however, can be largely explained by the higher basal ratio of apoptotic cells in the former group. Monitoring of several proteins involved in apoptosis has not revealed any conventional mechanisms contributing to the enhanced apoptotic rate of neutrophils in FMF. Although the exact molecular mechanisms of accelerated neutrophil apoptosis in FMF remain unknown, it may provide a protection against excessive inflammation and tissue damage due to a massive infiltration of neutrophils in the acute period of the disease.

DOI: 10.3389/fimmu.2015.00239

PMCID: PMC4435041

PMID: 26042122

1612. J Exp Med. 2015 Jun 1;212(6):829-30. doi: 10.1084/jem.2126insight3.

Inflammation on the move.

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Comment on

J Exp Med. 2015 Jun 1;212(6):927-38.

DOI: 10.1084/jem.2126insight3

PMCID: PMC4451123

PMID: 26034116 [Indexed for MEDLINE]

1613. J Med Case Rep. 2015 Jun 2;9:123. doi: 10.1186/s13256-015-0603-y.

Efficacy of inhibition of IL-1 in patients with rheumatoid arthritis and type 2 diabetes mellitus: two case reports and review of the literature.

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**INTRODUCTION:** Rheumatoid arthritis is an autoimmune arthritis in which two inflammatory cytokines, tumor necrosis factor- $\alpha$  and interleukin-1 $\beta$ , play a critical role in the induction and progression of the disease. Several reports and data from registries have discussed the association between chronic inflammatory diseases and disorders in intermediary metabolism, pointing out that prevalence of peripheral insulin resistance and type 2 diabetes mellitus is increased among patients with rheumatoid arthritis. In addition, several studies have shown that type 2 diabetes mellitus may be considered an interleukin-1 $\beta$  inflammatory-mediated process, and both preclinical and clinical observations have reported the usefulness of interleukin-1 antagonism therapy in this disease.

**CASE PRESENTATION:** We describe the case of a 58-year-old Caucasian woman and a 74-year-old Caucasian man with rheumatoid arthritis associated with type 2 diabetes mellitus. In these patients, the inhibition of interleukin-1 $\beta$  not only induced remission for rheumatoid arthritis, but successfully controlled their metabolic status.

**CONCLUSIONS:** We report the positive effects of the inhibition of interleukin-1 in two patients with rheumatoid arthritis associated with type 2 diabetes mellitus, with both reaching the therapeutic targets of their diseases by using a single biological agent and tapering or discontinuing their antidiabetic therapies. These findings suggest that targeting interleukin-1 might be considered a good therapeutic option for the treatment of rheumatoid arthritis associated with type 2 diabetes mellitus.

DOI: 10.1186/s13256-015-0603-y

PMCID: PMC4457168

PMID: 26033326 [Indexed for MEDLINE]

1614. Int J Rheum Dis. 2017 Aug;20(8):1046-1049. doi: 10.1111/1756-185X.12680. Epub 2015 May 27.

Interleukin-1 blockade in neuro-Behçet's disease: a case-based reflection.

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DOI: 10.1111/1756-185X.12680

PMID: 26032112 [Indexed for MEDLINE]

1615. Clin Med (Lond). 2015 Jun;15(3):295-8. doi: 10.7861/clinmedicine.15-3-295.

Autoinflammatory syndromes as causes of fever of unknown origin.

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The systemic autoinflammatory syndromes often present with recurrent fevers. They have proved exceptionally informative about the innate immune system. Although extremely rare, they are important to recognise, as many can now be completely controlled by long-term drug therapies. Diagnosis relies on clinical suspicion followed by genetic testing.

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DOI: 10.7861/clinmedicine.15-3-295

PMID: 26031984 [Indexed for MEDLINE]

1616. Clin Med (Lond). 2015 Jun;15(3):280-4. doi: 10.7861/clinmedicine.15-3-280.

Fever of unknown origin.

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More than 50 years after the first definition of fever of unknown origin (FUO), it still remains a diagnostic challenge. Evaluation starts with the identification of potential diagnostic clues (PDCs), which should guide further investigations. In the absence of PDCs a standardised diagnostic protocol should be followed with PET-CT as the imaging technique of first choice. Even with a standardised protocol, in a large proportion of patients from western countries the cause for FUO cannot be identified. The treatment of FUO is guided by the final diagnosis, but when no cause is found, antipyretic drugs can be prescribed. Corticosteroids should be avoided in the absence of a diagnosis, especially at an early stage. The prognosis of FUO is determined by the underlying cause. The majority of patients with unexplained FUO will eventually show spontaneous remission of fever. We describe the definition, diagnostic workup, causes and treatment of FUO.

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DOI: 10.7861/clinmedicine.15-3-280  
PMID: 26031980 [Indexed for MEDLINE]

1617. Eur J Paediatr Neurol. 2015 Sep;19(5):572-6. doi: 10.1016/j.ejpn.2015.05.004.  
Epub 2015 May 16.

Febrile seizures in children with familial Mediterranean fever: Coincidence or association?

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**BACKGROUND:** Familial Mediterranean fever (FMF) is an inherited disease characterized by recurrent bouts of fever and polyserositis and caused by MEditerranean FeVer gene (MEFV) mutations. Given the febrile characteristics of the disease one would expect higher frequency of febrile seizure in this group of pediatric patients.

**OBJECTIVES:** To evaluate the frequency of febrile seizure and related factors in patients with FMF.

**METHODS:** The children with the diagnosis of FMF were enrolled in the study. Information including clinical features, type of mutation and the history of febrile seizure were all noted.

**RESULTS:** A total of 97 patients, 43 (44.3%) girls with a median age of  $7.93 \pm 4.05$  years (2-16) and a median follow-up period of  $20.65 \pm 24.33$  months (6-135) were included in the study. The frequency of febrile seizure in children with FMF was found as 13.4%, which is higher than the general population [ $p = 0.04$ , OR: 2.9 (95% CI: 1.0-8.5)]. The allele frequency of exon 2 mutations in MEFV genes was higher in the patients with febrile seizure ( $p = 0.03$ ).

Frequency of FMF related clinical findings (fever, abdominal pain, arthralgia/myalgia, arthritis, chest pain and erysipelas-like erythema) was similar between the two groups. However, frequency of headache was higher in the patients with febrile seizure ( $p = 0.014$ ).

**CONCLUSION:** The frequency of febrile seizure in children with FMF was found to be higher than the general population. Although this finding may be related to high fever during FMF attacks in individuals with genetic propensity of febrile seizure, it may also be a neurologic complication of FMF.

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DOI: 10.1016/j.ejpn.2015.05.004

PMID: 26028444 [Indexed for MEDLINE]

1618. Intern Med. 2015;54(11):1343-7. doi: 10.2169/internalmedicine.54.3690. Epub 2015 Jun 1.

## Usefulness of Small Intestinal Endoscopy in a Case of Adult-onset Familial Mediterranean Fever Associated with Jejunoileitis.

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A 66-year-old Japanese man consulted our institution due to paroxysmal and repetitive bouts of fever and abdominal pain that had persisted for more than one week. Capsule and double-balloon endoscopy (DBE) showed petal-shaped mucosal redness with white hemming in the jejunum and ileum, and histopathology of the biopsy specimens revealed villous atrophy and cryptitis with extensive severe neutrophil infiltration. A genetic examination disclosed compound heterozygous MEFV mutations (E84K, P369S), and familial Mediterranean fever was diagnosed. Treatment with colchicine and infliximab was very effective in inducing the complete disappearance of symptoms and normalization of the endoscopic findings. To the best of our knowledge, this is the first report to describe the findings of small intestinal endoscopic images obtained using capsule and DBE.

DOI: 10.2169/internalmedicine.54.3690

PMID: 26027984 [Indexed for MEDLINE]

1619. J Allergy Clin Immunol. 2015 Nov;136(5):1337-45. doi: 10.1016/j.jaci.2015.04.016. Epub 2015 May 27.

Single amino acid charge switch defines clinically distinct proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1)-associated inflammatory diseases.

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**BACKGROUND:** Hyperzincemia and hypercalprotectinemia (Hz/Hc) is a distinct autoinflammatory entity involving extremely high serum concentrations of the proinflammatory alarmin myeloid-related protein (MRP) 8/14 (S100A8/S100A9 and calprotectin).

**OBJECTIVE:** We sought to characterize the genetic cause and clinical spectrum of Hz/Hc.

**METHODS:** Proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1) gene sequencing was performed in 14 patients with Hz/Hc, and their clinical phenotype was compared with that of 11 patients with pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome. PSTPIP1-pyrin interactions were analyzed by means of immunoprecipitation and Western blotting. A structural model of the PSTPIP1 dimer was generated. Cytokine profiles were analyzed by using the multiplex immunoassay, and MRP8/14 serum concentrations were analyzed by using an ELISA.

**RESULTS:** Thirteen patients were heterozygous for a missense mutation in the PSTPIP1 gene, resulting in a p.E250K mutation, and 1 carried a mutation resulting in p.E257K. Both mutations substantially alter the electrostatic potential of the PSTPIP1 dimer model in a region critical for protein-protein interaction.

Patients with Hz/Hc have extremely high MRP8/14 concentrations ( $2045 \pm 1300$   $\mu\text{g/mL}$ ) compared with those with PAPA syndrome ( $116 \pm 74$   $\mu\text{g/mL}$ ) and have a distinct clinical phenotype. A specific cytokine profile is associated with Hz/Hc. Hz/Hc mutations altered protein binding of PSTPIP1, increasing interaction with pyrin through phosphorylation of PSTPIP1.

**CONCLUSION:** Mutations resulting in charge reversal in the  $\gamma$ -domain of PSTPIP1 (E $\rightarrow$ K) and increased interaction with pyrin cause a distinct autoinflammatory disorder defined by clinical and biochemical features not found in patients with PAPA syndrome, indicating a unique genotype-phenotype correlation for mutations in the PSTPIP1 gene. This is the first inborn autoinflammatory syndrome in which inflammation is driven by uncontrolled release of members of the alarmin family.

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DOI: 10.1016/j.jaci.2015.04.016

PMID: 26025129 [Indexed for MEDLINE]

May 27.

Fluorescent tags influence the enzymatic activity and subcellular localization of procaspase-1.

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Subcellular localization studies and live cell imaging approaches usually benefit from fusion-reporter proteins, such as enhanced green fluorescent protein (EGFP) and mCherry to the proteins of interest. However, such manipulations have several risks, including protein misfolding, altered protein shuttling, or functional impairment when compared to the wild-type proteins. Here, we demonstrate altered subcellular distribution and function of the pro-inflammatory enzyme procaspase-1 as a result of fusion with the reporter protein mCherry. Our observations are of central importance to further investigations of subcellular behavior and possible protein-protein interactions of naturally occurring genetic variants of human procaspase-1 which have recently been linked to autoinflammatory disorders.

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DOI: 10.1016/j.clim.2015.05.011

PMID: 26025004 [Indexed for MEDLINE]

1621. Neurol Neuroimmunol Neuroinflamm. 2015 May 14;2(4):e109. doi: 10.1212/NXI.0000000000000109. eCollection 2015 Aug.

Expanding spectrum of neurologic manifestations in patients with NLRP3 low-penetrance mutations.

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**OBJECTIVE:** To evaluate the frequency of the cryoporin/NLRP3 low-penetrance mutations V198M and Q703K in patients who reported at least 2 symptoms compatible with cryopyrin-associated periodic syndromes (CAPS) and to characterize the phenotype in mutation-positive patients.

**METHODS:** The frequency of the V198M and Q703K mutations was investigated in a selected cohort of 108 patients from our neuroimmunology department. We describe the clinical, neurologic, immunologic, and neuroradiologic features of the mutation carriers.

**RESULTS:** Seventeen patients (16%) tested positive for either of the 2 mutations (V198M: n = 2; Q703K: n = 15). Eleven patients (65%) had severe headache syndromes. Six of these 11 patients were diagnosed with migraine. Nine patients (53%) had a concomitant diagnosis of multiple sclerosis (MS). In 3 patients, we identified additional family members with the respective mutation as well as the diagnosis of MS. Severe recurrent cranial nerve (CN) affection was the hallmark feature in 7 of the 8 (88%) non-MS mutation carriers. Brain MRI showed abnormalities in all but 2 patients (88%) and detected CN inflammation in 4 patients. Interleukin-6 was elevated in the CSF of 2 patients in the non-MS cohort during acute CAPS episodes with severe CNS inflammation. 5 of 9 treated patients (56%) responded to anti-interleukin-1 therapy.

**CONCLUSION:** CAPS constitute rare but treatable and commonly misdiagnosed autoinflammatory syndromes. Our data expand the spectrum of CAPS-associated neurologic manifestations. They also broaden our concept of autoimmunity and autoinflammation by linking CAPS and MS.

DOI: 10.1212/NXI.0000000000000109

PMCID: PMC4436598

PMID: 26020059

1622. Iran J Pediatr. 2014 Dec;24(6):770-4. Epub 2014 Dec 5.

Caseous granuloma: tuberculosis or chronic recurrent multifocal osteomyelitis?

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**BACKGROUND:** Chronic recurrent multifocal osteomyelitis (CREMO) is one of the autoinflammatory bone disorders due to disturbance in innate immune system. Up to now, there is no reported case of caseous granulomas in the CREMO. We report a boy with sterile granulomatous osteomyelitis.

**CASE PRESENTATION:** A four-year-old boy presented with swelling and pain in the left wrist, malaise and bilateral erythematous pustulosis on the palmar region which had resolved spontaneously after about 7 days. The histopathology of the lesions showed severe acute and chronic inflammatory process and chronic granulomatous reaction with caseating necrosis (granulomatous osteomyelitis). The direct smear, culture and PCR for the mycobacterium tuberculosis and atypical mycobacteria were negative. About five months after initiation of the anti-mycobacterial treatment, he was referred to the rheumatology clinic with left elbow pain, effusion and decreased range of motion, and bilateral erythematous palmar pustulosis. He was diagnosed as CREMO based on two exacerbations, repeatedly negative cultures, and concomitant acute and chronic lesions in the histopathology and X-ray. Naproxen and pamidronate every 3 months were started and all other medications were stopped. Two months after the first dose of pamidronate, he became symptom-free and forearm X-ray showed disappearance of the osteolytic lesions and periosteal reactions.

**CONCLUSION:** The diagnosis of CREMO should be considered in the patients with lytic bone lesions. In addition, the clinicians should be aware of the possibility of caseating granuloma in the cases with possible diagnosis of CREMO.



PMCID: PMC4442841

PMID: 26019785

1623. Aesthetic Plast Surg. 2015 Aug;39(4):506-13. doi: 10.1007/s00266-015-0499-3. Epub 2015 May 28.

Aesthetic Breast Augmentation Mastopexy Followed by Post-surgical Pyoderma Gangrenosum (PSPG): Clinic, Treatment, and Review of the Literature.

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**INTRODUCTION:** Pyoderma gangrenosum (PG) is a rare autoinflammatory neutrophilic ulcerative skin disease, often developing after a trauma or surgical wounds. In the literature there are several reports of post-surgical PG (PSPG) of the breast. The authors of this article experienced an impressive case of PSPG after an aesthetic breast augmentation mastopexy. PSPG is a rare but severe complication in this elective aesthetic surgical procedure.

**METHOD:** A systematic review of the literature was performed, focusing on PSPG after aesthetic breast surgery (augmentation mammoplasty/mastopexy). The online databases Pubmed, Medline, and Cochrane were used and additionally a Google© search was conducted. We compared the data obtained from a systematic literature review to an index case of PSPG after esthetic augmentation mammoplasty.

**RESULTS:** The literature search identified seven articles describing eight cases of PSPG after aesthetic breast surgery. In four of these cases augmentation mammoplasty had been carried out, in two cases mastopexy and in two cases augmentation mammoplasty and mastopexy (augmentation mastopexy). The patient we treated and describe in this paper underwent an augmentation mastopexy outside our clinic. Eight patients suffered from local disease, at the site of surgical wounds, one patient had disseminated disease. Leukocytosis was present in five cases (out of nine). Eight patients had received corticosteroid treatment, one

patient refused such treatment. The duration of corticosteroid treatment was on average for 41 days (range 21-60 days). In all cases, the areola had been spared. Complete healing of PSPG was observed on average after 5 months (range 1.5 months-1 year).

DISCUSSION: PSPG of the breast after aesthetic breast surgery is rare, but every plastic surgeon should consider this possibility, especially if skin disease develops post-surgery, mimicking wound infection that does not respond to broad-spectrum antibiotic treatment.

CONCLUSION: Although the literature does not recommend this step, implant removal is recommended by the authors because bacterial wound infection normally cannot be ruled out definitely in the early stages of disease. Additional surgical intervention should be limited to the absolute necessary and performed only under adequate systemic immunosuppressive therapy.

DOI: 10.1007/s00266-015-0499-3

PMID: 26017179 [Indexed for MEDLINE]

1624. Arq Gastroenterol. 2015 Jan-Mar;52(1):55-8. doi: 10.1590/S0004-28032015000100012.

The prevalence of celiac disease among patients with familial mediterranean Fever.

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BACKGROUND: Familial Mediterranean Fever and celiac disease are both related to auto-inflammation and/or auto-immunity and they share some common clinical features such as abdominal pain, diarrhea, bloating and flatulence. Objectives We aimed to determine the association of these two diseases, if present.

METHODS: Totally 112 patients diagnosed with Familial Mediterranean Fever and 32 cases as healthy control were included in the study. All participants were

examined for the evidence of celiac disease, with serum tissue transglutaminase IgA levels (tTG IgA).

**RESULTS:** Totally 144 cases, 112 with Familial Mediterranean Fever and 32 healthy control cases were included in the study. tTG IgA positivity was determined in three cases with Familial Mediterranean Fever and in one case in control group. In that aspect there was no significant difference regarding the tTG IgA positivity between groups ( $P=0.81$ ). Duodenum biopsy was performed to the tTG IgA positive cases and revealed Marsh Type 3b in two Familial Mediterranean Fever cases and Marsh Type 3c in the other one while the biopsy results were of the only tTG IgA positive case in control group was Marsh Type 3b. In HLA evaluation of the celiac cases; HLA DQ2 was present in two celiac cases of the Familial Mediterranean Fever group and in the only celiac case of the control group while HLA DQ8 was present in one celiac case of the Familial Mediterranean Fever group.

**CONCLUSIONS:** We did not determine an association of Familial Mediterranean Fever with celiac disease. Larger studies with subgroup analysis are warranted to determine the relationship of these two diseases.

DOI: 10.1590/S0004-28032015000100012

PMID: 26017084 [Indexed for MEDLINE]

1625. J Exp Med. 2015 Jun 1;212(6):927-38. doi: 10.1084/jem.20142384. Epub 2015 May 25.

Aberrant actin depolymerization triggers the pyrin inflammasome and autoinflammatory disease that is dependent on IL-18, not IL-1 $\beta$ .

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Comment in

J Exp Med. 2015 Jun 1;212(6):829-30.

Gain-of-function mutations that activate the innate immune system can cause systemic autoinflammatory diseases associated with increased IL-1 $\beta$  production. This cytokine is activated identically to IL-18 by an intracellular protein complex known as the inflammasome; however, IL-18 has not yet been specifically implicated in the pathogenesis of hereditary autoinflammatory disorders. We have now identified an autoinflammatory disease in mice driven by IL-18, but not IL-1 $\beta$ , resulting from an inactivating mutation of the actin-depolymerizing cofactor Wdr1. This perturbation of actin polymerization leads to systemic autoinflammation that is reduced when IL-18 is deleted but not when IL-1 signaling is removed. Remarkably, inflammasome activation in mature macrophages is unaltered, but IL-18 production from monocytes is greatly exaggerated, and depletion of monocytes *in vivo* prevents the disease. Small-molecule inhibition of actin polymerization can remove potential danger signals from the system and prevents monocyte IL-18 production. Finally, we show that the inflammasome sensor of actin dynamics in this system requires caspase-1, apoptosis-associated speck-like protein containing a caspase recruitment domain, and the innate immune receptor pyrin. Previously, perturbation of actin polymerization by pathogens was shown to activate the pyrin inflammasome, so our data now extend this guard hypothesis to host-regulated actin-dependent processes and autoinflammatory disease.

DOI: 10.1084/jem.20142384

PMCID: PMC4451132

PMID: 26008898 [Indexed for MEDLINE]

1626. J Endod. 2015 Sep;41(9):1565-70. doi: 10.1016/j.joen.2015.04.005. Epub 2015 May 23.

A Case of SAPHO Syndrome with Endodontic Implications and Treatment with Biologic Drugs.

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SAPHO syndrome (SS) is an autoinflammatory disease characterized by synovitis, acne, pustulosis, hyperostosis, and osteitis. Among the sites affected by the osteoarticular manifestations of SS are the anterior chest wall and the mandible. The etiology of SS is still unknown; theories advocate a genetic predisposition and an infectious cause in association with disorders of the immune system. We report a case of SS in which there was the involvement of the mandible with a lesion of endodontic origin. A 44-year-old white woman diagnosed with SS at the university hospital was referred to the Department of Conservative Dentistry and Endodontics for a consultation. She reported spontaneous pain localized to the periapical area of tooth #19 with a history of multiple restorative and endodontic treatments. It was diagnosed as a previously treated tooth with symptomatic apical periodontitis (AP) at the time of the endodontic evaluation. A second retreatment was then performed in 1 appointment under local anesthesia. During retreatment, a separated instrument and a ledge were found in the mesiobuccal canal, and attempts to bypass it were not successful; the canal was then obturated to the reachable length. Within the same month, the patient was

also administered an anti-tumor necrosis factor alpha biologic medication in association with a disease-modifying antirheumatic drugs for the treatment of SS. Within 3 months, the overall therapy had led to a marked improvement of the systemic and mandibular symptoms, and a periapical radiograph showed almost complete healing of the lesion. Medical examinations have shown a total remission of signs and symptoms starting 6 months after the initiation of treatment. After 5 years, the disease is under control, and tooth #19 is symptom free and shows absence of AP. The endodontists need to be aware of the existence of SS and the possible effects of the use of disease-modifying antirheumatic drugs and biologic medications on the treatment of persistent AP.

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DOI: 10.1016/j.joen.2015.04.005

PMID: 26008113 [Indexed for MEDLINE]

1627. Clin Exp Rheumatol. 2015 Nov-Dec;33(6 Suppl 94):S152-5. Epub 2015 May 25.

Familial Mediterranean fever with a single MEFV mutation: comparison of rare and common mutations in a Turkish paediatric cohort.

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**OBJECTIVES:** Presence of common MEFV gene mutations strengthened the diagnosis of FMF in addition to the typical clinical characteristics of FMF. However, there are also rare mutations. P369S, A744S, R761H, K695R, F479L are the main rare mutations in Turkish population. We aimed to evaluate FMF patients with a single allele MEFV mutation and to compare patients with common and rare mutations.

**METHODS:** We retrospectively reviewed the medical records of FMF patients with a single allele mutation who were followed up between 2008 and 2013 in six centres. We compared the patients with rare and common mutations for disease severity score, frequent exacerbations (>1 attack per month), long attack period (>3 day), symptoms, age at the onset of symptoms, gender, consanguinity, and family history.

**RESULTS:** Two hundred and seventeen patients (M/F=101/116) with the diagnosis of FMF and single mutation were included. Heterozygote mutations were defined as common (M694V, V726A, M680I) and rare mutations (A744S, P369S, K695R, R761H, F479L). Sixty-seven patients (27 males, 40 females) had one single rare mutation and 150 (74 males, 76 females) had one single common mutation. No difference was found between the rare and common mutations with respect to the disease severity score. There was no significant difference between common and rare heterozygote form of mutations in terms of disease severity.

**CONCLUSIONS:** Patients with typical characteristics of FMF, with some rare mutations (A744S, P369S) should be treated in the same manner as patients with a common mutation.

PMID: 26005881 [Indexed for MEDLINE]

1628. J Autoimmun. 2015 Jul;61:1-8. doi: 10.1016/j.jaut.2015.05.001. Epub 2015 May 23.

Inflammasomes and human autoimmunity: A comprehensive review.

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Inflammasomes are multi-protein complexes composed of a NOD-like receptor (NLR)/an AIM-like receptor (ALR), the adapter molecule apoptosis-associated speck-like protein that contains a CARD (ASC), and caspase-1. Active caspase-1 cleaves pro-IL-1 $\beta$  and pro-IL-18 to IL-1 $\beta$  and IL-18, resulting in inflammation. Genetic mutations in inflammasomes were first recognized to result in autoinflammatory diseases, which are characterized by the absence of both autoantibodies and autoreactive-T/B cells. However, there is increasing attention being placed on genetic polymorphisms that are involved in the components of inflammasomes, and these have implications for innate immunity and the natural history of autoimmune diseases. For example, while the NOD-like receptor family, pyrin domain containing 1 (NLRP1) haplotypes contributes to susceptibility to developing vitiligo; there are other single nucleotide polymorphisms (SNPs) that alters the susceptibility and severity of rheumatoid arthritis (RA) and juvenile idiopathic arthritis. Indeed, there are multiple factors that contribute to lowering the threshold of immunity and inflammasomes play a key role in this threshold. For example, IL-1 $\beta$  and IL-18 further perpetuate Th17 responses and endothelial cell damage, which potentiate a number of autoimmune diseases, including synovitis in RA, cardiovascular disease, and systemic lupus erythematosus (SLE). There is also increasing data on the role of innate immunity in experimental autoimmune encephalomyelitis (EAE), in lupus nephritis, and in a variety of autoimmune pathologies in which activation of the innate immune system is the driver for the adaptive system. Indeed, it is likely that the chronic pathology of autoimmunity is mediated in part by otherwise innocent bystander cells, augmented by inflammasomes.

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DOI: 10.1016/j.jaut.2015.05.001

PMID: 26005048 [Indexed for MEDLINE]

1629. Curr Rheumatol Rep. 2015 Jul;17(7):45. doi: 10.1007/s11926-015-0520-5.

Current knowledge on procaspase-1 variants with reduced or abrogated enzymatic



activity in autoinflammatory disease.

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Caspase-1 is a proinflammatory enzyme that is essential in many inflammatory conditions including infectious, autoimmune, and autoinflammatory disorders. The inflammation is mainly mediated by the generation of inflammasomes that activate caspase-1 and subsequently interleukin (IL)-1 $\beta$  and IL-18. In addition, homotypic CARD/CARD interaction of procaspase-1 with RIP2 and thereby activation of the NF- $\kappa$ B pathways may play some role in the inflammation. However, normally, this pathway seems to become downregulated rapidly by the cleavage and excretion of RIP2 by active (pro-)caspase-1. In patients with unexplained recurrent systemic inflammation, CASP1 variants were detected, which often destabilized the caspase-1 dimer interface. Obviously, the resulting decreased or abrogated enzymatic activity and IL-1 $\beta$  production did not prevent the febrile episodes. As an unexpected finding, the inactive procaspase-1 variants significantly enhanced proinflammatory signaling by increasing RIP2 mediated NF- $\kappa$ B activation in an in vitro cell transfection model. A likely reason is the failure of inactive procaspase-1 to cleave bound RIP2 and also to mediate its excretion out of the intracellular space thereby keeping the RIP2-NF- $\kappa$ B pathway upregulated. Hence, proinflammatory effects of enzymatically inactive procaspase-1 variants may partially explain the inflammatory episodes of the patients.

DOI: 10.1007/s11926-015-0520-5

PMID: 26003867 [Indexed for MEDLINE]

1630. Gene. 2015 Sep 1;568(2):170-5. doi: 10.1016/j.gene.2015.05.045. Epub 2015 May 21.

Familial Mediterranean fever gene mutations in north-eastern part of Anatolia with special respect to rare mutations.

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We aimed to determine the frequency of mutations, carrier rates and the association of rare mutations with Familial Mediterranean Fever (FMF) symptoms. There is a need to evaluate as many different populations as possible in order to determine either specific rare mutations or a range of disease-associated mutations. The demographic data and FMF symptoms related to MEFV gene mutations were collected from 731 participants. Exon 2 and exon 10 of the MEFV gene were tested by DNA sequencing. The rare mutations were identified as: M694I (1.1%, n=12), E148V (0.6%, n=6), T267I (0.5%, n=5), L110P (0.2%, n=2), E167D (0.2%, n=2), K695R (0.1%, n=1) and an insertion G (Guanine) mutation (0.4%, n=4) at the 777th codon of exon 10. We used routine comprehensive detection systems such as Sanger sequence that can catch rare mutations, for definite diagnosis and treatment of FMF disease.

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DOI: 10.1016/j.gene.2015.05.045

PMID: 26003477 [Indexed for MEDLINE]

1631. Rheumatol Int. 2015 Oct;35(10):1733-7. doi: 10.1007/s00296-015-3293-2. Epub 2015 May 23.

Treatment of colchicine-resistant Familial Mediterranean fever in children and

adolescents.

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Familial Mediterranean fever (FMF) is the most common autoinflammatory disease worldwide. Approximately 5-10 % of patients are unresponsive to colchicine. Aim of this study was to determine the short- and long-term efficacy and safety of anti-interleukin 1 (anti-IL1) and anti-tumor necrosis factor agents in colchicine-resistant FMF cases in Turkish children and adolescents. This is a single-center retrospective case series of colchicine-resistant FMF patients. The included patients were treated with biologics for either colchicine resistance or because of one of the following: (1) amyloidosis, (2) recurrent prolonged febrile myalgia and frequent need of steroid and (3) persistent arthritis. Colchicine resistance was defined as at least one attack per month for three consecutive months and elevated erythrocyte sedimentation rate or C-reactive protein or serum amyloid A in-between attacks despite taking adequate dose of colchicine. Response to biologicals was evaluated by the Autoinflammatory Diseases Activity Index (AIDAI) score sheet, patients/parents'/physicians' global assessment of disease severity and laboratory parameters every 3-6 months. Fourteen patients were included in the study. Three patients were treated with etanercept for median 7 months (range 3-11 months), and all patients had to be switched to anti-IL1 treatment because of adverse effects and/or partial response. Eleven patients were treated with anakinra with a median duration of 8 months (4-60 months). Nine patients responded to treatment at the third month, but four of them switched to canakinumab because of noncompliance, local side effects and active arthritis. Nine patients were treated with canakinumab, all responded. At follow-up, in two patients the dose had to be increased, and on the other hand, in three patients the interval was increased to every 12-16 weeks. In three patients, anti-IL1 treatment could be stopped and they are fine with colchicine. This case series describes the largest cohort of colchicine-resistant FMF patients in childhood

and adolescence. Anti-IL1 treatment is a safe and effective therapy to control inflammation. The treatment should be modified and decided for each patient on an individual basis.

DOI: 10.1007/s00296-015-3293-2

PMID: 26001859 [Indexed for MEDLINE]

1632. Front Immunol. 2015 Apr 24;6:185. doi: 10.3389/fimmu.2015.00185. eCollection 2015.

Early-onset autoimmune disease as a manifestation of primary immunodeficiency.

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Autoimmune disorders (AID) have been increasingly observed in association with primary immunodeficiencies (PIDs). Here, we discuss the interface between PID and AID, focusing on autoimmune manifestations early in life, which can be diagnostic clues for underlying PIDs. Inflammatory bowel disease in infants and children has been associated with IL-10 and IL-10R deficiencies, chronic granulomatous disease, immunodysregulation-polyendocrinopathy-enteropathy-X-linked syndrome (IPEX), autoinflammatory disorders, and others. Some PIDs have been identified as underlying defects in juvenile systemic lupus erythematosus: C1q-, IgA-, IgM deficiencies, alterations of the IFN- $\alpha$  pathway (in Aicardi-Goutières syndrome due to TREX1 mutation). IPEX (due to FOXP3 mutation leading to Treg cell deficiency), usually appearing in the first months of life, was recently observed in miscarried fetuses with hydrops who presented with CD3+ infiltrating lymphocytes in the pancreas. Hemophagocytic lymphohistiocytosis due to perforin deficiency was also identified as a cause of fetal hydrops. In conclusion, PID should be suspected in any infant with signs of autoimmunity after excluding transferred maternal effects, or in children with multiple and/or severe AID.

DOI: 10.3389/fimmu.2015.00185

PMCID: PMC4419659

PMID: 25999944

1633. Semin Immunopathol. 2015 Jul;37(4):349-57. doi: 10.1007/s00281-015-0500-x. Epub 2015 May 22.

Type I interferonopathies--an expanding disease spectrum of immunodysregulation.

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Type I interferons (IFNs) play a central role in the immune defense against viral infections. Type I IFN signaling is activated by pattern recognition receptors upon sensing of viral nucleic acids and induces antiviral programs through modulation of innate and adaptive immune responses. Type I interferonopathies comprise a heterogeneous group of genetically determined diseases that are characterized by inappropriate activation of type I IFN. While their phenotypic spectrum is broad, ranging from severe neurological impairment to mild cutaneous disease, systemic autoinflammation, and autoimmunity are commonly shared signs of type I interferonopathies. Although the mechanisms underlying various disease phenotypes associated with inappropriate type I IFN activation have yet to be fully elucidated, our current understanding of the molecular pathogenesis of type I interferonopathies has provided a set of candidate molecules that can be interrogated in search of targeted therapies.

DOI: 10.1007/s00281-015-0500-x

PMID: 25998914 [Indexed for MEDLINE]

1634. Semin Immunopathol. 2015 Jul;37(4):359-62. doi: 10.1007/s00281-015-0495-3. Epub 2015 May 22.

The autoinflammatory diseases: a fashion with blurred boundaries!

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Monogenic autoinflammatory diseases are defined as a group of conditions with a clinical and biological inflammatory syndrome but little or no evidence of autoimmunity. Over 17 years have passed since the discovery of the first autoinflammatory gene, MEFV, responsible for familial Mediterranean fever. Substantive progress has been made since then, highlighting the key role of the inflammasome in the maintenance of the cell homeostasis but also unravelling new pathophysiological pathways involved in these diseases. The history of autoinflammatory gene discovery demonstrates the powerfulness of next-generation sequencing approaches in linking inflammatory disorders with various overlapping phenotypes. It can be easily anticipated that new genes will be exponentially identified in the coming years. Integrating these new concepts should help to promote personalized patient care through novel therapeutic opportunities.

DOI: 10.1007/s00281-015-0495-3

PMID: 25998913 [Indexed for MEDLINE]

1635. Clin Rev Allergy Immunol. 2016 Jun;50(3):287-300. doi: 10.1007/s12016-015-8493-8.

Environmental Basis of Autoimmunity.

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The three common themes that underlie the induction and perpetuation of autoimmunity are genetic predisposition, environmental factors, and immune regulation. Environmental factors have gained much attention for their role in

triggering autoimmunity, with increasing evidence of their influence as demonstrated by epidemiological studies, laboratory research, and animal studies. Environmental factors known to trigger and perpetuate autoimmunity include infections, gut microbiota, as well as physical and environmental agents. To address these issues, we will review major potential mechanisms that underlie autoimmunity including molecular mimicry, epitope spreading, bystander activation, polyclonal activation of B and T cells, infections, and autoinflammatory activation of innate immunity. The association of the gut microbiota on autoimmunity will be particularly highlighted by their interaction with pharmaceutical agents that may lead to organ-specific autoimmunity. Nonetheless, and we will emphasize this point, the precise mechanism of environmental influence on disease pathogenesis remains elusive.

DOI: 10.1007/s12016-015-8493-8

PMID: 25998909 [Indexed for MEDLINE]

1636. Semin Immunopathol. 2015 Jul;37(4):311-2. doi: 10.1007/s00281-015-0497-1. Epub 2015 May 21.

Broadening the definition of autoinflammation.

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Initially, the concept of autoinflammation posited that there be no involvement of autoreactive B or T cells, and no evidence of infection. These criteria served well to help establish the concept, and distinguish autoinflammatory diseases from autoimmune or infectious conditions. However, the characterisation of additional monogenic autoinflammatory diseases has established that a primary trigger of the innate immune system may also be accompanied by infection or manifestations of autoimmunity, which may even contribute to pathogenesis. This issue of Seminars in Immunopathology draws out these themes and also shows how autoinflammation can help to maintain homeostasis, which is its primary evolutionary function. Elucidating the fundamental innate immune pathways underlying autoinflammatory disease leads back to these same homeostatic

parameters, to inform about how infection is sensed, and providing for new targets against chronic inflammatory disease.

DOI: 10.1007/s00281-015-0497-1

PMID: 25994947 [Indexed for MEDLINE]

1637. Semin Immunopathol. 2015 Jul;37(4):335-47. doi: 10.1007/s00281-015-0496-2. Epub 2015 May 21.

Protein misfolding and dysregulated protein homeostasis in autoinflammatory diseases and beyond.

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Cells have a number of mechanisms to maintain protein homeostasis, including proteasome-mediated degradation of ubiquitinated proteins and autophagy, a regulated process of "self-eating" where the contents of entire organelles can be recycled for other uses. The unfolded protein response prevents protein overload in the secretory pathway. In the past decade, it has become clear that these fundamental cellular processes also help contain inflammation through degrading pro-inflammatory protein complexes such as the NLRP3 inflammasome. Signaling pathways such as the UPR can also be co-opted by toll-like receptor and mitochondrial reactive oxygen species signaling to induce inflammatory responses. Mutations that alter key inflammatory proteins, such as NLRP3 or TNFR1, can overcome normal protein homeostasis mechanisms, resulting in autoinflammatory diseases. Conversely, Mendelian defects in the proteasome cause protein accumulation, which can trigger interferon-dependent autoinflammatory disease. In non-Mendelian inflammatory diseases, polymorphisms in genes affecting the UPR or autophagy pathways can contribute to disease, and in diseases not formerly considered inflammatory such as neurodegenerative conditions and type 2 diabetes, there is increasing evidence that cell intrinsic or environmental alterations in protein homeostasis may contribute to pathogenesis.



DOI: 10.1007/s00281-015-0496-2  
PMID: 25994946 [Indexed for MEDLINE]

1638. Semin Immunopathol. 2015 Jul;37(4):371-6. doi: 10.1007/s00281-015-0492-6. Epub 2015 May 20.

Hyper-IgD syndrome/mevalonate kinase deficiency: what is new?

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Mevalonate kinase deficiency or hyper-IgD syndrome is a hereditary autoinflammatory syndrome caused by mutations in the mevalonate kinase gene. In this review, we will discuss new findings in this disorder that have been published in the last 2 years. This includes new insights into pathophysiology, treatment, and the clinical phenotype linked to the genetic defect.

DOI: 10.1007/s00281-015-0492-6  
PMCID: PMC4491100  
PMID: 25990874 [Indexed for MEDLINE]

1639. Klin Monbl Augenheilkd. 2015 May;232(5):652-7. doi: 10.1055/s-0035-1545830. Epub 2015 May 19.

[Non-Invasive Diagnosis of Ocular Graft-versus-Host Disease].

[Article in German]

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Ocular graft-vs-host disease (GvHD) is a major complication following allogeneic blood stem cell transplantation (aBSCT) leading to a disturbance of the ocular surface integrity with a broad range of severity. Leading symptom is a pronounced autoinflammatory reaction in particular at the ocular surface with typical features of dry eye disease. Potential complications include visual loss, pain and damage to the ocular structures with, e.g. corneal ulcerations. Diagnosis and treatment of ocular GvHD are a challenge for attending ophthalmologists and require intensive interdisciplinary patient care in particular with haemato-oncologists. First and follow-up examinations consist of several diagnostic steps that include quantitative and qualitative analysis of tearfilm, visual acuity, ocular surface and retinal integrity, cataract development and subjective symptoms. Available tests are mostly evaluated for usage in dry eye diagnosis but are, however, mostly unspecific for diagnosing ocular GvHD reliably. Only combinations of several clinical tests together with the experience of specialised ophthalmologists may lead to the certain diagnosis and treatment decisions at state. This review illustrates the available established and innovative non-invasive diagnostic tests and evaluates their potential use for diagnosing ocular GvHD.

Georg Thieme Verlag KG Stuttgart · New York.

DOI: 10.1055/s-0035-1545830

PMID: 25989034 [Indexed for MEDLINE]

1640. Sci Rep. 2015 May 19;5:10200. doi: 10.1038/srep10200.

Analysis of the genetic basis of periodic fever with aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome.

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PFAPA syndrome is the most common autoinflammatory syndrome in children from Western countries. In spite of its strong familial clustering, its genetic basis and inheritance pattern are still unknown. We performed a comprehensive genetic study on 68 individuals from 14 families. Linkage analysis suggested a susceptibility locus on chromosome 8, but direct molecular sequencing did not support this initial statistical finding. Exome sequencing revealed the absence of any gene that was mutated in all patients. Exhaustive screening of genes involved in other autoinflammatory syndromes or encoding components of the human inflammasome showed no DNA variants that could be linked to PFAPA molecular pathology. Among these, the previously-reported missense mutation V198M in the NLRP3 gene was clearly shown not to co-segregate with PFAPA. Our results on this relatively large cohort indicate that PFAPA syndrome is unlikely to be a monogenic condition. Moreover, none of the several genes known to be involved in inflammation or in autoinflammatory disorders seem to be relevant, alone, to its etiology, suggesting that PFAPA results from oligogenic or complex inheritance of variants in multiple disease genes and/or non-genetic factors.

DOI: 10.1038/srep10200

PMCID: PMC4437314

PMID: 25988833 [Indexed for MEDLINE]

1641. Aust Dent J. 2015 Sep;60(3):e1. doi: 10.1111/adj.12361.

Withdrawn: An unusual urticarial eruption: familial cold autoinflammatory syndrome.

Nguyen R, Robinson A, Nicholls K, Varigos G, Dolianitis C.

Retraction of

Nguyen R, Robinson A, Nicholls K, Varigos G, Dolianitis C. Australas J Dermatol. 2015 Jun 26;. doi: 10.1111/ajd.12361.

DOI: 10.1111/adj.12361

PMID: 25988551 [Indexed for MEDLINE]

1642. J Mol Neurosci. 2015 Jul;56(3):608-12. doi: 10.1007/s12031-015-0549-y. Epub 2015 May 19.

The Effect of Vitamin A Supplementation on FoxP3 and TGF- $\beta$  Gene Expression in Avonex-Treated Multiple Sclerosis Patients.

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Multiple sclerosis (MS) is an autoinflammatory condition of the central nervous system with impaired T helper (Th)17 and regulatory T cell (Treg) balance that is involved in disease immunopathogenesis. The vitamin A active metabolite, retinoic acid, can re-establish this imbalance through the modulation of gene expression of specific nuclear receptors including Forkhead box P3 (FoxP3). At present, few data exist on the impact of vitamin A supplementation on T cell balance. This study reports the results of a clinical trial, over a 6-month period, of 36 relapsing-remitting MS (RRMS) patients that received vitamin A (25,000 IU retinyl palmitate) or placebo (one capsule of placebo per day). Peripheral blood mononuclear cells were isolated from patients, and the expression of FoxP3 and transforming growth factor (TGF)- $\beta$  gene expression was measured using real-time PCR at the beginning and end of the study. The results of this study showed that vitamin A upregulated TGF- $\beta$  and FoxP3 gene expression. Therefore, vitamin A supplementation can be considered as a new approach in MS prevention and treatment.

DOI: 10.1007/s12031-015-0549-y

PMID: 25985851 [Indexed for MEDLINE]

1643. Clin Biochem. 2015 Aug;48(12):781-7. doi: 10.1016/j.clinbiochem.2015.05.007. Epub 2015 May 13.

Quantification of mevalonate-5-phosphate using UPLC-MS/MS for determination of mevalonate kinase activity.

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**OBJECTIVES:** Mevalonate kinase deficiency, a rare autosomal recessive autoinflammatory disease, is caused by mutations in the MVK gene encoding mevalonate kinase (MK). MK catalyzes the phosphorylation of mevalonic acid to mevalonate-5-phosphate (MVAP) in the pathway of isoprenoid and sterol synthesis. The disease phenotype correlates with residual activity ranging from <0.5% for mevalonic aciduria to 1-7% for the milder hyperimmunoglobulinemia D and periodic fever syndrome (HIDS). Hence, assessment of loss-of-function requires high accuracy measurements. We describe a method using isotope dilution UPLC-MS/MS for precise and sensitive determination of MK activity.

**DESIGN AND METHODS:** Wild-type MK and the variant V261A, which is associated with HIDS, were recombinantly expressed in *Escherichia coli*. Enzyme activity was determined by formation of MVAP over time quantified by isotope dilution UPLC-MS/MS. The method was validated according to the FDA Guidance for Bioanalytical Method Validation.

**RESULTS:** Sensitivity for detection of MAVP by UPLC-MS/MS was improved by derivatization with butanol-HCl (LLOQ, 5.0 fmol) and the method was linear from 0.5 to 250  $\mu\text{mol/L}$  ( $R(2) > 0.99$ ) with a precision of  $\geq 89\%$  and an accuracy of  $\pm$

2.7%. The imprecision of the activity assay, including the enzymatic reaction and the UPLC-MS/MS quantification, was 8.3%. The variant V261A showed a significantly decreased activity of 53.1%.

**CONCLUSION:** Accurate determination of MK activity was enabled by sensitive and reproducible detection of MVAP using UPLC-MS/MS. The novel method may improve molecular characterization of MVK mutations, provide robust genotype-phenotype correlations, and accelerate compound screening for drug candidates restoring variant MK activity.

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DOI: 10.1016/j.clinbiochem.2015.05.007

PMID: 25982894 [Indexed for MEDLINE]

1644. Expert Rev Clin Immunol. 2015;11(7):827-35. doi: 10.1586/1744666X.2015.1047765. Epub 2015 May 15.

Diagnosis of cryopyrin-associated periodic syndrome: challenges, recommendations and emerging concepts.

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Cryopyrin-associated periodic syndrome are rare autosomal dominantly inherited diseases. They include three overlapping phenotypes: familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and chronic infantile neurological cutaneous articular syndrome/neonatal onset multisystem autoinflammatory syndrome (NOMID/CINCA). Recurrent fevers, joint pain, and urticarial skin rash are the main clinical features of these conditions. Renal amyloidosis and sensorineural complications may occur. Gain-of-function mutations in NLRP3 gene are responsible for the overactivation of the NLRP3 inflammasome, a multimolecular complex involved in the inflammatory process. Missense mutations are almost always encountered, particularly in exon 3, which encodes the nucleotide-binding domain. Mosaicism is not rare, especially in CINCA/NOMID.

Next-generation sequencing will grant access to new insights about NLRP3 implication in oligogenic and multifactorial diseases.

DOI: 10.1586/1744666X.2015.1047765

PMID: 25979514 [Indexed for MEDLINE]

1645. Biomed Res Int. 2015;2015:504784. doi: 10.1155/2015/504784. Epub 2015 Apr 22.

High variability of Fabry disease manifestations in an extended Italian family.

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Fabry disease (FD) is an inherited metabolic disorder caused by partial or full inactivation of the lysosomal hydrolase  $\alpha$ -galactosidase A ( $\alpha$ -GAL). The impairment of  $\alpha$ -GAL results in the accumulation of undegraded glycosphingolipids in lysosomes and subsequent cell and microvascular dysfunctions. This study reports the clinical, biochemical, and molecular characterization of 15 members of the same family. Eight members showed the exonic mutation M51I in the GLA gene, a

disease-causing mutation associated with the atypical phenotype. The clinical history of this family highlights a wide phenotypic variability, in terms of involved organs and severity. The phenotypic variability of two male patients is not related to differences in  $\alpha$ -GAL enzymatic activity: though both have no enzymatic activity, the youngest shows severe symptoms, while the eldest is asymptomatic. It is noticeable that for two female patients with the M51I mutation the initial clinical diagnosis was different from FD. One of them was diagnosed with Familial Mediterranean Fever, the other with Multiple Sclerosis. Overall, this study confirms that the extreme variability of the clinical manifestations of FD is not entirely attributable to different mutations in the GLA gene and emphasizes the need to consider other factors or mechanisms involved in the pathogenesis of Fabry Disease.

DOI: 10.1155/2015/504784

PMCID: PMC4421032

PMID: 25977923 [Indexed for MEDLINE]

1646. PLoS One. 2015 May 14;10(5):e0125938. doi: 10.1371/journal.pone.0125938. eCollection 2015.

Identification of Disease-Promoting HLA Class I and Protective Class II Modifiers in Japanese Patients with Familial Mediterranean Fever.

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**OBJECTIVES:** The genotype-phenotype correlation of MEFV remains unclear for the familial Mediterranean fever (FMF) patients, especially without canonical MEFV mutations in exon 10. The risk of FMF appeared to be under the influence of other factors in this case. The contribution of HLA polymorphisms to the risk of FMF was examined as strong candidates of modifier genes.

**METHODS:** Genotypes of HLA-B and -DRB1 loci were determined for 258 mutually unrelated Japanese FMF patients, who satisfied modified Tel-Hashomer criteria, and 299 healthy controls. The effects of carrier status were evaluated for the risk of FMF by odds ratio (OR). The HLA effects were also assessed for clinical forms of FMF, subsets of FMF with certain MEFV genotypes and responsiveness to colchicine treatment.

**RESULTS:** The carriers of B\*39:01 were increased in the patients (OR = 3.25,  $p = 0.0012$ ), whereas those of DRB1\*15:02 were decreased (OR = 0.45,  $p = 0.00050$ ), satisfying Bonferroni's correction for multiple statistical tests ( $n = 28$ ,  $p < 0.00179$ ). The protective effect of DRB1\*15:02 was completely disappeared in the co-existence of B\*40:01. The HLA effects were generally augmented in the patients without a canonical MEFV variant allele M694I, in accordance with the notion that the lower penetrance of the mutations is owing to the larger contribution of modifier genes in the pathogenesis, with a few exceptions. Further, 42.9% of 14 colchicine-resistant patients and 13.5% of 156 colchicine-responders possessed B\*35:01 allele, giving OR of 4.82 ( $p = 0.0041$ ).

**CONCLUSIONS:** The differential effects of HLA class I and class II polymorphisms were identified for Japanese FMF even in those with high-penetrance MEFV mutations.

DOI: 10.1371/journal.pone.0125938

PMCID: PMC4431852

PMID: 25974247 [Indexed for MEDLINE]

1647. N Engl J Med. 2015 May 14;372(20):1970. doi: 10.1056/NEJMc1503146.

More on Sweet's syndrome in patients with MDS and MEFV mutations.

Koné-Paut I, Hentgen V, Touitou I; CeRéMAI, the French Reference Center for Autoinflammatory Diseases.

Comment in

N Engl J Med. 2015 May 14;372(20):1971-2.

Comment on

N Engl J Med. 2015 Feb 12;372(7):686-8.

DOI: 10.1056/NEJMc1503146

PMID: 25970068 [Indexed for MEDLINE]

1648. Thromb J. 2015 May 12;13:19. doi: 10.1186/s12959-015-0049-x. eCollection 2015.

Autoinflammatory diseases: a possible cause of thrombosis?

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Autoinflammatory diseases are a group of disorders due to acquired or hereditary disfunction of innate immune system and characterized by systemic or localized manifestations. The prototype is Familial Mediterranean Fever, a monogenic hereditary disorder, whose causing gene (MeFV gene) was identified in 1997 and opened the way to a new fascinating chapter of rheumatology. A growing body of monogenic and poligenic autoinflammatory disorders has been described since then. Arterial and venous thrombosis is a common medical problem, with significant morbidity and mortality. Strong evidences from basic research and clinical epidemiological studies support the theory that inflammation and thrombosis can be associated. Because of their recurrent/chronic inflammatory nature,

autoinflammatory diseases are a putative cause of thrombotic manifestations. In the present work, we reviewed the available evidences about monogenic autoinflammatory disorders, complicated by thrombotic manifestations.

DOI: 10.1186/s12959-015-0049-x

PMCID: PMC4428094

PMID: 25969671

1649. Nat Rev Rheumatol. 2015 Aug;11(8):483-92. doi: 10.1038/nrrheum.2015.60. Epub 2015 May 12.

Perception of self: distinguishing autoimmunity from autoinflammation.

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Rheumatic diseases can be divided in two groups, autoinflammatory and autoimmune disorders. The clinical presentation of both types of diseases overlap, but the pathological pathways underlying rheumatic autoinflammation and autoimmunity are distinct and are the subject of ongoing research. There are a number of ways in which these groups of diseases differ in terms of disease mechanisms and therapeutic responses. First, autoinflammatory diseases are driven by endogenous danger signals, metabolic mediators and cytokines, whereas autoimmunity involves the activation of T and B cells, the latter requiring V-(D)-J recombination of receptor-chain gene segments for maturation. Second, the efficacy of biologic agents directed against proinflammatory cytokines (for example IL-1 $\beta$  and TNF) also highlights differences between autoinflammatory and autoimmune processes. Finally, whereas autoinflammatory diseases are mostly driven by inflammasome-induced IL-1 $\beta$  and IL-18 production, autoimmune diseases are associated with type I interferon (IFN) signatures in blood. In this Review, we provide an overview of the monocyte intracellular pathways that drive autoinflammation and autoimmunity. We convey recent findings on how the type I

IFN pathway can modulate IL-1 $\beta$  signalling (and vice versa), and discuss why IL-1 $\beta$ -mediated autoinflammatory diseases do not perpetuate into autoimmunity. The origins of intracellular autoantigens in autoimmune disorders are also discussed. Finally, we suggest how new mechanistic knowledge of autoinflammatory and autoimmune diseases might help improve treatment strategies to benefit patient care.

DOI: 10.1038/nrrheum.2015.60

PMID: 25963881 [Indexed for MEDLINE]

1650. Semin Immunopathol. 2015 Jul;37(4):387-94. doi: 10.1007/s00281-015-0493-5. Epub 2015 May 12.

New monogenic autoinflammatory diseases--a clinical overview.

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Translating pathogenic insights gained from monogenic defects that cause autoinflammatory diseases into novel therapies has dramatically improved the lives of patients with these syndromes. The last 15 years have focused on the central role of IL-1 in driving autoinflammatory phenotypes and on therapies blocking IL-1 signaling. Recent discoveries from patients unresponsive to IL-1 blockade have highlighted other key inflammatory mediators and pathways. New genetic discoveries have confirmed unifying mechanisms of autoinflammation, including dysregulation of danger sensing, cell stress, and immune-receptor signaling. Recent gene discovery in novel diseases has demonstrated new concepts. First, several complex clinical syndromes, caused by mutations leading to chronic type I interferon (IFN) production present with organ manifestations different from IL-1 mediated diseases including cerebral calcifications, myositis, and interstitial lung disease and the frequent occurrence of autoantibodies. These disorders introduce type I IFN's as inflammatory mediators that cause autoinflammatory phenotypes. Second, conditions associated with high IL-18 production may provide a direct link between autoinflammation and macrophage

activation syndrome. Third, dysregulation of inflammatory and cell differentiation pathways in nonhematopoietic cells, such as aberrant calcium signaling and impaired endothelial or keratinocyte development, provide an understanding of organ specificity in autoinflammatory disorders. Many of these discoveries highlight the intricate interconnections between autoinflammation, autoimmunity, immunodeficiency, and lymphoproliferation and suggest ways in which we may better diagnose and treat autoinflammatory diseases.

DOI: 10.1007/s00281-015-0493-5

PMCID: PMC4556430

PMID: 25963521 [Indexed for MEDLINE]

1651. Semin Immunopathol. 2015 Jul;37(4):377-85. doi: 10.1007/s00281-015-0491-7. Epub 2015 May 12.

CAPS--pathogenesis, presentation and treatment of an autoinflammatory disease.

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The cryopyrin-associated periodic syndrome (CAPS) is a severity spectrum of rare diseases. CAPS comprises the three conditions previously described as familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disorder (NOMID), also known as chronic infantile neurologic, cutaneous, and articular (CINCA) syndrome. The clinical phenotype of CAPS is characterized by systemic inflammation. General symptoms are fatigue and fever. Local manifestations affect multiple tissues such as skin, joints, muscles, eyes, and the central nervous system. Distinct clinical features are characteristic for each subphenotype. In FCAS, these are cold-induced urticaria and fever, in MWS systemic amyloidosis and hearing loss and in NOMID/CINCA central nervous system inflammation and bone deformities. CAPS is caused by single heterozygous germline or somatic gain of function mutations in the NLRP3 gene encoding the protein cryopyrin. Cryopyrin nucleates an NLRP3 inflammasome, which regulates the activation and cleavage of caspase-1 that

cleaves the pro-inflammatory cytokines, IL-1 $\beta$  and IL-18. IL-1 $\beta$  plays the key role in the induction of inflammation in CAPS. This has been confirmed by the application of IL-1 blocking agents, which lead not only to a rapid and sustained reversal of daily symptoms but also to some extent of long-term disease sequelae. To prevent CAPS-induced organ damage, early diagnosis and swift initiation of effective treatment are mandatory.

DOI: 10.1007/s00281-015-0491-7

PMID: 25963520 [Indexed for MEDLINE]

1652. Semin Immunopathol. 2015 Jul;37(4):323-33. doi: 10.1007/s00281-015-0486-4. Epub 2015 May 12.

Dysfunction in protein clearance by the proteasome: impact on autoinflammatory diseases.

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During innate immune responses, proteostasis is greatly impacted by synthesis of pathogen proteins as well as by inflammatory tissue damage through radicals or other damaging molecules released by phagocytes. An adequate adaptation of cellular clearance pathways to the increased burden of damaged proteins is thus of fundamental importance for cells and tissues to prevent protein aggregation, inclusion body formation, and ultimately cell death. We here review the current understanding of the pivotal role of the ubiquitin proteasome system (UPS) in this proteostasis network. The proteolytic capacity of the UPS can be adjusted by differential gene expression, the incorporation and maturation kinetics of alternative active sites, and the attachment of different regulators. Dysregulation of this fine-tuning is likely to induce cell death but seen more often to promote inflammation as well. The link between proteostasis impairment and inflammation may play a crucial role in autoinflammation as well as in age-related diseases and currently uncharacterized diseases. Recent studies on proteasome-associated autoinflammatory syndromes (PRAAS) discovered that IFN signaling drives the inflammation caused by reduction of degradation capacity.

Elucidation of these syndromes will reveal further insights in the understanding of inadequate immune responses. Knowledge related to the diversity of this degradation system will raise the awareness of potential pitfalls in the molecular diagnostics of autoinflammatory syndromes and may help to identify novel drug targets.

DOI: 10.1007/s00281-015-0486-4

PMID: 25963519 [Indexed for MEDLINE]

1653. Clin Exp Rheumatol. 2015 May-Jun;33(3):411-3. Epub 2015 May 11.

Effects of tumor necrosis factor- $\alpha$  inhibitors in mothers and daughters concordant for HLA-B27-positive ankylosing spondylitis.

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**OBJECTIVES:** Pharmacogenomics is considered as the new frontier to predict the response to treatments and it can also be based on the comparison of family

members being treated for the same condition. No data are available on the impact of anti-tumour necrosis factor (TNF)- $\alpha$  therapies in members of the same family with ankylosing spondylitis (AS).

**METHODS:** We describe three mother-daughter couples concordant for AS and HLA-B27, both treated with TNF- $\alpha$  inhibitors, for whom the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), and Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP were evaluated during a follow-up of 24 months.

**RESULTS:** All patients manifested improvements of all scores, but the daughters had a more prominent effect achieving faster complete disease remission.

**CONCLUSIONS:** We hypothesise that longer standing chronic inflammation and older age may cause a less prompt and effective response to treatment in SA when compared with their genetically related controls.

PMID: 25962691 [Indexed for MEDLINE]

1654. J Dermatol. 2015 Sep;42(9):903-5. doi: 10.1111/1346-8138.12929. Epub 2015 May 11.

Familial Mediterranean fever variant with repeated atypical skin eruptions.

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Familial Mediterranean fever (FMF) is characterized by self-limited bouts of fever and polyserositis. Skin involvement is not common in FMF, and erysipelas-like erythema is found to be the most frequent skin eruption which is often accompanied by arthritis and fever, and disappears within 12-72 h. We report a 40-year-old Japanese woman who presented with a 2-year history of recurrent fever with general fatigue, polyarthralgia and transient maculopapular eruptions on her lower extremities and trunk. The histological findings of the



maculopapular eruption showed lymphocyte infiltration around the capillaries in the entire dermis. Mutation analysis showed a heterozygous E148Q-P369S mutation of MEFV. These findings suggested a diagnosis of late-onset FMF variant with atypical skin eruptions. The patient was successfully treated with colchicine. Thus, we should pay attention to repeated atypical skin eruptions for the early detection of atypical FMF.

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DOI: 10.1111/1346-8138.12929

PMID: 25959027 [Indexed for MEDLINE]

1655. Med Hypotheses. 2015 Aug;85(2):186-91. doi: 10.1016/j.mehy.2015.04.032. Epub 2015 May 2.

C-type lectin domain family 12, member A: A common denominator in Behçet's syndrome and acute gouty arthritis.

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C-type lectin domain family 12, member A (CLEC12A) is a C-type lectin-like pattern recognition receptor capable of recognizing monosodium urate crystals. Monosodium urate crystals, the causative agents of gout are also among the danger-associated molecular patterns reflecting cellular injury/cell death. In response to monosodium urate crystals, CLEC12A effectively inhibits granulocyte and monocyte/macrophage functions and hence acts as a negative regulator of inflammation. Behçet's syndrome and gout are autoinflammatory disorders sharing certain pathological (neutrophilic inflammation), clinical (exaggerated response to monosodium urate crystals) and therapeutic (colchicine) features. We propose the hypothesis that decreased expression of CLEC12A is a common denominator in

the hyperinflammatory responses observed in Behçet's syndrome and gout. Major lines of evidence supporting this hypothesis are: (1) Downregulation/deficiency of CLEC12A is associated with hyperinflammatory responses. (2) CLEC12A polymorphisms with functional and clinical implications have been documented in other inflammatory diseases. (3) Colchicine, a fundamental therapeutic agent used both in Behçet's syndrome and gout is shown to oppose the downregulation of CLEC12A. (4) Behçet's syndrome and gout are characterized by a hyperinflammatory response to monosodium urate crystals and other than gout, Behçet's syndrome is the only inflammatory condition exhibiting this exaggerated response. (5) Genomewide linkage and association studies of Behçet's syndrome collectively point to 12p12-13, the chromosomal region harboring CLEC12A. (6) Patients with severe forms of Behçet's syndrome underexpress CLEC12A with respect to patients with mild forms of the disease. If supported by well-designed, rigorous experiments, the forementioned hypothesis pertinent to CLEC12A will carry important implications for therapy, designing experimental models, and uncovering immunopathogenic mechanisms in Behçet's syndrome and gout.

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DOI: 10.1016/j.mehy.2015.04.032

PMID: 25957656 [Indexed for MEDLINE]

1656. Isr Med Assoc J. 2015 Mar;17(3):137-40.

The familial Mediterranean fever (FMF) 50 score: does it work in a controlled clinical trial? Re-analysis of the trial of rilonacept for patients with colchicine-resistant or intolerant FMF.

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**BACKGROUND:** The familial Mediterranean fever 50 score (FMF50) score was recently devised to define response to treatment and as an outcome measure for clinical trials of FMF.

**OBJECTIVES:** To examine the performance of the FMF50 score in a previously published trial of rilonacept for patients whose FMF was resistant or intolerant to colchicine.

**METHODS:** We re-analyzed the data from our controlled trial of rilonacept vs. placebo in 14 patients with colchicine-resistant or intolerant FMF using the

FMF50 score as the primary outcome. The FMF50 score required improvement by  $\geq 50$  in five of six criteria (attack frequency, attack duration, global patient assessment, global physician assessment, frequency of attacks with arthritis, and levels of acute-phase reactants) without worsening of the sixth criterion.

RESULTS: In the original trial rilonacept was considered effective according to the primary outcome measure (differences in the attack frequency) with eight analyzable patients considered responders and four as non-responders. According to the FMF50 score, only two participants would have been considered responders to rilonacept, and one to placebo. Only two participants had  $\geq 50\%$  differences between rilonacept and placebo in five criteria. The major explanation for non-response to treatment was that with rilonacept the duration of attack decreased by  $\geq 50\%$  in only 2 participants and 5 participants had no attacks of arthritis either during screening (before randomization) or during treatment with rilonacept.

CONCLUSIONS: The proposed FMF50 score did not differentiate well between responders and non-responders compared to the a priori defined primary outcome measure in this successful controlled study.

PMID: 25946762 [Indexed for MEDLINE]

1657. Drug Des Devel Ther. 2015 Apr 17;9:1983-7. doi: 10.2147/DDDT.S69117. eCollection 2015.

Canakinumab as rescue therapy in familial Mediterranean fever refractory to conventional treatment.

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Familial Mediterranean fever is an autosomal recessive autoinflammatory disorder mainly affecting Mediterranean populations, which is associated with mutations of the MEFV gene that encodes pyrin. Functional studies suggest that pyrin is implicated in the maturation and secretion of interleukin-1 (IL-1). The IL-1

receptor antagonist or anti-IL-1 monoclonal antibody may therefore represent a rational approach for the treatment of the rare patients who are refractory to conventional therapy. We report the case of a young female affected by familial Mediterranean fever who proved to be resistant to colchicine and was successfully treated with canakinumab.

DOI: 10.2147/DDDT.S69117

PMCID: PMC4408939

PMID: 25945034 [Indexed for MEDLINE]

1658. Minerva Pediatr. 2015 Jun;67(3):219-26.

[Effectiveness of pidotimod in combination with bacterial lysates in the treatment of the pfapa (periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis) syndrome].

[Article in Italian]

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AIM: PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis) syndrome is the most common autoinflammatory syndrome in pediatrics, accepted as an hyperimmune condition. Pidotimod is a molecule with immunomodulatory activity on both innate and adaptive immune responses; it also has the capacity to modulate the function of the respiratory epithelial cells through the activation of a NK-KB pathway which would involve the host-virus interaction. Moreover, the proven beneficial effect of Pidotimod in enhancing the immune response during vaccination, and its benefits in the prevention of respiratory tract infections, should be noted.

METHODS: A joint combination of Pidotimod and bacterial lysates was used to treat 37 children with a clinical diagnosis of PFAPA; within the end of the first year of therapy, the healing rate of PFAPA symptoms was 67.5% (25 children), with a 10.8% (4 cases) still in complete remission within the end of the second year of follow-up.

**RESULTS:** It is important to highlight that 29 children (78.3%) had benefitted from this therapy, in terms of healing, with a marked decrease in the incidence of fever from a total of 360 to 106 episodes, and episodes of periodic fever occurring almost 4 times less frequently. The use of Pidotimod determined a significant reduction of surgical tonsillectomy's treatment.

**CONCLUSION:** This approach had a strong impact on the children's quality of life; a significant decrement in the use of antipyretic drugs, as well as a lower rate of antibiotic prescription, were also noted. It also had a dramatic impact on families' lives, because the treatment lowers the number of absences of family members from work or school/kindergarten.

PMID: 25941128 [Indexed for MEDLINE]

1659. Balkan J Med Genet. 2015 Apr 10;17(2):67-71. doi: 10.2478/bjmg-2014-0076. eCollection 2014 Dec.

Frequencies of the Common MEFV Gene Mutations in Adiyaman, Southeast Anatolia, Turkey.

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Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by fever and serosal inflammation. The reasons for the disorder are mutations in the Mediterranean fever (MEFV) gene; the most common of which are M694V, M680I, M694I and V726A. In this study, we aimed to screen these common mutations of the MEFV gene and then determine the prevalence of FMF according to these mutations in Adiyaman, Southeast Anatolia, Turkey. Seven hundred and sixty-seven healthy individuals from the region of Adiyaman participated in the study. Polymerase chain reaction-amplification refractory mutation system (PCR-ARMS) methods were used to determine the common mutations of the MEFV gene.

Twenty-six (3.9%) individuals had only one mutation in the MEFV gene, 25 individuals were heterozygous and one person was homozygous for the V726A mutation (0.15%). In the present study, the V726A mutation (50.0%) was the most frequent, followed by M694V (38.5%), M680I (7.7%) and M694I (3.8%). It was seen that the carrier rate was very low and the prevalence of FMF was 0.15%, according to the common mutations of the MEFV gene in Adiyaman, Southeast Anatolia, Turkey.

DOI: 10.2478/bjmg-2014-0076

PMCID: PMC4413444

PMID: 25937800

1660. Clin Exp Rheumatol. 2015 Nov-Dec;33(6 Suppl 94):S171-2. Epub 2015 May 1.

Adult-onset tumour necrosis factor receptor-associated periodic syndrome presenting with refractory chronic arthritis.

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PMID: 25936627 [Indexed for MEDLINE]

1661. CEN Case Rep. 2015 May;4(1):1-5. doi: 10.1007/s13730-014-0129-y. Epub 2014 Jun 14.

A case of cryopyrin-associated periodic syndrome with kidney transplant failure.

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The cryopyrin-associated periodic syndrome (CAPS) is an autosomal dominant autoinflammatory disease characterized by fever, skin rash, and joint involvement with acute inflammatory response. The genetic defect involves the NLRP3 gene that encodes cryopyrin and leads to an abnormal production of interleukin-1 (IL-1). Therefore, anti-IL-1 treatment represents an effective therapy. One of the most severe manifestations of the disease is secondary amyloidosis that causes renal failure. We present a patient with CAPS who underwent renal transplantation for renal insufficiency caused by amyloidosis. The function of the transplanted kidney deteriorated because of the late administration of IL-1 receptor antagonist, anakinra. This case may indicate the importance of early initiation of anti-IL-1 treatment in CAPS patients who have undergone kidney transplantation.

DOI: 10.1007/s13730-014-0129-y

PMCID: PMC5411619

PMID: 28509262

1662. Cytokine. 2015 Aug;74(2):213-8. doi: 10.1016/j.cyto.2015.03.022. Epub 2015 Apr 25.

Mechanisms of unconventional secretion of IL-1 family cytokines.

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One of the most poorly understood processes in cell biology is the peculiar ability of specific leaderless proteins to be secreted via ER/Golgi-independent mechanisms ('unconventional protein secretion'). One such leaderless protein is the major immune-activating cytokine, interleukin-1 $\beta$  (IL-1 $\beta$ ). Unusual amongst cytokines, IL-1 $\beta$  is expressed in the cytosol as an inactive precursor protein. It requires maturation by the caspase-1 protease, which itself requires activation upon immune cell sensing of infection or cell stress. Despite 25 years of intensive research into IL-1 $\beta$  secretory mechanisms, how it exits the cell is still not well understood. Here we will review the various mechanisms by which macrophages have been proposed to secrete IL-1 family cytokines, and the potential involvement of caspase-1 therein. Since aberrant IL-1 $\beta$  production drives inherited and acquired human diseases (e.g. autoinflammatory diseases, arthritic diseases, gout, Alzheimer's disease), elucidation of the IL-1 $\beta$  secretory pathway may offer new therapeutic opportunities for treatment across this wide range of human conditions.

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DOI: 10.1016/j.cyto.2015.03.022

PMID: 25922276 [Indexed for MEDLINE]

1663. Curr Opin Infect Dis. 2015 Jun;28(3):240-5. doi: 10.1097/QCO.000000000000155.

Current concepts in pathogenesis of acute and chronic osteomyelitis.

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**PURPOSE OF REVIEW:** The term osteomyelitis covers a wide range of inflammatory bone disorders caused by microbial invasion or due to autoinflammatory processes, but furthermore osteomyelitis also occurs at different ages and at preferred localizations in the human skeleton. This article aims to give an overview of the



current literature focussing on pathognomonic aspects of osteomyelitis because of microbial invasion.

RECENT FINDINGS: Outlining the chronological sequence of osteomyelitis originating from the invasion of microbes finally leading to destruction of bone tissue, the formation and proliferation of biofilm structures play a key role in the development of inflammatory bone disorders. The components of the biofilm on the one hand mediate an immune response leading to an increase of local cytokines and induction of osteoclastogenesis but on the other hand also directly interact with the osteoblasts. As a result, the bone-remodelling process is immensely diminished by induction of proapoptotic pathways, decreased proliferation and differentiation of osteoblasts and an additional promotion of osteoclastogenesis.

SUMMARY: Although microbial invasion is responsible to be the cause for inflammatory bone disorders, except for an autoinflammatory origin, the underlying and detailed mechanisms in the pathogenesis of osteomyelitis are not yet fully understood, but represent an absolute precondition for the development of effective causal treatment strategies in the future.

DOI: 10.1097/QCO.0000000000000155

PMID: 25918958 [Indexed for MEDLINE]

1664. Mediators Inflamm. 2015;2015:408935. doi: 10.1155/2015/408935. Epub 2015 Mar 31.

Free DNA in cystic fibrosis airway fluids correlates with airflow obstruction.

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Chronic obstructive lung disease determines morbidity and mortality of patients with cystic fibrosis (CF). CF airways are characterized by a nonresolving neutrophilic inflammation. After pathogen contact or prolonged activation, neutrophils release DNA fibres decorated with antimicrobial proteins, forming neutrophil extracellular traps (NETs). NETs have been described to act in a beneficial way for innate host defense by bactericidal, fungicidal, and virucidal actions. On the other hand, excessive NET formation has been linked to the pathogenesis of autoinflammatory and autoimmune disease conditions. We quantified free DNA structures characteristic of NETs in airway fluids of CF patients and a mouse model with CF-like lung disease. Free DNA levels correlated with airflow obstruction, fungal colonization, and CXCL chemokine levels in CF patients and CF-like mice. When viewed in combination, our results demonstrate that neutrophilic inflammation in CF airways is associated with abundant free DNA characteristic for NETosis, and suggest that free DNA may be implicated in lung function decline in patients with CF.

DOI: 10.1155/2015/408935

PMCID: PMC4397025

PMID: 25918476 [Indexed for MEDLINE]

1665. J Clin Oncol. 2015 Jun 20;33(18):2092-9. doi: 10.1200/JCO.2014.60.0379. Epub 2015 Apr 27.

Toxicities of Immunotherapy for the Practitioner.

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The toxicities of immunotherapy for cancer are as diverse as the type of treatments that have been devised. These range from cytokine therapies that induce capillary leakage to vaccines associated with low levels of autoimmunity to cell therapies that can induce damaging cross-reactivity with normal tissue to checkpoint protein inhibitors that induce immune-related adverse events that are autoinflammatory in nature. The thread that ties these toxicities together is their mechanism-based immune nature and the T-cell-mediated adverse events seen. The basis for the majority of these adverse events is a hyperactivated T-cell response with reactivity directed against normal tissue, resulting in the generation of high levels of CD4 T-helper cell cytokines or increased migration of cytolytic CD8 T cells within normal tissues. The T-cell immune response is not tissue specific and may reflect a diffuse expansion of the T-cell repertoire that induces cross-reactivity with normal tissue, effectively breaking tolerance that is active with cytokines, vaccines, and checkpoint protein inhibitors and passive in the case of adoptive cell therapy. Cytokines seem to generate diffuse and nonspecific T-cell reactivity, whereas checkpoint protein inhibition, vaccines, and adoptive cell therapy seem to activate more specific T cells that interact directly with normal tissues, potentially causing specific organ damage. In this review, we summarize the toxicities that are unique to immunotherapies, emphasizing the need to familiarize the oncology practitioner with the spectrum of adverse events seen with newly approved and emerging modalities.

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DOI: 10.1200/JCO.2014.60.0379

PMCID: PMC4881375

PMID: 25918278 [Indexed for MEDLINE]

1666. J Leukoc Biol. 2015 Jul;98(1):99-106. doi: 10.1189/jlb.4AB1114-543R. Epub 2015 Apr 27.

The inhibitory effect of secretory leukocyte protease inhibitor (SLPI) on formation of neutrophil extracellular traps.

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Neutrophil extracellular traps (NETs), web-like DNA structures, provide efficient means of eliminating invading microorganisms but can also present a potential threat to its host because it is a likely source of autoantigens or by promoting bystander tissue damage. Therefore, it is important to identify mechanisms that inhibit NET formation. Neutrophil elastase (NE)-dependent chromatin decondensation is a key event in the release of NETs release. We hypothesized that inhibitors of NE, secretory leukocyte protease inhibitor (SLPI) and  $\alpha(1)$ -proteinase inhibitor ( $\alpha(1)$ -PI), has a role in restricting NET generation. Here, we demonstrate that exogenous human SLPI, but not  $\alpha(1)$ -PI markedly inhibited NET formation in human neutrophils. The ability of exogenous SLPI to attenuate NET formation correlated with an inhibition of a core histone, histone 4 (H4), cleavage, and partial dependence on SLPI-inhibitory activity against NE.

Moreover, neutrophils from SLPI(-/-) mice were more efficient at generating NETs than were neutrophils from wild-type mice in vitro, and in experimental psoriasis in vivo. Finally, endogenous SLPI colocalized with NE in the nucleus of human neutrophils in vitro, as well as in vivo in inflamed skin of patients with psoriasis. Together, these findings support a controlling role for SLPI in NET generation, which is of potential relevance to infectious and autoinflammatory diseases.

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DOI: 10.1189/jlb.4AB1114-543R

PMCID: PMC4467168

PMID: 25917460 [Indexed for MEDLINE]

1667. Br J Pharmacol. 2016 Feb;173(4):716-28. doi: 10.1111/bph.13175. Epub 2015 Jun 12.

Immunoinflammatory diseases of the central nervous system - the tale of two cytokines.

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Cytokines are potent mediators of cellular communication that have crucial roles in the regulation of innate and adaptive immunoinflammatory responses. Clear evidence has emerged in recent years that the dysregulated production of cytokines may in itself be causative in the pathogenesis of certain immunoinflammatory disorders. Here we review current evidence for the involvement of two different cytokines, IFN- $\alpha$  and IL-6, as principal mediators of specific immunoinflammatory disorders of the CNS. IFN- $\alpha$  belongs to the type I IFN family and is causally linked to the development of inflammatory encephalopathy exemplified by the genetic disorder, Aicardi-Goutières syndrome. IL-6 belongs to the gp130 family of cytokines and is causally linked to a number of immunoinflammatory disorders of the CNS including neuromyelitis optica, idiopathic transverse myelitis and genetically linked autoinflammatory neurological disease. In addition to clinical evidence, experimental studies, particularly in genetically engineered mouse models with astrocyte-targeted,

CNS-restricted production of IFN- $\alpha$  or IL-6 replicate many of the cardinal neuropathological features of these human cytokine-linked immunoinflammatory neurological disorders giving crucial evidence for a direct causative role of these cytokines and providing further rationale for the therapeutic targeting of these cytokines in neurological diseases where indicated.

© 2015 The British Pharmacological Society.

DOI: 10.1111/bph.13175

PMCID: PMC4742300

PMID: 25917268 [Indexed for MEDLINE]

1668. Br J Dermatol. 2015 Aug;173(2):448-56. doi: 10.1111/bjd.13857. Epub 2015 Jul 20.

Mast-cell interleukin-1 $\beta$ , neutrophil interleukin-17 and epidermal antimicrobial proteins in the neutrophilic urticarial dermatosis in Schnitzler's syndrome.

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Comment in

Br J Dermatol. 2015 Aug;173(2):323-4.

**BACKGROUND:** Schnitzler's syndrome (SchS) is an autoinflammatory disease characterized by a chronic urticarial rash, a monoclonal component and signs of systemic inflammation. Interleukin (IL)-1 $\beta$  is pivotal in the pathophysiology.

**OBJECTIVES:** Here we investigated the cellular source of proinflammatory mediators in the skin of patients with SchS.

**METHODS:** Skin biopsies of lesional and nonlesional skin from eight patients with SchS and healthy controls, and patients with cryopyrin-associated periodic syndrome (CAPS), delayed-pressure urticaria (DPU) and cold-contact urticaria (CCU) were studied. We studied in vivo IL-1 $\beta$ , IL-17 and antimicrobial protein (AMP) expression in resident skin cells and infiltrating cells. In addition we investigated the in vitro effect of IL-1 $\beta$ , IL-17 and polyinosinic-polycytidylic acid (poly:IC) stimulation on cultured epidermal keratinocytes.

**RESULTS:** Remarkably, we found IL-1 $\beta$ -positive dermal mast cells in both lesional and nonlesional skin of patients with SchS, but not in healthy control skin and CCU, and fewer in CAPS. IL-17-positive neutrophils were observed only in lesional SchS and DPU skin. In lesional SchS epidermis, mRNA and protein expression levels of AMPs were strongly increased compared with nonlesional skin and that of healthy controls. When exposed to IL-1 $\beta$ , poly:IC or IL-17, patient and control primary human keratinocytes produced AMPs in similar amounts.

**CONCLUSIONS:** Dermal mast cells of patients with SchS produce IL-1 $\beta$ . This presumably leads to activation of keratinocytes and neutrophil influx, and further amplification of inflammation by IL-17 (from neutrophils and mast cells) and epidermal AMP production leading to chronic histamine-independent neutrophilic urticarial dermatosis.

© 2015 British Association of Dermatologists.

DOI: 10.1111/bjd.13857

PMID: 25904179 [Indexed for MEDLINE]

1669. Clin Exp Rheumatol. 2015 Mar-Apr;33(2):137-40. Epub 2015 Apr 10.

Adult-onset autoinflammatory disorders: a still debated entity?

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PMID: 25896471 [Indexed for MEDLINE]

1670. Semin Immunopathol. 2015 Jul;37(4):313-22. doi: 10.1007/s00281-015-0485-5. Epub 2015 Apr 21.

Protective and detrimental roles of inflammasomes in disease.

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Over recent years, inflammasomes have emerged as key regulators of immune and inflammatory responses. They induce programmed cell death and direct the release of danger signals and the inflammatory cytokines interleukin (IL)-1 $\beta$  and IL-18. The concerted actions of inflammasomes are of utmost importance for responding adequately to harmful environmental agents and infections. However, deregulated inflammasome signaling is increasingly linked to a diversity of human pathologies, including rheumatoid arthritis, inflammatory bowel disease, and rare, hereditary periodic fever syndromes. In this review, we discuss recent insight in the protective and detrimental roles of inflammasomes in selected infectious, autoinflammatory and autoimmune diseases, and cover clinically approved therapies that interfere with inflammasome signaling. These findings highlight the importance of fine-balancing the Ying and Yang activities of inflammasomes for sustained homeostasis and suggest that further understanding of inflammasome mechanisms may offer new cures for human diseases.

DOI: 10.1007/s00281-015-0485-5

PMID: 25895577 [Indexed for MEDLINE]

1671. Semin Immunopathol. 2015 Jul;37(4):407-12. doi: 10.1007/s00281-015-0488-2. Epub 2015 Apr 17.

New discoveries in CRMO: IL-1 $\beta$ , the neutrophil, and the microbiome implicated in disease pathogenesis in Pstpip2-deficient mice.



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Chronic non-bacterial osteomyelitis (CNO), chronic recurrent multifocal osteomyelitis (CRMO) and synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome are autoinflammatory disorder(s) in which sterile osteomyelitis is frequently accompanied by inflammatory conditions of the joints, skin, or intestine. Patients with CRMO commonly have a personal or family history of psoriasis, inflammatory bowel disease, and inflammatory arthritis, suggesting shared disease pathogenesis. Work by our group and others has demonstrated that dysregulation of interleukin-1 (IL-1) signaling can drive sterile osteomyelitis in the two human monogenic forms of the disease. Recent work in the chronic multifocal osteomyelitis (cmo) mouse model demonstrates that the disease is IL-1-mediated, that neutrophils are critical effector cells and that both caspase-1 and caspase-8 play redundant roles in mediating the cleavage of pro-IL-1 $\beta$  into its biologically active form. Recent data in the cmo mouse demonstrate that dietary manipulation alters the cmo microbiome and can prevent the development of osteomyelitis. Further investigation is needed to determine the specific components of the diet that result in protection from disease and if this finding can be translated into a treatment for human CRMO.

DOI: 10.1007/s00281-015-0488-2

PMID: 25894861 [Indexed for MEDLINE]

1672. Arthritis Res Ther. 2015 Apr 3;17:93. doi: 10.1186/s13075-015-0604-7.

The novel S59P mutation in the TNFRSF1A gene identified in an adult onset TNF receptor associated periodic syndrome (TRAPS) constitutively activates NF- $\kappa$ B pathway.

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**INTRODUCTION:** Mutations in the TNFRSF1A gene, encoding tumor necrosis factor receptor 1 (TNF-R1), are associated with the autosomal dominant autoinflammatory disorder, called TNF receptor associated periodic syndrome (TRAPS). TRAPS is clinically characterized by recurrent episodes of long-lasting fever and systemic inflammation. A novel mutation (c.262 T > C; S59P) in the TNFRSF1A gene at residue 88 of the mature protein was recently identified in our laboratory in an adult TRAPS patient. The aim of this study was to functionally characterize this novel TNFRSF1A mutation evaluating its effects on the TNF-R1-associated signaling pathways, firstly NF- $\kappa$ B, under particular conditions and comparing the results with suitable control mutations.

**METHODS:** HEK-293 cell line was transfected with pCMV6-AC construct expressing wild-type (WT) or c.262 T > C (S59P), c.362G > A (R92Q), c.236C > T (T50M) TNFRSF1A mutants. Peripheral blood mononuclear cells (PBMCs) were instead isolated from two TRAPS patients carrying S59P and R92Q mutations and from five healthy subjects. Both transfected HEK-293 and PBMCs were stimulated with tumor necrosis factor (TNF) or interleukin 1 $\beta$  (IL-1 $\beta$ ) to evaluate the expression of TNF-R1, the activation of TNF-R1-associated downstream pathways and the pro-inflammatory cytokines by means of immunofluorescent assay, array-based technique, immunoblotting and immunometric assay, respectively.

**RESULTS:** TNF induced cytoplasmic accumulation of TNF-R1 in all mutant cells. Furthermore, all mutants presented a particular set of active TNF-R1 downstream pathways. S59P constitutively activated IL-1 $\beta$ , MAPK and SRC/JAK/STAT3 pathways and inhibited apoptosis. Also, NF- $\kappa$ B pathway involvement was demonstrated in vitro by the enhancement of p-I $\kappa$ B- $\alpha$  and p65 nuclear subunit of NF- $\kappa$ B expression in all mutants in the presence of TNF or IL-1 $\beta$  stimulation. These in vitro results correlated with patients' data from PBMCs. Concerning the pro-inflammatory cytokines secretion, mainly IL-1 $\beta$  induced a significant and persistent enhancement of IL-6 and IL-8 in PBMCs carrying the S59P mutation.

**CONCLUSIONS:** The novel S59P mutation leads to defective cellular trafficking and to constitutive activation of TNF-R1. This mutation also determines constitutive activation of the IL-1R pathway, inhibition of apoptosis and enhanced and persistent NF- $\kappa$ B activation and cytokine secretion in response to IL-1 $\beta$  stimulation.

DOI: 10.1186/s13075-015-0604-7

PMCID: PMC4416318

PMID: 25888769 [Indexed for MEDLINE]

1673. Immunity. 2015 Apr 21;42(4):654-64. doi: 10.1016/j.immuni.2015.03.006. Epub 2015 Apr 14.

The NLRP12 Sensor Negatively Regulates Autoinflammatory Disease by Modulating Interleukin-4 Production in T Cells.

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Comment in

Immunity. 2015 Apr 21;42(4):595-7.

Missense mutations in the nucleotide-binding oligomerization domain (NOD)-like receptor pyrin domain containing family of gene 12 (Nlrp12) are associated with periodic fever syndromes and atopic dermatitis in humans. Here, we have

demonstrated a crucial role for NLRP12 in negatively regulating pathogenic T cell responses. Nlrp12(-/-) mice responded to antigen immunization with hyperinflammatory T cell responses. Furthermore, transfer of CD4(+)CD45RB(hi)Nlrp12(-/-) T cells into immunodeficient mice led to more severe colitis and atopic dermatitis. NLRP12 deficiency did not, however, cause exacerbated ascending paralysis during experimental autoimmune encephalomyelitis (EAE); instead, Nlrp12(-/-) mice developed atypical neuroinflammatory symptoms that were characterized by ataxia and loss of balance. Enhanced T-cell-mediated interleukin-4 (IL-4) production promotes the development of atypical EAE disease in Nlrp12(-/-) mice. These results define an unexpected role for NLRP12 as an intrinsic negative regulator of T-cell-mediated immunity and identify altered NF-κB regulation and IL-4 production as key mediators of NLRP12-associated disease.

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DOI: 10.1016/j.immuni.2015.03.006

PMCID: PMC4412374

PMID: 25888258 [Indexed for MEDLINE]

1674. Ital J Pediatr. 2015 Feb 22;41:15. doi: 10.1186/s13052-015-0120-z.

Assessment of epicardial adipose tissue thickness and the mean platelet volume in children with familial Mediterranean fever.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is an inflammatory disease, which is suggested to be associated with increased risk of atherosclerosis. Epicardial adipose tissue (EAT) thickness and the mean platelet volume (MPV) are parameters used in prediction of atherosclerotic risk in various conditions. These parameters were evaluated in children with FMF and compared with healthy controls.

**METHODS:** Forty-five patients with FMF and 54 age- and gender-matched healthy controls were assessed. Duration of symptoms, age at diagnosis, duration of delay in diagnosis, frequency and duration of FMF attacks, disease severity scores, response to colchicine therapy, MEditerraneanFeVer (MEFV) gene mutations, and MPV values were recorded. EAT thicknesses were measured by echocardiography.

**RESULTS:** Epicardial adipose tissue thicknesses of the children with FMF were found to be significantly greater than that of controls ( $5.1 \pm 1.4$  vs.  $4.5 \pm 0.9$  mm,  $p=0.036$ ). FMF patients had significantly higher MPV values compared with the controls ( $7.8 \pm 1.1$  vs.  $7.3 \pm 1.4$  fl,  $p=0.044$ ). Age at diagnosis, duration of delay in diagnosis, and MPV values were found to be correlated with EAT thickness in the patient group ( $r=0.49$ ,  $p=0.001$  for the former parameters and  $r=0.32$ ,  $p=0.04$  for MPV).

**CONCLUSION:** Epicardial adipose tissue thickness and MPV values seem to be increased in children with FMF. These findings may indicate an increased risk of atherosclerosis in FMF patients.

DOI: 10.1186/s13052-015-0120-z

PMCID: PMC4348162

PMID: 25887962 [Indexed for MEDLINE]

1675. Orphanet J Rare Dis. 2015 Mar 25;10:34. doi: 10.1186/s13023-015-0252-7.

Familial Mediterranean fever without MEFV mutations: a case-control study.

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**BACKGROUND:** Although familial Mediterranean fever (FMF) was originally defined as an autosomal recessive disorder, approximately 10-20% of FMF patients do not carry any FMF gene (MEFV) mutations. Fine phenotype characterization may facilitate the elucidation of the genetic background of the so called "FMF without MEFV mutations". In this study we clinically and demographically characterize this subset.

**METHODS:** MEFV mutation-negative FMF and control patients were recruited randomly from a cohort followed in a dedicated FMF clinic. The control subjects comprised 2 groups: 1. typical population of FMF, consisting of genetically heterogeneous patients manifesting the classical spectrum of FMF phenotype and 2. a severe phenotype of FMF, consisting of FMF patients homozygous for the p.M694V mutation.

**RESULTS:** Forty-seven genetic-negative, 60 genetically heterogeneous and 57 p.M694V homozygous FMF patients were enrolled to the study. MEFV-mutation negative FMF patients showed a phenotype closely resembling that of the other 2 populations. It differed however from the p.M694V homozygous subset by its milder severity (using Mor et al. scoring method), as determined by the lower proportion of patients with chest and erysipelas like attacks, lower frequency of some of the chronic manifestations, lower colchicine dose and older age of disease onset.

**CONCLUSIONS:** MEFV mutation-negative FMF by virtue of its classical FMF phenotype is probably associated with a genetic defect upstream or downstream to MEFV related metabolic pathway.

DOI: 10.1186/s13023-015-0252-7

PMCID: PMC4377009

PMID: 25887307 [Indexed for MEDLINE]

1676. Scand J Immunol. 2015 Jul;82(1):76-83. doi: 10.1111/sji.12303.

Reduced Number of CD8+ Cells in Tonsillar Germinal Centres in Children with the Periodic Fever, Aphthous Stomatitis, Pharyngitis and Cervical Adenitis Syndrome.

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The syndrome of periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) is an autoinflammatory disorder of unknown aetiology. Tonsillectomy may cause a prompt resolution of the syndrome. The aim was to study the histologic and immunological aspects of the palatine tonsils in PFAPA, to help understand the pathophysiology of the syndrome. Tonsils from children with PFAPA (n = 11) and children with tonsillar hypertrophy (n = 16) were evaluated histologically after haematoxylin and eosin staining. The number of different cell types was identified immunohistochemically by cluster of differentiation (CD) markers: CD3 (T cells), CD4 (T helper cells), CD8 (cytotoxic T cells), CD15 (neutrophils), CD20 (B cells), CD45 (all leucocytes), CD57 (NK cells) and CD163 (monocytes and macrophages). Tonsils from children with PFAPA showed reactive lymphoid hyperplasia dominated by well-developed germinal centres with many tingible body macrophages. The histologic findings were unspecific, and a similar morphologic appearance was also found in the tonsils from controls. The number of CD8+ cells in germinal centres differed between children with PFAPA [median 9 cells (quartiles: 5, 15)] and controls [18 cells (12, 33) ( $P = 0.001$ )] and between children with PFAPA with (median 14 cells; 9, 16) and without (4 cells; 3, 8) aphthous stomatitis ( $P = 0.015$ ). For the other cell types, no differences in germinal centres were found between children with PFAPA and controls. In conclusion, a lower number of CD8+ cells were found in germinal centres of tonsils in children with PFAPA compared to controls, which may be a feature linked to the aetiology of the syndrome.

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DOI: 10.1111/sji.12303

PMID: 25882211 [Indexed for MEDLINE]

1677. Immunol Rev. 2015 May;265(1):85-102. doi: 10.1111/imr.12293.

The NAIP-NLRC4 inflammasome in innate immune detection of bacterial flagellin and type III secretion apparatus.

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Bacterial flagella and type III secretion system (T3SS) are evolutionarily related molecular transport machineries. Flagella mediate bacterial motility; the T3SS delivers virulence effectors to block host defenses. The inflammasome is a cytosolic multi-protein complex that activates caspase-1. Active caspase-1 triggers interleukin-1 $\beta$  (IL-1 $\beta$ )/IL-18 maturation and macrophage pyroptotic death to mount an inflammatory response. Central to the inflammasome is a pattern recognition receptor that activates caspase-1 either directly or through an adapter protein. Studies in the past 10 years have established a NAIP-NLRC4 inflammasome, in which NAIPs are cytosolic receptors for bacterial flagellin and T3SS rod/needle proteins, while NLRC4 acts as an adapter for caspase-1 activation. Given the wide presence of flagella and the T3SS in bacteria, the NAIP-NLRC4 inflammasome plays a critical role in anti-bacteria defenses. Here, we review the discovery of the NAIP-NLRC4 inflammasome and further discuss recent advances related to its biochemical mechanism and biological function as well as its connection to human autoinflammatory disease.

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DOI: 10.1111/imr.12293

PMID: 25879286 [Indexed for MEDLINE]

1678. Mod Rheumatol. 2017 Nov;27(6):1098-1100. doi: 10.3109/14397595.2015.1040609.  
Epub  
2015 Jun 13.

CINCA syndrome with surgical intervention for valgus deformity and flexion contracture of the knee joint: A case report.

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Erratum in

Mod Rheumatol. 2018 Jan;28(1):vi.

Chronic infantile neurological, cutaneous, and articular (CINCA) syndrome is a systemic autoinflammatory disease caused by increased production of interleukin (IL)-1 $\beta$ . We present a case of CINCA syndrome followed up to skeletal maturity. Joint contracture and valgus deformity of the knee had developed before diagnosis. Surgical interventions by soft tissue release and hemiepiphysiodesis improved the contracture and the deformity, and IL-1 receptor antagonist dramatically controlled systemic inflammation, and the patient lives without any disabilities.

DOI: 10.3109/14397595.2015.1040609

PMID: 25867226 [Indexed for MEDLINE]

1679. Pediatr Rheumatol Online J. 2015 Apr 10;13:11. doi: 10.1186/s12969-015-0006-z. eCollection 2015.

Genetic profiling of autoinflammatory disorders in patients with periodic fever: a prospective study.

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**BACKGROUND:** Periodic fever syndromes (PFS) are an emerging group of autoinflammatory disorders. Clinical overlap exists and multiple genetic analyses may be needed to assist diagnosis. We evaluated the diagnostic value of a 5-gene

sequencing panel (5GP) in patients with undiagnosed PFS.

**METHODS:** Simultaneous double strand Sanger sequencing of MEFV, MVK, TNFRSF1A, NLRP3, NLRP12 genes was performed in 42 patients with unexplained PFS. Clinical features were correlated with genetic results.

**RESULTS:** None of 42 patients analyzed displayed a causative genotype. However, single or multiple genetic variants of uncertain significance were detected in 24 subjects. Only in 5 subjects a definite diagnosis was made by taking into account both genetic and clinical data (2 TRAPS syndrome; 2 FMF; 1 FCAS). Statistical analysis showed that patients carrying genetic variants in one or more of the five selected genes displayed a significantly lower response to glucocorticoids compared with subjects who had completely negative genetic results.

**CONCLUSIONS:** The sequencing of multiple genes is of little help in the diagnostics of PFS and can often lead to results of uncertain interpretation, thus the clinically driven sequencing of single genes should remain the recommended approach. However, the presence of single or multiple genetic variants of uncertain significance, even if not allowing any specific diagnosis, correlated with a poorer response to glucocorticoids, possibly indicating a multifactorial subgroup of PFS with differential response to pharmacological treatment.

DOI: 10.1186/s12969-015-0006-z

PMCID: PMC4393620

PMID: 25866490 [Indexed for MEDLINE]

1680. J Biol Regul Homeost Agents. 2015 Jan-Mar;29(1):125-30.

Transcriptional activity of neutrophils exposed to high doses of colchicine: short communication.

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Colchicine is an antimitotic drug which binds to tubulin and at high doses results in cytoskeleton disruption. Colchicine is believed to be an anti-inflammatory agent, though its modulatory effects on the level and transcriptional activity of genes is still a matter of debate. There is growing evidence that alterations in the cytoskeleton exert specific effects on the expression of various genes. This study was undertaken to analyze whether disrupting the microtubule cytoskeleton by colchicine modulates transcriptional levels of MEFV, NF- $\kappa$ B p65, NLRP3, HMGB1, and caspase-3 in neutrophils from patients with familial Mediterranean fever (FMF) and healthy subjects. In the present study, colchicine caused increased expression of NLRP3 ( $p=0.007$ ) and MEFV ( $p=0.03$ ), but had no effect on caspase-3, NF- $\kappa$ B p65 and HMGB1 genes in healthy neutrophils. FMF neutrophils were less responsive to the drug treatment. This study supports the hypothesis that, being an anti-inflammatory agent, colchicine at relatively high concentrations might lead to the activation of pro-inflammatory signalling pathways in neutrophils.

PMID: 25864748 [Indexed for MEDLINE]

1681. Semin Immunopathol. 2015 Jul;37(4):395-401. doi: 10.1007/s00281-015-0478-4. Epub 2015 Apr 10.

Update on genetics and pathogenesis of autoinflammatory diseases: the last 2 years.

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Autoinflammatory diseases are a genetically heterogeneous group of rheumatologic diseases that are driven by abnormal activation of the innate immune system. Patients present with recurrent episodes of systemic inflammation and a spectrum of organ-specific comorbidities. These diseases are mediated by the overproduction of various inflammatory cytokines, such as IL-1, IL-18, IL-6,

TNF $\alpha$ , and type I interferon. Treatments with biologic agents that inhibit these cytokines have been very efficient in most patients. During the past 2 years, remarkable progress has been made in the identification of disease-associated genes owing mostly to new technologies. Next generation sequencing technologies (NGS) have become instrumental in finding single-gene defects in undiagnosed patients with early onset symptoms. NGS has advanced the field of autoinflammation by identifying disease-causing genes that point to pathways not known to regulate cytokine signaling or inflammation. They include a protein that has a role in differentiation of myeloid cells, a ubiquitously expressed enzyme that catalyzes the addition of the CCA terminus to the 3-prime end of tRNA precursors, and an enzyme that catalyzes the oxidation of a broad range of substrates. Lastly, newly described mutations have informed a whole new dimension on genotype-phenotype relationships. Mutations in the same gene can give rise to a range of phenotypes with a common inflammatory component. This suggests greater than anticipated contributions by modifying alleles and environmental factors to disease expressivity.

DOI: 10.1007/s00281-015-0478-4

PMID: 25860799 [Indexed for MEDLINE]

1682. J Gen Intern Med. 2015 Nov;30(11):1633-8. doi: 10.1007/s11606-015-3285-7. Epub 2015 Apr 9.

Reductions in Use of Colchicine after FDA Enforcement of Market Exclusivity in a Commercially Insured Population.

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Comment in

J Gen Intern Med. 2015 Nov;30(11):1581-3.

**BACKGROUND:** A brand-name version of colchicine (Colcrys) was introduced after its manufacturer conducted a clinical trial in acute gout patients, leading to higher prices for this drug.

**OBJECTIVE:** We analyzed the impact of the new single-source colchicine product on prescribing and patient health spending as well as incidence rates of potentially dangerous concomitant use of clarithromycin and cyclosporine after formal FDA approval.

**DESIGN/PARTICIPANTS:** We conducted a retrospective cohort study of UnitedHealth-affiliated enrollees newly diagnosed with gout or FMF.

**MAIN MEASURES:** Among gout and FMF patients separately, we assessed linear trends in colchicine prescriptions, prescription drug costs, and total health care costs from 2009 to September 2010 (market exclusivity announced) compared to January 2011 (market exclusivity enforced) through 2012. Next, we estimated trends in co-prescription within 15 days of clarithromycin, azithromycin (indicated on the Colcrys label for use in place of clarithromycin), and cyclosporine.

**KEY RESULTS:** Among gout patients, before Colcrys' market exclusivity, the odds of receiving colchicine within 30 days of gout diagnosis increased 1.4 %/month (OR: 1.014, 95 % CI: 1.011-1.018). Following FDA action, the odds decreased by 0.5 %/month (OR: 0.995, 95 % CI: 0.992-0.999) ( $p < 0.001$ ). Similarly, among FMF patients, odds of initiating colchicine changed from an increase of 2.8 %/month to a decrease by 7.6 %/month ( $p = 0.01$ ). Patients receiving colchicine experienced increases in average monthly prescription drug costs (\$418 vs. \$651,  $p < 0.001$ ) and health care costs (\$3,406 vs. \$3,534,  $p < 0.001$ ). Incidence rates of colchicine/clarithromycin co-prescription before and after FDA action did not change, while co-prescription of colchicine/cyclosporine increased after introduction of Colcrys [-0.75 monthly change in patients (95 % CI: -1.07, -0.43) vs. 0.13 (95 % CI: -0.16, 0.42),  $p < 0.001$ ].

**CONCLUSIONS:** The FDA's actions were associated with a reduction in colchicine initiation and an increase in patient spending. By contrast, we did not observe any association with improvements in avoidance of potentially dangerous co-prescriptions.

DOI: 10.1007/s11606-015-3285-7

PMCID: PMC4617917

PMID: 25855479 [Indexed for MEDLINE]

1683. Lupus. 2015 Aug;24(9):1006. doi: 10.1177/0961203315580874. Epub 2015 Apr 8.

Coexistence of systemic lupus erythematosus and familial Mediterranean fever.

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Comment on

Lupus. 2015 Mar;24(3):343-4.

DOI: 10.1177/0961203315580874

PMID: 25854828 [Indexed for MEDLINE]

1684. Clin Kidney J. 2014 Jun;7(3):314-7. doi: 10.1093/ckj/sfu044. Epub 2014 May 14.

Fever of unknown origin in a haemodialysis patient: a late diagnosis requiring a novel treatment.

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Tsakiris DJ(1).

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DOI: 10.1093/ckj/sfu044

PMCID: PMC4377762

PMID: 25852898



1685. Clin Kidney J. 2014 Apr;7(2):219-20. doi: 10.1093/ckj/sft164. Epub 2014 Jan 12.

Colchicine-resistant familial Mediterranean fever in a renal transplantation patient: successful treatment with anakinra.

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DOI: 10.1093/ckj/sft164

PMCID: PMC4377770

PMID: 25852877

1686. World J Gastroenterol. 2015 Apr 7;21(13):4078-81. doi: 10.3748/wjg.v21.i13.4078.

Treatment of Crohn's disease and familial Mediterranean fever by leukopheresis: single shot for two targets.

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Coexistence of Crohn's disease (CD) and familial Mediterranean fever (FMF) is a rare condition and knowledge about this clinical situation is limited with a few case reports in the literature. The treatment of both diseases depends on their individual therapies. However, it is very hard to deal with this coexistence when CD is refractory to standard therapies. Ongoing activity of CD triggers the

clinical attacks of FMF and the symptoms like abdominal pain interfere with both disease presentations which can cause problems about diagnostic and therapeutic approach. The main therapeutic agent for FMF is colchicine and diarrhea is the most common side effect of this drug. This side effect also causes problems about management of these diseases when both of them are clinically active. Here we report probably the first case in the literature with coexisting CD and FMF who was successfully treated by leukopheresis since he was refractory to conventional therapies for CD.

DOI: 10.3748/wjg.v21.i13.4078

PMCID: PMC4385558

PMID: 25852296 [Indexed for MEDLINE]

1687. Int J Pediatr Otorhinolaryngol. 2015 Jun;79(6):879-82. doi: 10.1016/j.ijporl.2015.03.022. Epub 2015 Apr 1.

Vestibular evoked myogenic potentials in pediatric patients with familial Mediterranean fever.

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**OBJECTIVES:** We aimed to investigate whether the chronic autoinflammatory process in familial Mediterranean fever (FMF), which affects numerous systems, results in vestibular dysfunction in pediatric patients being followed up for diagnosis of FMF using VEMP recordings.

**METHODS:** 30 patients (60 ears) diagnosed with FMF and 20 (40 ears) healthy volunteers were included in the study. Following routine ear, nose, and throat

examination, transient-evoked otoacoustic emissions (TEOAE) and vestibular-evoked myogenic potential (VEMP) tests were performed.

RESULTS: A total of 30 FMF pediatric patients (13 male, 17 female) and 20 controls (8 male, 12 female) were included in the study. The mean age of FMF patients was  $12.13 \pm 2.88$  years, while that of the controls was  $12.90 \pm 2.80$  years. All of the otoacoustic emission results of the patient and control groups were "pass VEMP recordings received in both ears of patients with FMF (60 ears) and both ears of controls (40 ears). There was no statistically significant difference for latencies or amplitudes for either patients or controls ( $p > 0.05$ ).

CONCLUSION: In order to research the effect of FMF on vestibular functions, we measured VEMP. However, we did not detect alterations of VEMP in FMF patients.

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DOI: 10.1016/j.ijporl.2015.03.022

PMID: 25851176 [Indexed for MEDLINE]

1688. Trends Endocrinol Metab. 2015 May;26(5):263-71. doi: 10.1016/j.tem.2015.03.004. Epub 2015 Apr 4.

Mitochondria in autoinflammation: cause, mediator or bystander?

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People suffering from autoinflammatory disease (AID) have recurring sterile inflammation due to dysregulated inflammasome activation. Although certain genes have been associated with several AIDs, the molecular underpinnings of seemingly spontaneous inflammation are not well understood. Emerging data now suggest that

mitochondrial reactive oxygen species (ROS), mitochondrial DNA (mtDNA), and autophagy might drive key signaling pathways towards activation of the inflammasome. In this review, we discuss recent findings and highlight common features between different AIDs and mitochondrial (dys)function. Although it is still early to identify clear therapeutic targets, the emerging paradigms in inflammation and mitochondrial biology show that mitochondria play an important role in AIDs, and understanding this interplay will be key in the development of new therapies.

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DOI: 10.1016/j.tem.2015.03.004

PMID: 25850613 [Indexed for MEDLINE]

1689. Tuberk Toraks. 2015;63(1):67-70.

A rare case of recurrent pneumonia: FMF.

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PMID: 25849061 [Indexed for MEDLINE]

1690. Rev Mal Respir. 2015 Mar;32(3):271-4. doi: 10.1016/j.rmr.2014.06.029. Epub 2014 Aug 6.

[Mesothelioma and familial Mediterranean fever: A relationship?].

[Article in French]

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**INTRODUCTION:** The majority of pleural and peritoneal mesotheliomas are linked to asbestos exposure but, in around 20% of cases, no history of such exposure is found. Periodic disease is associated with recurrent serositis, which could favor the development of mesothelioma.

**CASE REPORT:** We report a case of pleural mesothelioma in a 50-year-old Lebanese woman, with no detectable exposure to asbestos but suffering from periodic disease (familial Mediterranean fever) with recurrent episodes of serositis.

**DISCUSSION:** Many cases of peritoneal mesothelioma in patients with FMF are reported in the literature. This is the second reported case of pleural mesothelioma associated with periodic disease. Because of the low incidence of both diseases, further publications are required to support the hypothesis of a causal link. It is important, therefore, that all cases of an association of periodic disease and mesothelioma are reported.

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DOI: 10.1016/j.rmr.2014.06.029

PMID: 25847205 [Indexed for MEDLINE]

1691. Clin Rheumatol. 2015 Aug;34(8):1333-9. doi: 10.1007/s10067-015-2923-0. Epub 2015 Apr 8.

Macrophage activation syndrome in the course of monogenic autoinflammatory disorders.

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An overwhelming activation of cytotoxic T cells and well-differentiated macrophages leading to systemic overload of inflammatory mediators characterizes the so-called macrophage activation syndrome (MAS); this potentially life-threatening clinical entity may derive from several genetic defects involved in granule-mediated cytotoxicity but has been largely observed in patients with juvenile idiopathic arthritis, many rheumatologic diseases, infections, and malignancies. The occurrence of MAS in the natural history or as the revealing clue of monogenic autoinflammatory disorders (AIDs), rare conditions caused by disrupted innate immunity pathways with overblown release of proinflammatory cytokines, has been only reported in few isolated patients with cryopyrin-associated periodic syndrome, mevalonate kinase deficiency, familial Mediterranean fever, and tumor necrosis factor receptor-associated periodic syndrome since 2001. All these patients displayed various clinical, laboratory, and histopathologic features of MAS and have often required intensive care support. Only one patient has died due to MAS. Defective cytotoxic cell function was documented in a minority of patients. Corticosteroids were the first-line treatment, but anakinra was clinically effective in three refractory cases. Even if MAS and AIDs share multiple clinical features as well as heterogeneous pathogenetic scenes and a potential response to anti-interleukin-1 targeted therapies, MAS requires a prompt specific recognition in the course of AIDs due to its profound severity and high mortality rate.

DOI: 10.1007/s10067-015-2923-0

PMID: 25846831 [Indexed for MEDLINE]

1692. Expert Rev Clin Immunol. 2015 May;11(5):575-88. doi: 10.1586/1744666X.2015.1032257. Epub 2015 Apr 4.

Complications of systemic juvenile idiopathic arthritis: risk factors and management recommendations.

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Systemic juvenile idiopathic arthritis (SJIA) is an inflammatory condition characterized by fever, lymphadenopathy, arthritis, rash and serositis. Systemic inflammation has been associated with dysregulation of the innate immune system, suggesting that SJIA is an autoinflammatory disorder. IL-1 and IL-6 play a major role in the pathogenesis of SJIA, and treatment with IL-1 and IL-6 inhibitors has shown to be highly effective. However, complications of SJIA, including macrophage activation syndrome, limitations in functional outcome by arthritis and long-term damage from chronic inflammation, continue to be a major issue in SJIA patients' care. Translational research leading to a profound understanding of the cytokine crosstalk in SJIA and the identification of risk factors for SJIA complications will help to improve long-term outcome.

DOI: 10.1586/1744666X.2015.1032257

PMID: 25843554 [Indexed for MEDLINE]

1693. J Pak Med Assoc. 2015 Feb;65(2):196-200.

Higher frequency of methicillin resistant bacteria in children with familial mediterranean fever.

Yengil E, Cevik C, Silfeler I, Yula E, Kurtoglu IA, Arica V, Ozer C.

**OBJECTIVE:** To investigate resistant microorganisms in nasal mucosa of children with Familial Mediterranean Fever.

**METHODS:** The study was conducted from March to May 2013 at Mustafa Kemal University, Turkey, and comprised children with Familial Mediterranean Fever and healthy controls. All subjects had no history of antibiotic or local and/or systemic steroid use within the preceding 2 weeks. Nasal swab samples were obtained from all the subjects. Strain identification was done by using standard methods. SPSS 13 was used for statistical analysis.

**RESULTS:** Of the 151 subjects in the study, 73 (48.34%) were cases and 78 (51.65%) were controls. Among the cases, there were 26(35.6%) girls, while among the controls, there were 40(51.3%) girls ( $p=0.052$ ). The mean age of the cases was  $7.78 \pm 3.34$  years (range: 3-15 years), while it was  $8.15 \pm 2.71$  years (range: 3-16) among the controls ( $p = 0.208$ ). Methicillin-resistant coagulase-negative staphylococcus and methicillin-resistant staphylococcus aureus were isolated in both the groups. The growth rate of resistant bacteria was 63% ( $n = 46$ ) in the

cases, in the controls ( $p = 0.003$ ; odds ratio [OR]: 2.7; 95% confidence interval [CI]: 1.4-5.2). Among the controls, history of hospitalisation increased the risk for the presence of resistant bacteria by 7.7 fold (OR: 7.7; 95% CI: 1.4-40.4).  
CONCLUSION: Higher rates of resistant bacteria showed that they were at risk of comorbidities related to antibiotic resistance.

PMID: 25842558 [Indexed for MEDLINE]

1694. Clin Rheumatol. 2015 Jul;34(7):1171-80. doi: 10.1007/s10067-015-2920-3. Epub 2015 Apr 2.

The protean ocular involvement in monogenic autoinflammatory diseases: state of the art.

Bascherini V(1), Granato C, Lopalco G, Emmi G, Vannozzi L, Bacherini D, Franceschini R, Iannone F, Salerni A, Molinaro F, Messina M, Frediani B, Selmi C, Rigante D, Cantarini L.

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Ocular involvement is frequent in the monogenic autoinflammatory disorders and generally occurs as spontaneously recurring inflammatory events at different ocular sites caused by the aberrant release of proinflammatory cytokines, mainly IL-1 $\beta$ . Over the past decade, we witnessed a significant growth of eye abnormalities associated with idiopathic granulomatous disorders, familial Mediterranean fever, tumor necrosis factor receptor-associated periodic syndrome, mevalonate kinase deficiency, and cryopyrin-associated periodic syndrome. The pathogenetic mechanisms of these disorders have shown the evidence of disrupted cytokine signaling, but the explanation for the heterogeneous ocular involvement remains to be elucidated. We herein review the monogenic autoinflammatory disorders affecting the eye, describing their main clinical features with specific regard to the ocular involvement, which can lead to decreased visual acuity and even blindness, if the primary disorder is undetected or left untreated.



DOI: 10.1007/s10067-015-2920-3  
PMID: 25833143 [Indexed for MEDLINE]

1695. Semin Immunopathol. 2015 Jul;37(4):363-9. doi: 10.1007/s00281-015-0484-6. Epub 2015 Apr 2.

The myths we believed in familial Mediterranean fever: what have we learned in the past years?

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Familial Mediterranean fever is the most common monogenic periodic fever syndrome over the world especially in the eastern Mediterranean. It presents with recurrent and self-limited inflammatory attacks of fever and polyserositis along with high acute-phase reactants. The disease is associated with mutations in the MEFV gene that encodes pyrin, a component of inflammasome, which leads to exaggerated inflammatory response through uncontrolled production of interleukin 1. With the identification of the gene associated with the disease, we believed that everything was solved and that this was an ordinary monogenic disease with autosomal recessive inheritance. However, through the breathtaking progress in the basic research field as well as the clinical care of these patients, we have understood that the picture for this monogenic disorder was more complicated than we had anticipated. In this review, we have discussed the myths we believed in familial Mediterranean fever and how they have evolved during the past years.

DOI: 10.1007/s00281-015-0484-6  
PMID: 25832989 [Indexed for MEDLINE]

1696. Rom J Morphol Embryol. 2015;56(1):7-14.

Dermatology facing autoinflammatory syndrome.

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Cutaneous symptoms are characteristic for the autoinflammatory disorders (AIDs), both in the classical autoinflammatory phenotype and in most disorders included in this syndrome, but they are not specific and inconstant. Several skin disorders (pyoderma gangrenosum and pustular acne) may be encountered either isolate or associated with autoinflammatory symptoms, forming well-defined clinical entities within the autoinflammatory syndrome. The high prevalence of cutaneous manifestations is an important characteristic of AIDs. The presence of cutaneous symptoms in AIDs opens the perspective of understanding the contribution of innate immunity mechanisms involved in skin pathology. It is possible that many diseases present the alteration, in various degrees, of the innate immune mechanisms. Recently, dermatology faced two challenges connected to AIDs. The first involves the diagnosis of skin symptoms in a clinical autoinflammatory setting and the investigative approach to identify a disorder classified as AID. The second is to identify the altered mechanisms of inborn immunity among the pathogenetic mechanisms of known dermatological diseases (e.g., neutrophilic dermatoses). On the other hand, cutaneous symptoms are in certain cases regarded as a criterion to assess the efficacy of specific or non-specific therapies with monoclonal antibodies in disorders included in AIDs. Dermatology mostly benefits from the identification and knowledge of AIDs due to the role of innate immunity in skin pathogeny and also due to the large extent of clinical forms resulting from the association of skin symptoms with other disorders included in this group.

PMID: 25826481 [Indexed for MEDLINE]

1697. Nat Rev Rheumatol. 2015 Jun;11(6):338-48. doi: 10.1038/nrrheum.2015.20. Epub 2015 Mar 31.

Uveitis associated with juvenile idiopathic arthritis.

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Uveitis is a potentially sight-threatening complication of juvenile idiopathic arthritis (JIA). JIA-associated uveitis is recognized to have an autoimmune aetiology characterized by activation of CD4(+) T cells, but the underlying mechanisms might overlap with those of autoinflammatory conditions involving activation of innate immunity. As no animal model recapitulates all the features of JIA-associated uveitis, questions remain regarding its pathogenesis. The most common form of JIA-associated uveitis is chronic anterior uveitis, which is usually asymptomatic initially. Effective screening is, therefore, essential to detect early disease and commence treatment before the development of visually disabling complications, such as cataracts, glaucoma, band keratopathy and cystoid macular oedema. Complications can result from uncontrolled intraocular inflammation as well as from its treatment, particularly prolonged use of high-dose topical corticosteroids. Accumulating evidence supports the early introduction of systemic immunosuppressive drugs, such as methotrexate, as steroid-sparing agents. Prospective randomized controlled trials of TNF inhibitors and other biologic therapies are underway or planned. Future research should aim to identify biomarkers to predict which children are at high risk of developing JIA-associated uveitis or have a poor prognosis. Such biomarkers could help to ensure that patients receive earlier interventions and more-potent therapy, with the ultimate aim of reducing loss of vision and ocular morbidity.

DOI: 10.1038/nrrheum.2015.20

PMID: 25825278 [Indexed for MEDLINE]

1698. Mediators Inflamm. 2015;2015:293417. doi: 10.1155/2015/293417. Epub 2015 Mar 4.

Clinical features and genetic background of the periodic Fever syndrome with aphthous stomatitis, pharyngitis, and adenitis: a single center longitudinal study of 81 patients.

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PFAPA syndrome is the most common autoinflammatory disorder in childhood with unknown etiology. The aim of our study was clinical evaluation of PFAPA patients from a single tertiary care center and to determine whether variations of AIM2, MEFV, NLRP3, and MVK genes are involved in PFAPA pathogenesis. Clinical and laboratory data of consecutive patients with PFAPA syndrome followed up at the University Children's Hospital, Ljubljana, were collected from 2008 to 2014. All four genes were PCR amplified and directly sequenced. Eighty-one patients fulfilled criteria for PFAPA syndrome, 50 (63%) boys and 31 (37%) girls, with mean age at disease onset of  $2.1 \pm 1.5$  years. Adenitis, pharyngitis, and aphthae were present in 94%, 98%, and 56%, respectively. Family history of recurrent fevers in childhood was positive in 78%. Nineteen variants were found in 17/62 (27%) patients, 4 different variants in NLRP3 gene in 13 patients, and 6 different variants in MEFV gene in 5 patients, and 2 patients had 2 different variants. No variants of clinical significance were found in MVK and AIM2 genes. Our data suggest that PFAPA could be the result of multiple low-penetrant variants in different genes in combination with epigenetic and environmental factors leading to uniform clinical picture.

DOI: 10.1155/2015/293417

PMCID: PMC4364074

PMID: 25821352 [Indexed for MEDLINE]

1699. Cytokine. 2015 Aug;74(2):237-46. doi: 10.1016/j.cyto.2015.02.012. Epub 2015 Mar 23.

Monogenic autoinflammatory diseases: Cytokinopathies.

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Rapid advances in genetics are providing unprecedented insight into functions of the innate immune system with identification of the mutations that cause monogenic autoinflammatory disease. Cytokine antagonism is profoundly effective in a subset of these conditions, particularly those associated with increased interleukin-1 (IL-1) activity, the inflammasomopathies. These include syndromes where the production of IL-1 is increased by mutation of innate immune sensors such as NLRP3, upstream signalling molecules such as PSTPIP1 and receptors or downstream signalling molecules, such as IL-1Ra. Another example of this is interferon (IFN) and the interferonopathies, with mutations in the sensors STING and MDA5, the upstream signalling regulator AP1S3, and a downstream inhibitor of IFN signalling, ISG15. We propose that this can be extended to cytokines such as IL-36, with mutations in IL-36Ra, and IL-10, with mutations in IL-10RA and IL-10RB, however mutations in sensors or upstream signalling molecules are yet to be described in these instances. Additionally, autoinflammatory diseases can be caused by multiple cytokines, for example with the activation of NF- $\kappa$ B/Rel, for which we propose the term Relopathies. This nosology is limited in that some cytokine pathways may be degenerate in their generation or execution, however provides insight into likely autoinflammatory disease candidates and the cytokines with which newly identified mutations may be associated, and therefore targeted.

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DOI: 10.1016/j.cyto.2015.02.012

PMID: 25814341 [Indexed for MEDLINE]

1700. Iran J Basic Med Sci. 2015 Jan;18(1):53-7.

MEFV mutations in Northwest of Iran: a cross sectional study.

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**OBJECTIVES:** Familial Mediterranean Fever (FMF) is an autosomal recessive disorder characterized by recurrent episodes of fever accompanied by peritonitis, pleurisy, and arthritis. FMF affects mainly Mediterranean populations and is caused by mutations in the familial Mediterranean fever (MEFV) gene. The aim of this study was to identify the frequency and distribution of MEFV mutations in Iranian Azerbaijanis with FMF.

**MATERIALS AND METHODS:** Medical records of 1330 Iranian Azerbaijanis who were diagnosed with FMF according to Tel-Hashomer criteria from May 2006 to April 2013 were reviewed and 10 MEFV mutations were found in affected individuals.

**RESULTS:** 243 patients (18.27%) were homozygous, 370 (27.82%) were compound heterozygous and 717 (53.91%) were identified as heterozygous for one of the studied mutations. Of the studied mutations, M694V, E148Q, V726A, M680I, and M694I accounted for 42%, 21%, 19%, 14% and 2% of mutations respectively.

**CONCLUSION:** In our study, M694V was found to be the most prevalent mutation. M694I, the most common mutation among Arabs, is rare in this cohort. Allele frequencies of the common mutations in our studied population have some similarities to those of the Turkish population reported previously. However, M680I is less common in our cohort.

PMCID: PMC4366743

PMID: 25810876

1701. Immunotherapy. 2015;7(3):243-54. doi: 10.2217/imt.14.106.

The inflammasome and IL-1 $\beta$ : implications for the treatment of inflammatory diseases.

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The bioactive form of IL-1 $\beta$ , a key immunoregulatory and proinflammatory cytokine, is produced by the inflammasome - a caspase-1 activating molecular platform - in response to selected danger-associated molecular patterns and pathogen-associated molecular patterns. Advances in understanding the role of IL-1 $\beta$  in inflammatory conditions has resulted in IL-1 $\beta$  becoming a therapeutic target for a number of inflammatory diseases beyond the rare monogenic autoinflammatory diseases characterized by aberrant inflammasome function and enhanced bioactive IL-1 $\beta$  production. In the monogenic autoinflammatory diseases known as cryopyrin-associated periodic syndromes, neutralization of IL-1 $\beta$  results in a rapid and sustained reduction in disease severity without severe side effects, which has consequently driven off-label applications of IL-1 $\beta$ -targeted therapy in other inflammatory diseases. This review summarizes inflammatory diseases for which accumulating evidence suggests a therapeutic potential for IL-1 $\beta$  antagonists.

DOI: 10.2217/imt.14.106

PMID: 25804477 [Indexed for MEDLINE]

1702. Medicine (Baltimore). 2015 Feb;94(8):1. doi: 10.1097/01.md.0000462395.68470.98.

Association of Pyoderma Gangrenosum, Acne, and Suppurative Hidradenitis (PASH) Shares Genetic and Cytokine Profiles With Other Autoinflammatory Diseases: Erratum.

[No authors listed]

Erratum for

Medicine (Baltimore). 2014 Dec;93(27):e187.

[In the article "Association of Pyoderma Gangrenosum, Acne, and Suppurative Hidradenitis (PASH) Shares Genetic and Cytokine Profiles With Other Autoinflammatory Diseases", which appeared in Volume 93, Issue 27 of Medicine, one of Orietta M. Borghi's affiliations was omitted. The article should have stated that Orietta M. Borghi is associated with the IRCCS Istituto Auxologico Italiano, Milano, Italy as well as the Dipartimento di Scienze Cliniche e di Comunità, Università di Milano.].

DOI: 10.1097/01.md.0000462395.68470.98

PMCID: PMC4554146

PMID: 25803365

1703. Autoimmun Rev. 2015 Jul;14(7):622-32. doi: 10.1016/j.autrev.2015.03.003. Epub 2015 Mar 20.

The 2014 ACR annual meeting: a bird's eye view of autoimmunity in 2015.

Selmi C(1), Cantarini L(2), Kivity S(3), Dagaan A(3), Shovman O(3), Zandman-Goddard G(4), Perricone C(5), Amital H(3), Toubi E(6), Shoenfeld Y(7).

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Our understanding of the mechanisms leading to rheumatic diseases is growing at unprecedented pace thanks to the worldwide network of clinical and translational researchers who gather at major scientific meetings to share their progresses. Further, these meetings allow the contamination of unrelated research areas and thus the spreading of ideas, hypotheses, and research tools. The annual meeting of the American College of Rheumatology (ACR) serves this purpose by allowing thousands of rheumatologists, immunologists, health care professionals, and basic scientists to attend the same sessions and present their work. The 2014 ACR meeting was held in Boston, MA, and was attended by over 16,000 participants who had the opportunity to directly witness the presentation of over 3000 abstracts. As such is the case, a full attendance of all update opportunities was not feasible. To fill this gap we arbitrarily selected the abstracts that appeared most interesting in a few fields of interest and we herein discuss the presented data and their further implications. In particular, we were intrigued by research advances in biomarkers for rheumatic diseases, and by advances on Sjögren syndrome, neuropsychiatric systemic lupus erythematosus, fibromyalgia, and B cell mechanisms. While we are well aware of the numerous blind spots that are expected in this type of article, we submit that this is far from a comprehensive overview and refer to the abstract book for a more complete analysis of the presented abstracts.

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DOI: 10.1016/j.autrev.2015.03.003

PMID: 25801806 [Indexed for MEDLINE]

1704. Mod Rheumatol. 2017 Sep;27(5):905-909. doi: 10.3109/14397595.2015.1031722. Epub 2015 Apr 30.

Protracted arthritis in a Japanese patient with familial Mediterranean fever.

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The most common arthritic involvement in familial Mediterranean fever (FMF) is acute self- limiting monoarthritis which typically lasts for 72 h. Hip joint involvement is uncommon in FMF and can result either from a process specific to this disease or from a coexisting inflammatory joint disease. We describe a 37-year-old woman with FMF and right osteoarthritis secondary to congenital hip dislocation. Periodic fever with right coxalgia lasting for 6 months was treated using colchicine. Genetic analysis revealed homozygous mutation in the MEFV gene (L110P-E148Q/L110P-E148Q), confirming the FMF diagnosis. Although the clinical presentation and course of FMF arthritis are diverse, delineating these clinical patterns may help with early recognition and treatment to prevent destructive arthritis in FMF. Clinicians should consider the possibility of FMF development in unusual monoarthritis patients with recurrent febrile attacks.

DOI: 10.3109/14397595.2015.1031722

PMID: 25800639 [Indexed for MEDLINE]

1705. Iran J Pediatr. 2014 Oct;24(5):598-602. Epub 2014 Oct 24.

Periodic Fever, Aphthous Stomatitis, Pharyngitis and Cervical Adenitis (PFAPA) Syndrome in Iranian Children First Report of Iranian Periodic Fever and Autoinflammatory Registry (IPFAIR).

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**OBJECTIVE:** The periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome is a nonhereditary idiopathic febrile syndrome belonging to the group of autoinflammatory diseases. No longtime sequel was reported in this disease. Early diagnosis can lead physicians to treatment of this disorder with a short course steroid application and provide satisfaction of the patient's family.

**METHODS:** This study is a prospective review of patients diagnosed with PFAPA syndrome who were registered in Iranian Periodic Fever and Autoinflammatory Registry (IPFAIR) through periodic fever clinic in the Children's Medical Center, Pediatric Center of Excellence in Tehran, Iran from January 2013 to March 2014.

**FINDINGS:** One hundred thirty patients were registered in our databases.

Twenty-one (16.1%) patients including 15 males and 6 females had PFAPA. Normal growth was seen in all patients. The median age at onset was 18 months. The mean duration of fever was 4 days and the mean duration of intervals between fever episodes 21 days. Along with fever, all patients had characteristic symptoms. All patients were asymptomatic between fever episodes. Steroid was used in all patients and causing immediate reduction by 84.61%. Two patients received both steroid and colchicine because of their clinical feature and positive laboratory tests for PFAPA and familial Mediterranean fever. No patient received biological therapy or a tonsillectomy.

**CONCLUSION:** The long diagnostic delay of PFAPA gives cause to concern indicating a need for greater awareness of the disease so that the diagnosis may be made timely.

PMCID: PMC4359414

PMID: 25793068

1706. Iran J Pediatr. 2014 Feb;24(1):1-13. Epub 2013 Nov 16.

Periodic Fever: a review on clinical, management and guideline for Iranian patients - part I.

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Periodic fever syndromes are a group of diseases characterized by episodes of fever with healthy intervals between febrile episodes. The first manifestation of these disorders are present in childhood and adolescence, but infrequently it may be presented in young and middle ages. Genetic base has been known for all types of periodic fever syndromes except periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA). Common periodic fever disorders are Familial Mediterranean fever (FMF) and PFAPA. In each patient with periodic fever, acquired infection with chronic and periodic nature should be ruled out. It depends on epidemiology of infectious diseases. Some of them such as Familial Mediterranean fever and PFAPA are common in Iran. In Iran and other Middle East countries, brucellosis, malaria and infectious mononucleosis should be considered in differential diagnosis of periodic fever disorders especially with fever and arthritis manifestation. In children, urinary tract infection may be presented as periodic disorder, urine analysis and culture is necessary in each child with periodic symptoms. Some malignancies such as leukemia and tumoral lesions should be excluded in patients with periodic syndrome and weight loss in any age. After excluding infection, malignancy and cyclic neutropenia, FMF and PFAPA are the most common periodic fever disorders. Similar to other countries, Hyper IgD, Chronic Infantile Neurologic Cutaneous and Articular, TRAPS and other auto-inflammatory syndromes are rare causes of periodic fever in Iranian system registry. In part 1 of this paper we reviewed the prevalence of FMF and PFAPA in Iran. In part 2, some uncommon auto-inflammatory disorders such as TRAPS, Hyper IgD syndrome and cryopyrin associated periodic syndromes will be reviewed.

1707. Cochrane Database Syst Rev. 2015 Mar 20;(3):CD010893. doi: 10.1002/14651858.CD010893.pub2.

Interventions for reducing inflammation in familial Mediterranean fever.

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Update in

Cochrane Database Syst Rev. 2018 Oct 19;10:CD010893.

**BACKGROUND:** Familial Mediterranean fever, a hereditary auto-inflammatory disease, mainly affects ethnic groups living in the Mediterranean region. Early studies reported colchicine as a potential drug for preventing attacks of familial Mediterranean fever. For those people who are colchicine-resistant or intolerant, drugs such as rilonacept, anakinra, etanercept, infliximab, thalidomide and interferon-alpha might be beneficial.

**OBJECTIVES:** To evaluate the efficacy and safety of interventions for reducing inflammation in people with familial Mediterranean fever.

**SEARCH METHODS:** We used detailed search strategies to search the following databases: CENTRAL; MEDLINE; Embase; Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure Database (CNKI); Wan Fang; and VIP. In addition, we also searched the clinical trials registries including ClinicalTrials.gov, the International Standard Randomized Controlled Trial Number Register, the WHO International Clinical Trials Registry Platform and the Chinese Clinical Trial Registry, as well as references listed in relevant reports. Date of last search: 21 May 2014.

**SELECTION CRITERIA:** Randomized controlled studies of people with diagnosis of familial Mediterranean fever, comparing active interventions (including colchicine, anakinra, rilonacept, etanercept, infliximab, thalidomide, interferon-alpha, ImmunoGuard™ (a herbal dietary supplement) and non-steroidal anti-inflammatory drugs) with placebo or no treatment, or comparing active drugs to each other.

**DATA COLLECTION AND ANALYSIS:** The authors independently selected studies,

extracted data and assessed risk of bias. We pooled data to present the risk ratio or mean difference with their 95% confidence intervals. We assessed overall evidence quality according to the GRADE approach.

**MAIN RESULTS:** We included four randomized placebo-controlled studies with a total of 75 participants (aged three to 53 years); three were of cross-over and one of parallel design. Two studies used the active intervention of oral colchicine (0.6 mg three times daily or 0.5 mg twice daily), one study used oral ImmunoGuard™ and the fourth used rilonacept as a subcutaneous injection. The duration of each study arm ranged from one to three months. The two most recent studies were generally well-designed, except for an unclear risk of detection bias in one of these. However, some inadequacy existed in the other two older studies, where each had an unclear risk of selection bias, a high risk of attrition bias, an unclear risk of reporting bias and a high risk of other potential bias (baseline characteristics such as mutation status and disease severity were not described); one of these studies additionally had an unclear risk of detection bias. We aimed to report on the number of participants experiencing an attack, the timing of attacks, any adverse drug reactions and the response of a number of biochemical markers from the acute phase of an attack, but data were not available for all outcomes across all comparisons. Based on one study (15 participants), there was a significant reduction in the number of people experiencing attacks at three months when colchicine was administered at a dose of 0.6 mg three times daily (14% versus 100%), risk ratio 0.21 (95% confidence interval 0.05 to 0.95); however, the GRADE evidence quality was low. Based on two further studies, there was no significant reduction in the number of participants experiencing attacks at two months when colchicine was administered at a dose of 0.5 mg twice daily (22 participants) in people with familial Mediterranean fever, or at three months when rilonacept was used in individuals who were colchicine-resistant or colchicine-intolerant (14 participants). In the ImmunoGuard™ study (24 participants) acute phase response indicators (including erythrocyte sedimentation rate, white blood cell count and C-reactive protein) were not reduced after one month treatment.

**AUTHORS' CONCLUSIONS:** There were limited randomized controlled studies assessing interventions for people with familial Mediterranean fever. Based on the evidence, colchicine appears to reduce the number of people experiencing attacks; however, only a few low-quality randomized controlled studies contributed data for analysis. Further randomized controlled studies examining active interventions, not only colchicine, are necessary before a comprehensive conclusion regarding the efficacy and safety of interventions for reducing inflammation in familial Mediterranean fever can be drawn.

DOI: 10.1002/14651858.CD010893.pub2  
PMID: 25791871 [Indexed for MEDLINE]

1708. An Pediatr (Barc). 2015 Aug;83(2):130-2. doi: 10.1016/j.anpedi.2015.02.004. Epub 2015 Mar 17.

[Arthritis as presentation of familial Mediterranean fever].

[Article in Spanish]

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DOI: 10.1016/j.anpedi.2015.02.004  
PMID: 25791192 [Indexed for MEDLINE]

1709. Turk J Med Sci. 2015;45(1):136-40.

Evaluation of autoinflammatory disease genes in nasal polyposis.

Köseoğlu S, Özcan KM, İkinçioğulları A, Cetin MA, Özdaş T, Özdaş S, Ensari S, Dere HH.

**BACKGROUND/AIM:** To investigate cold-induced autoinflammatory syndrome 1 (CIAS 1) gene polymorphisms that cause autoinflammatory diseases in patients with nasal polyposis (NP).

**MATERIALS AND METHODS:** The study included 30 patients diagnosed with NP and 30 healthy age-matched individuals as a control group. CIAS1 polymorphisms were assessed by DNA sequence analysis. Patients with nasal polyps and the control group were compared in terms of gene polymorphisms. Each of the 8 polymorphisms

of the CIAS1 gene was analyzed separately in the patient group.

RESULTS: The most frequently observed polymorphisms in the patient group were c.732G > A in 83%, c.663C > T in 23%, and c.1308C > A in 23% of the patients. c.732G > A polymorphism was evaluated separately. Guanine was transformed to adenine at the 732nd nucleotide position of the CIAS1 gene in the cDNA of chromosome 1.

CONCLUSION: The CIAS1 gene c.732G > A polymorphism was thought to be responsible for an increase in disease susceptibility. The frequency of the "A" allele is higher in the patient group compared to the control group. Autoinflammatory diseases seem like a candidate to be one of these factors. This is the first report to define the role of autoinflammatory diseases among these factors.

PMID: 25790542 [Indexed for MEDLINE]

1710. Wien Klin Wochenschr. 2015 Mar;127(5-6):185-90. doi: 10.1007/s00508-015-0714-x. Epub 2015 Mar 19.

Relation of fragmented QRS to tissue Doppler-derived parameters in patients with familial Mediterranean fever.

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BACKGROUND: Familial Mediterranean fever (FMF) may pose a risk for cardiovascular diseases due to continuous inflammatory status observed during the course of the disease. Recently, the presence of fragmented QRS (fQRS) has been recognized as a predictor of myocardial fibrosis. In this study, we aim to investigate the frequency of fQRS and its relation to Doppler-based indices.

METHODS: This study consisted of 80 FMF patients and 30 healthy control subjects. fQRS pattern was defined as the presence of additional R waves or RSR', evidenced by notched R or S wave on electrocardiography (ECG). The patient and the control groups underwent conventional echocardiography and tissue Doppler echocardiography.



RESULTS: There was no significant difference between groups regarding age ( $29 \pm 12$  vs  $29 \pm 15$ ). FMF patients exhibited a statistically higher frequency of fQRS (% 56 vs % 13) ( $p < 0.01$ ). E/Em ratio showed a statistically significant increase in the FMF group with fQRS ( $p < 0.0001$ ), while the mean Em value was markedly lower ( $p < 0.0001$ ).

CONCLUSIONS: FMF patients displayed a statistically significant increase in frequency of fQRS. Doppler-derived diastolic index was statistically significantly impaired in FMF patients with fQRS as compared with the patients without fQRS. In conclusion, fQRS might be a new noninvasive marker for cardiac involvement in FMF patients.

DOI: 10.1007/s00508-015-0714-x

PMID: 25787212 [Indexed for MEDLINE]

1711. Mediators Inflamm. 2015;2015:194864. doi: 10.1155/2015/194864. Epub 2015 Feb 16.

Interleukin-1 as a common denominator from autoinflammatory to autoimmune disorders: premises, perils, and perspectives.

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A complex web of dynamic relationships between innate and adaptive immunity is now evident for many autoinflammatory and autoimmune disorders, the first deriving from abnormal activation of innate immune system without any conventional danger triggers and the latter from self-/non-self-discrimination loss of tolerance, and systemic inflammation. Due to clinical and pathophysiologic similarities giving a crucial role to the multifunctional cytokine interleukin-1, the concept of autoinflammation has been expanded to include nonhereditary collagen-like diseases, idiopathic inflammatory diseases,

and metabolic diseases. As more patients are reported to have clinical features of autoinflammation and autoimmunity, the boundary between these two pathologic ends is becoming blurred. An overview of monogenic autoinflammatory disorders, PFAPA syndrome, rheumatoid arthritis, type 2 diabetes mellitus, uveitis, pericarditis, Behçet's disease, gout, Sjögren's syndrome, interstitial lung diseases, and Still's disease is presented to highlight the fundamental points that interleukin-1 displays in the cryptic interplay between innate and adaptive immune systems.

DOI: 10.1155/2015/194864

PMCID: PMC4345261

PMID: 25784780 [Indexed for MEDLINE]

1712. Antioxid Redox Signal. 2015 May 1;22(13):1079-83. doi: 10.1089/ars.2015.6319. Epub 2015 Apr 1.

Cardiovascular pathobiology of inflammasomes: inflammatory machinery and beyond.

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**SIGNIFICANCE:** In response to infection or cellular stress, inflammasomes are assembled and activated to mediate host defense and to initiate or promote the development of different diseases, in particular, autoinflammatory diseases and chronic degenerative diseases. Understanding of inflammasomes and related physiological and pathological relevance to the cardiovascular system will open a new chapter on the pathogenesis of inflammation and related diseases and will help develop novel therapeutic strategies for prevention or treatment of cardiovascular diseases.

**RECENT ADVANCES:** The inflammasome, in particular the nucleotide oligomerization domain-like receptor containing pyrin domain 3 (NLRP3) inflammasome, has been recently recognized as a fundamental mechanism to mediate or promote the pathogenesis of degenerative diseases. Some important mechanisms responsible for NLRP3 inflammasome activation have been proposed and many molecular targets associated with this inflammasome activation are shown to be the possible

candidates of therapeutic targets for treatment of cardiovascular diseases.

**CRITICAL ISSUES:** The concepts that NLRP3 inflammasome activation occurs just in immune cells or phagocytes and that its role is only for the inflammatory progression of cardiovascular diseases are oversimplified. A large body of other cell types are capable of NLRP3 inflammasome activation, and many uncanonical effects of this inflammasome may also be implicated in the development of cardiovascular diseases, which are discussed in a great detail by this Forum.

**FUTURE DIRECTIONS:** More mechanistic and translational studies will rapidly widen the horizon of knowledge on NLRP3 inflammasome activation and regulation, which may help develop novel effective therapeutic strategies to target this inflammasome for treatment or prevention of cardiovascular diseases.

DOI: 10.1089/ars.2015.6319

PMCID: PMC4403011

PMID: 25779752 [Indexed for MEDLINE]

1713. Case Rep Rheumatol. 2015;2015:732095. doi: 10.1155/2015/732095. Epub 2015 Feb 12.

Elevated Troponin Serum Levels in Adult Onset Still's Disease.

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Adult onset Still's disease (AOSD) is a rare inflammatory systemic disease that occasionally may affect myocardium. Diagnosis is based on typical AOSD symptoms after the exclusion of well-known infectious, neoplastic, or autoimmune/autoinflammatory disorders. In the case of abrupt, recent onset AOSD, it could be particularly difficult to make the differential diagnosis and in particular to early detect the possible heart involvement. This latter event is suggested by the clinical history of the four patients described here, incidentally observed at our emergency room. All cases were referred because of

acute illness (high fever, malaise, polyarthralgias, skin rash, and sore throat), successively classified as AOSD, and they presented abnormally high levels of serum troponin without overt symptoms of cardiac involvement. The timely treatment with steroids (3 cases) or ibuprofen (1 case) leads to the remission of clinicoserological manifestations within few weeks. These observations suggest that early myocardial injury might be underestimated or entirely overlooked in patients with AOSD; routine cardiac assessment including troponin evaluation should be mandatory in all patients with suspected AOSD.

DOI: 10.1155/2015/732095

PMCID: PMC4341859

PMID: 25767733

1714. Clin Rheumatol. 2015 Sep;34(9):1503-11. doi: 10.1007/s10067-015-2916-z. Epub 2015 Mar 13.

Non-canonical manifestations of familial Mediterranean fever: a changing paradigm.

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Paroxysmal crises of fever and systemic inflammation herald familial Mediterranean fever (FMF), considered as the archetype of all inherited systemic autoinflammatory diseases. Inflammatory bouts are characterized by short-term and self-limited abdominal, thoracic, and/or articular symptoms which subside spontaneously. Erysipelas-like findings, orchitis, and different patterns of myalgia may appear in a minority of patients. In recent years, many non-classical manifestations have been reported in the clinical context of FMF, such as vasculitides and thrombotic manifestations, neurologic and sensory organ abnormalities, gastrointestinal diseases, and even macrophage activation syndrome. As FMF left unrecognized and untreated is ominously complicated by the occurrence of AA-amyloidosis, it is highly desirable that diagnosis of this autoinflammatory disorder with its multiple clinical faces can be contemplated at whatever age and brought forward.

DOI: 10.1007/s10067-015-2916-z  
PMID: 25761640 [Indexed for MEDLINE]

1715. Ocul Immunol Inflamm. 2016 Aug;24(4):422-30. doi: 10.3109/09273948.2015.1010012.  
Epub 2015 Mar 11.

Clinical Review: Familial Mediterranean Fever-An Overview of Pathogenesis,  
Symptoms, Ocular Manifestations, and Treatment.

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Familial Mediterranean fever is an autoinflammatory multisystem disease, which most commonly affects patients from the Mediterranean basin. This review discusses the common polymorphisms in the MEFV gene as well as the role of pyrin in disease pathogenesis. Patients with familial Mediterranean fever typically develop peritonitis, pleuritis, arthritis, and fever. In addition, a number of authors have reported ophthalmic features. These case reports and series are further explored in this review. Colchicine has transformed the prognosis for patients with familial Mediterranean fever. The rationale for the use of colchicine, as well as the evidence for newer biologic agents is also covered.

DOI: 10.3109/09273948.2015.1010012  
PMID: 25760918 [Indexed for MEDLINE]

1716. Curr Med Chem. 2015;22(16):1986-91.

Biological agents in familial Mediterranean fever focusing on colchicine  
resistance and amyloidosis.

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Familial Mediterranean fever (FMF) is the most common hereditary autoinflammatory syndrome. FMF is caused by mutations in the MEFV gene which encodes the pyrin protein. FMF is characterized by sporadic, paroxysmal attacks of fever and serosal inflammation, lasting 1-3 days. Patients may develop renal amyloidosis. Colchicine prevents attacks and renal amyloidosis. 5% to 10% of the patients with FMF are resistant or intolerant to colchicine. Colchicine resistant patients may receive biological therapies. Anti-interleukin-1 drugs are the most important agents of biological treatments. In this review, colchicine resistance and treatment options will be evaluated.

PMID: 25760087 [Indexed for MEDLINE]

1717. Orphanet J Rare Dis. 2015 Feb 15;10:19. doi: 10.1186/s13023-015-0228-7.

Tolerance and efficacy of off-label anti-interleukin-1 treatments in France: a nationwide survey.

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Comment in

Orphanet J Rare Dis. 2017 May 11;12 (1):87.

**BACKGROUND:** Despite their limited licensed indications, anti-interleukin-1 (anti-IL-1) agents are often used in clinical practice for an increasing number of auto-inflammatory diseases. We conducted a national cross-sectional observational study from January 2011 to January 2013 to record the off-label use of such agents in France. We aimed to estimate the off-label use of anti-IL-1 treatments in France, assess their efficacy in rare diseases, and increase the reporting of their possible side effects.

**METHODS:** Physicians answered a questionnaire that covered patient and disease data, anti-IL-1 agent use, efficacy and adverse events. The study involved adult or paediatric patient who had received an anti-IL-1 agent after January 2005 in France.

**RESULTS:** In total, 189 patients from 38 centres were included. The main diseases were adult-onset Still's disease (AOSD) (35), gout (28), systemic juvenile idiopathic arthritis (27), cryopyrin-associated periodic syndrome (CAPS) (21), familial Mediterranean fever (14) and mevalonate kinase deficiency (12). The main off-label used agent was anakinra, used at least once for 185 patients, with canakinumab used for 25. Anakinra was effective in most patients (90%), with higher complete clinical response rates for Schnitzler's syndrome, gout, CAPS and AOSD. Overall, 58% of patients showed at least one adverse event, mainly minor injection-site reactions. The main reported serious adverse event was severe infection. Injection-site reactions and liver toxicity were significantly more

frequent in children than adults. The main non-cutaneous adverse event was liver toxicity, significantly associated with treatment duration. Weight gain was reported in about 10% of patients and was associated with treatment duration and CAPS. Canakinumab was rarely used and showed better cutaneous tolerance than anakinra but similar rates of non-cutaneous and severe adverse events.

CONCLUSIONS: Anakinra was well tolerated and effective in most patients with various inflammatory diseases. The main adverse events were mild injection-site reactions, especially in children. The survey allowed for collecting limited information on the off-label use of canakinumab.

DOI: 10.1186/s13023-015-0228-7

PMCID: PMC4340831

PMID: 25758134 [Indexed for MEDLINE]

1718. Clin Rheumatol. 2016 Jan;35(1):247-50. doi: 10.1007/s10067-015-2906-1. Epub 2015 Mar 8.

Development of de novo major involvement during follow-up in Behçet's syndrome.

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The primary aim of the study was to evaluate the incidence of de novo major involvement during follow-up in a cohort of patients with Behçet's syndrome (BS); the secondary aim was to analyse the epidemiological profile and the long-term outcome of those patients who developed new major involvement. Among our cohort of 120 BS patients, we evaluated all subjects who had no major organ involvement during the early years of their disease; specifically, at disease onset, the 52% of the cohort presented a prevalent mucocutaneous involvement. The primary



outcomes were represented by the following: Hatemi et al. (Rheum Dis Clin North Am 39(2):245-61, 2013) the incidence of de novo major involvement during the follow-up and Hatemi et al. (Clin Exp Rheumatol 32(4 Suppl 84):S112-22, 2014) the use of immunosuppressive drugs during the follow-up. We have defined the development of de novo major involvement during the follow-up as the occurrence of severe ocular, vascular or CNS involvement after a latency period from the diagnosis of at least 3 years. Among 62 patients characterized by a mild onset of disease, we observed that after at least 3 years from the diagnosis, 21 BS patients (34%) still developed serious morbidities. Specifically, three patients developed ocular involvement, nine patients developed neurological involvement and nine patients presented vascular involvement. Comparing main epidemiological and clinical findings of the two groups, we observed that patients who developed de novo major involvement were more frequently males and younger; furthermore, 95% of these patients were characterized by a young onset of disease ( $p < 0.001$ ). Being free of major organ complication in the first years of BS is not necessary a sign of a favourable outcome. Globally, the development of de novo major involvement during the course of BS suggests that a tight control is strongly recommended during the course of the disease.

DOI: 10.1007/s10067-015-2906-1

PMID: 25750177 [Indexed for MEDLINE]

1719. Scand J Rheumatol. 2015 May;44(3):255-6. doi: 10.3109/03009742.2015.1005663. Epub 2015 Mar 6.

Autosomal recessive transmission of TRAPS in a family with a novel TNFRSF1A mutation.

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DOI: 10.3109/03009742.2015.1005663

PMID: 25744939 [Indexed for MEDLINE]

1720. Tohoku J Exp Med. 2015 Jan;235(1):25-8. doi: 10.1620/tjem.235.25.

Resolution of polyserositis after removal of appendix mucinous cystadenoma.

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Mucinous cystadenoma is a rare benign neoplasm and is usually discovered incidentally. Pleuritis and pericarditis, inflammation of the pleura and pericardium, may represent manifestations of autoimmune disorders especially in female subjects. We report a patient with polyserositis that was resolved after removal of the mucinous cystadenoma. To the best of our knowledge, this is a first report describing pleuritis and pericarditis as an initial presentation of mucinous cystadenoma of an appendix. A forty-year-old Caucasian female patient with a history of pleuritis and recurrent pericarditis was admitted to the hospital due to acute abdomen. At that time she was taking indomethacin and colchicine due to pericarditis that was controlled only with the combination of these two drugs. The patient had elevated erythrocyte sedimentation rate (ESR), increased C-reactive protein (CRP) and normocytic anemia. Immunological tests, including antinuclear antibody, anti-neutrophil cytoplasmic antibody, rheumatoid factor, and anti-cyclic citrullinated peptide antibodies, were repeatedly negative. Emergency surgery revealed acute appendicitis with perforation and subsequent diffuse peritonitis. Histopathological examination showed acute appendicitis and mucinous cystadenoma. Following the surgery the patient did not take any drugs. Fourteen months later the patient was symptom free. Pleuritis and pericarditis in female patients are most often associated with autoimmune diseases. We assume that increased ESR and CRP with anemia detected in the patient may reflect the altered immunity that is due to mucinous cystadenoma. We believe that this report has a broader clinical impact, implying that benign tumor could alter immunity, which can lead to unusual presentation such as polyserositis.

DOI: 10.1620/tjem.235.25

PMID: 25744068 [Indexed for MEDLINE]

1721. Isr Med Assoc J. 2015 Jan;17(1):47-9.

The autoinflammatory side of systemic sclerosis.

De Santis M, Selmi C.

PMID: 25739177 [Indexed for MEDLINE]

1722. Proc Natl Acad Sci U S A. 2015 Mar 3;112(9):2835-40. doi: 10.1073/pnas.1424741112. Epub 2015 Feb 17.

Cell stress increases ATP release in NLRP3 inflammasome-mediated autoinflammatory diseases, resulting in cytokine imbalance.

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Cell stress is implicated in triggering bouts of systemic inflammation in patients with autoinflammatory disorders. Blood monocytes from patients affected by NLRP3-mediated cryopyrin-associated periodic syndromes (CAPS) release greater amounts of IL-1 $\beta$  than monocytes from unaffected subjects. Here we show that stress lowers the threshold of activation; blood monocytes from CAPS patients maintain the high levels of secreted IL-1 $\beta$  (fivefold) and IL-18 (10-fold) when stimulated with 1,000-fold less LPS than that required for full IL-1 $\beta$  secretion in control subjects. Unexpectedly, IL-1 $\alpha$  secretion is increased 10-fold,

indicating that inflammatory episodes in CAPS may not be entirely a result of IL-1 $\beta$  but may also involve IL-1 $\alpha$ . In CAPS monocytes, LPS induces the externalization of copious amounts of ATP (10-fold), which drive IL-1 $\beta$ , IL-18, and IL-1 $\alpha$  release via activation of the P2X purinoceptor 7. This enhanced ATP release appears to be the link between cell stress and increased cytokine secretion in CAPS. In the later phase after LPS stimulation, CAPS monocytes undergo oxidative stress, which impairs production of the anti-inflammatory IL-1 receptor antagonist (IL-1Ra). Remarkably, IL-1Ra secretion is fully restored by treatment with antioxidants. In two patients with the same NLRP3 mutation, but different disease severity, monocytes from the mildly affected patient exhibited more efficient redox response, lower ATP secretion, and more balanced cytokine production. Thus, the robustness of the individual antioxidant response increases the tolerance to stress and reduces the negative effect of the disease. Pharmacologic block of P2X purinoceptor 7 and improved stress tolerance may represent novel treatment strategies in stress-associated inflammatory diseases.

DOI: 10.1073/pnas.1424741112

PMCID: PMC4352822

PMID: 25730877 [Indexed for MEDLINE]

1723. Arch Argent Pediatr. 2015 Apr;113(2):133-9. doi: 10.5546/aap.2015.133.

High frequency of E148Q sequence variation in children with familial Mediterranean fever in southeast Turkey.

[Article in English, Spanish]

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OBJECTIVE: The aim of this study was to investigate the spectrum of Mediterranean

fever (MEFV) gene mutations and genotype-phenotype correlation in children with familial Mediterranean fever (FMF) in southeast Turkey.

**METHODS:** A total of 507 children (274 females) with FMF and MEFV gene mutation(s) were included. A 15-year retrospective evaluation was conducted; parameters analyzed were: age, sex, age at symptoms onset, age at FMF diagnosis, delay between symptoms onset and diagnosis, FMF attack symptoms, and response to colchicine. Disease severity scores were calculated and MEFV mutation analysis was performed via real-time PCR for the 6 most frequent mutations. Children with comorbid diseases or tested negative for MEFV gene mutations were excluded to provide homogeneity.

**RESULTS:** A family history of FMF was found in 60.2% (n=305) of patients. The most common symptoms reported for FMF attacks were abdominal pain (98.0%), fever (93.9%) and arthralgia (47.3%); 75.0% of patients (n=380) were heterozygous, 14.2% were homozygous (n=72) and 10.8% were compound heterozygous (n=55). The following MEFV gene mutation alleles were identified: E148Q (40.1%), M694V (25.9%), V726A (15.8%), R761H (7.4%), M680I (6.8%), and P369S (4.1%). The M694V subgroup had the lowest mean age of disease onset and the highest mean disease severity score, whereas the E148Q group had later mean disease onset and the lowest mean disease severity score (p<0.05).

**CONCLUSION:** The highest E148Q mutation frequency and milder disease in the course of FMF in our study population may be due to geographic and ethnic background dissimilarities of southeast Turkey.

DOI: 10.5546/aap.2015.133

PMID: 25727825 [Indexed for MEDLINE]

1724. *Pediatr Dermatol*. 2015 Jul-Aug;32(4):437-46. doi: 10.1111/pde.12502. Epub 2015 Feb 26.

A Review and Proposed Approach to the Neutrophilic Dermatoses of Childhood.

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Neutrophilic dermatoses (NDs) are inflammatory skin conditions that are not associated with infection. The classification and clinical approach to these conditions in children is poorly described. This review classifies these conditions into five nosological subtypes: Sweet's syndrome, pyoderma gangrenosum, aseptic pustules, neutrophilic urticarial dermatoses, and Marshall's syndrome. In addition, we review the various secondary diseases that need to be excluded in the clinical management of the NDs of childhood, with a focus on the autoinflammatory conditions that the reader may not be familiar with. We propose a practical clinical approach to these disorders.

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DOI: 10.1111/pde.12502

PMID: 25727235 [Indexed for MEDLINE]

1725. Eur J Rheumatol. 2015 Mar;2(1):35-36. Epub 2015 Mar 1.

Successful treatment of tumor necrosis factor receptor-associated periodic syndrome (TRAPS) with tocilizumab: A case report.

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Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is an autosomal dominant autoinflammatory disease linked to chromosome 12p13 and, more specifically, with mutations within the tumor necrosis factor receptor superfamily, member 1A gene (TNFRSF1A gene). It is characterized by the presence of fever, abdominal pain, myalgia, arthralgia or arthritis, and skin rash. In

this report, we describe the case of a patient with tumor necrosis factor receptor-associated periodic syndrome (TRAPS) treated successfully with the anti-interleukin-6 (anti-IL-6) receptor monoclonal antibody tocilizumab, while treatment with anti-TNF  $\alpha$  etanercept and infliximab had both failed.

DOI: 10.5152/eurjrheumatol.2014.14053

PMCID: PMC5047242

PMID: 27708919

1726. Eur J Rheumatol. 2015 Mar;2(1):20-23. Epub 2015 Mar 1.

Neutrophil-lymphocyte ratio in children with familial Mediterranean fever:  
Original article.

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**OBJECTIVE:** The aim of present study was (a) to evaluate the relationship between the neutrophil/lymphocyte (N/L) ratio and mutation types of familial Mediterranean fever (FMF) in children and (b) to evaluate the relationship between the N/L ratio and age.

**MATERIAL AND METHODS:** Three hundred forty-three children with familial Mediterranean fever in the attack-free period and 283 healthy control children were included in the study. Patients were divided into subgroups according to mutation types. Neutrophil and lymphocyte counts were retrieved from medical records of patients and the N/L ratio was calculated from these parameters.

**RESULTS:** The N/L ratio of patients was found to be significantly higher than that of controls ( $p<0.001$ ). Among 343 patients, homozygous, heterozygous, and compound mutations were observed in 39, 253, and 51 patients, respectively. The differences in the N/L ratio among patients with homozygous, heterozygous, and

compound mutations were not statistically significant. The most common mutations were M694V (n=126), E148Q (n=70), M680I, (n=33), and V726A (n=28). Significant differences were not observed among these mutations in terms of the N/L ratio ( $p>0.05$ ). In all subjects, there was a weak but significant relationship between age and the N/L ratio ( $r: 0.215$ ,  $p<0.001$ ).

**CONCLUSION:** The N/L ratio, which can be determined by simple methods in routine blood tests, may be used for the follow-up monitoring of chronic inflammation in patients. In addition, the N/L ratio may give an idea to clinicians regarding the early initiation of treatment in patients with typical clinical findings of FMF.

DOI: 10.5152/eurjrheumatol.2015.0093

PMCID: PMC5047238

PMID: 27708915

1727. Eur J Pediatr. 2015 Jun;174(6):707-14. doi: 10.1007/s00431-015-2505-9. Epub 2015 Feb 27.

Treatment of hyperimmunoglobulinemia D syndrome with biologics in children: review of the literature and Finnish experience.

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Hyperimmunoglobulinemia D syndrome (HIDS) is an autoinflammatory disorder that is caused by mevalonate kinase deficiency (MKD). Recent advances in the pathogenesis of MKD, including the proposed mechanisms of inflammasome activation, provide the basis for the development of new treatment modalities. So far, feedback on the treatment of HIDS with biological medicines has come from case reports with limited numbers of patients. In this review, we summarize the data that is currently available on the treatment of HIDS in children, with the emphasis on new therapies, and present three Finnish pediatric cases treated with anakinra. Case reports have been published on 33 pediatric HIDS patients who have been treated with biological medicines, and in some cases, they were treated with more than one drug. Of these patients, 21 were treated with anakinra and 16 with etanercept, resulting in complete or partial responses in 90 and 50% of cases,



respectively. A further five patients were treated with canakinumab, with complete or partial responses. **CONCLUSION:** The accumulating evidence on the efficacy and safety of biological drugs in pediatric HIDS suggests that the anti-interleukin-1 agent anakinra is the drug of choice for HIDS in children.

**WHAT IS KNOWN:** • Various biologic drugs have been tried for the treatment of HIDS. **What is New:** • Based on the 90% response rate, anakinra seems to be the drug of choice for HIDS in children.

DOI: 10.1007/s00431-015-2505-9

PMID: 25721923 [Indexed for MEDLINE]

1728. J Clin Immunol. 2015 Apr;35(3):249-53. doi: 10.1007/s10875-015-0140-x. Epub 2015 Feb 24.

Overlap of familial Mediterranean fever and hyper-IgD syndrome in an Arabic kindred.

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Hyperimmunoglobulinemia D Syndrome (HIDS) has rarely been reported in Arabs. Moreover, the simultaneous presence of mutations in MEFV and MVK segregating in the same family is exceptional. We report an Arabic girl presenting since the age of 8-years with two patterns of recurrent episodes of fever, and associated with a spectrum of clinical features suggestive of overlap between familial Mediterranean fever (FMF) and HIDS. Her 19-year old brother presented since the age of 1 year with prolonged episodes of fever and was diagnosed with HIDS at the age of 7 years based on clinical features and homozygosity for p.V377I mutation in MVK. Shorter episodes of fever and abdominal pain more consistent with FMF ensued since the age of 17 years. Genetic testing done for both patients and all other family members revealed simultaneous presence of mutations in MEFV and MVK but with a variable clinical spectrum ranging from asymptomatic to severe manifestations. Both of our patients are homozygous for p.V377I MVK mutation; the girl is a compound heterozygote for p.E148Q/p.P369S/p.R408G and p.E167D/p.F479L MEFV mutations whereas the brother is a compound heterozygote for

p.E148Q/p.P369S/p.R408G and p.M680I MEFV mutations. The clinical implications of having more than one mutation in different genes of monogenic autoinflammatory diseases in the same individual are not clear but may explain atypical clinical manifestations such as the overlap features of both FMF and HIDS in this family.

DOI: 10.1007/s10875-015-0140-x

PMID: 25708585 [Indexed for MEDLINE]

1729. Annu Rev Immunol. 2015;33:823-74. doi: 10.1146/annurev-immunol-032414-112227. Epub 2015 Feb 20.

Molecular mechanisms in genetically defined autoinflammatory diseases: disorders of amplified danger signaling.

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Patients with autoinflammatory diseases present with noninfectious fever flares and systemic and/or disease-specific organ inflammation. Their excessive proinflammatory cytokine and chemokine responses can be life threatening and lead to organ damage over time. Studying such patients has revealed genetic defects that have helped unravel key innate immune pathways, including excessive IL-1 signaling, constitutive NF- $\kappa$ B activation, and, more recently, chronic type I IFN signaling. Discoveries of monogenic defects that lead to activation of proinflammatory cytokines have inspired the use of anticytokine-directed treatment approaches that have been life changing for many patients and have led to the approval of IL-1-blocking agents for a number of autoinflammatory conditions. In this review, we describe the genetically characterized autoinflammatory diseases, we summarize our understanding of the molecular pathways that drive clinical phenotypes and that continue to inspire the search for novel treatment targets, and we provide a conceptual framework for classification.

DOI: 10.1146/annurev-immunol-032414-112227

PMCID: PMC4563985

PMID: 25706096 [Indexed for MEDLINE]

1730. J Clin Invest. 2015 Apr;125(4):1396-400. doi: 10.1172/JCI71081. Epub 2015 Feb 23.

Cherubism allele heterozygosity amplifies microbe-induced inflammatory responses in murine macrophages.

Prod'Homme V, Boyer L, Dubois N, Mallavialle A, Munro P, Mouska X, Coste I, Rottapel R, Tartare-Deckert S, Deckert M.

Cherubism is a rare autoinflammatory bone disorder that is associated with point mutations in the SH3-domain binding protein 2 (SH3BP2) gene, which encodes the adapter protein 3BP2. Individuals with cherubism present with symmetrical fibro-osseous lesions of the jaw, which are attributed to exacerbated osteoclast activation and defective osteoblast differentiation. Although it is a dominant trait in humans, cherubism appears to be recessively transmitted in mice, suggesting the existence of additional factors in the pathogenesis of cherubism. Here, we report that macrophages from 3BP2-deficient mice exhibited dramatically reduced inflammatory responses to microbial challenge and reduced phagocytosis. 3BP2 was necessary for LPS-induced activation of signaling pathways involved in macrophage function, including SRC, VAV1, p38MAPK, IKK $\alpha/\beta$ , RAC, and actin polymerization pathways. Conversely, we demonstrated that the presence of a single Sh3bp2 cherubic allele and pathogen-associated molecular pattern (PAMP) stimulation had a strong cooperative effect on macrophage activation and inflammatory responses in mice. Together, the results from our study in murine genetic models support the notion that infection may represent a driver event in the etiology of cherubism in humans and suggest limiting inflammation in affected individuals may reduce manifestation of cherubic lesions.

DOI: 10.1172/JCI71081

PMCID: PMC4396483

PMID: 25705883 [Indexed for MEDLINE]

1731. Pediatr Rheumatol Online J. 2014 Nov 25;12:49. doi: 10.1186/1546-0096-12-49. eCollection 2014.

## Health related quality of life measure in systemic pediatric rheumatic diseases and its translation to different languages: an international collaboration.

Moorthy LN(1), Roy E(2), Kurra V(2), Peterson MG(3), Hassett AL(4), Lehman TJ(3), Scott C(5), El-Ghoneimy D(6), Saad S(7), El Feky R(7), Al-Mayouf S(8), Dolezalova P(9), Malcova H(10), Herlin T(11), Nielsen S(12), Wulffraat N(13), van Royen A(14), Marks SD(15), Belot A(16), Brunner J(17), Huemer C(18), Foeldvari I(19), Horneff G(20), Saurenman T(21), Schroeder S(21), Pratsidou-Gertsi P(22), Trachana M(22), Uziel Y(23), Aggarwal A(24), Constantin T(25), Cimaz R(26), Giani T(26), Cantarini L(27), Falcini F(28), Manzoni SM(29), Ravelli A(30), Rigante D(31), Zulian F(32), Miyamae T(33), Yokota S(33), Sato J(34), Magalhaes CS(34), Len CA(35), Appenzeller S(36), Knupp SO(37), Rodrigues MC(38), Sztajn bok F(39), de Almeida RG(39), de Jesus AA(40), de Arruda Campos LM(40), Silva C(41), Lazar C(42), Susic G(43), Avcin T(44), Cuttica R(45), Burgos-Vargas R(46), Faugier E(47), Anton J(48), Modesto C(49), Vazquez L(50), Barillas L(51), Barinstein L(52), Sterba G(53), Maldonado I(54), Ozen S(55), Kasapcopur O(56), Demirkaya E(57), Benseler S(58).

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BACKGROUND: Rheumatic diseases in children are associated with significant morbidity and poor health-related quality of life (HRQOL). There is no health-related quality of life (HRQOL) scale available specifically for children with less common rheumatic diseases. These diseases share several features with systemic lupus erythematosus (SLE) such as their chronic episodic nature, multi-systemic involvement, and the need for immunosuppressive medications. HRQOL

scale developed for pediatric SLE will likely be applicable to children with systemic inflammatory diseases.

**FINDINGS:** We adapted Simple Measure of Impact of Lupus Erythematosus in Youngsters (SMILEY©) to Simple Measure of Impact of Illness in Youngsters (SMILY©-Illness) and had it reviewed by pediatric rheumatologists for its appropriateness and cultural suitability. We tested SMILY©-Illness in patients with inflammatory rheumatic diseases and then translated it into 28 languages. Nineteen children (79% female, n=15) and 17 parents participated. The mean age was 12±4 years, with median disease duration of 21 months (1-172 months). We translated SMILY©-Illness into the following 28 languages: Danish, Dutch, French (France), English (UK), German (Germany), German (Austria), German (Switzerland), Hebrew, Italian, Portuguese (Brazil), Slovene, Spanish (USA and Puerto Rico), Spanish (Spain), Spanish (Argentina), Spanish (Mexico), Spanish (Venezuela), Turkish, Afrikaans, Arabic (Saudi Arabia), Arabic (Egypt), Czech, Greek, Hindi, Hungarian, Japanese, Romanian, Serbian and Xhosa.

**CONCLUSION:** SMILY©-Illness is a brief, easy to administer and score HRQOL scale for children with systemic rheumatic diseases. It is suitable for use across different age groups and literacy levels. SMILY©-Illness with its available translations may be used as useful adjuncts to clinical practice and research.

DOI: 10.1186/1546-0096-12-49

PMCID: PMC4334772

PMID: 25705138 [Indexed for MEDLINE]

1732. Gene. 2015 May 10;562(1):128-31. doi: 10.1016/j.gene.2015.02.059. Epub 2015 Feb 20.

The spectrum of MEFV gene mutations and genotypes in Van province, the eastern region of Turkey, and report of a novel mutation (R361T).

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Familial Mediterranean fever (FMF) is the most common hereditary inflammatory periodic disease, characterized by recurrent episodes of fever and abdominal pain, synovitis, and pleuritis. The aim of this study was to determine the frequency and distribution of Mediterranean fever (MEFV) gene mutations in Van province of Eastern Anatolia and to compare them with the other studies from various regions of Turkey. Therefore, we retrospectively evaluated MEFV gene mutations in 1058 pediatric patients with suspected FMF. The MEFV gene mutations were investigated using Sanger sequencing and the multiplex minisequencing technique. We identified 37 different genotypes and 16 different mutations. The four most common mutations and allelic frequencies were M694V (36.50%), E148Q (32.77%), V726A (14.09%), and M694I (4.41%). M694V was the most common mutation, and the M694I frequency was found to be higher compared to studies from other regions of Turkey. In addition, we identified a novel missense mutation (R361T, c.1082G>C) in exon 3 of the MEFV gene in a 12-year-old boy, who had a typical FMF phenotype. In conclusion, this study evaluated the distribution of MEFV gene mutations in children with FMF as the first study conducted in Van province, Eastern Anatolia.

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DOI: 10.1016/j.gene.2015.02.059

PMID: 25703702 [Indexed for MEDLINE]

1733. Curr Med Chem. 2015;22(16):1890-1.

Editorial: Switching to biological agents in autoimmune and autoinflammatory disorders: current targets and therapy.

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PMID: 25693591 [Indexed for MEDLINE]

1734. Case Rep Rheumatol. 2015;2015:463959. doi: 10.1155/2015/463959. Epub 2015 Jan 27.

A new mutation in blau syndrome.

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Blau syndrome is a rare, autosomal dominant, granulomatous autoinflammatory disease. The classic triad of the disease includes recurrent uveitis, granulomatous dermatitis, and symmetrical arthritis. Blau syndrome is related to mutations located at the 16q12.2-13 gene locus. To date, 11 NOD2 gene mutations causing Blau syndrome have been described. Here, we describe a 5-year-old male patient who presented with Blau syndrome associated with a novel sporadic gene mutation that has not been reported previously.

DOI: 10.1155/2015/463959

PMCID: PMC4322824

PMID: 25692065

1735. Case Rep Rheumatol. 2015;2015:182731. doi: 10.1155/2015/182731. Epub 2015 Jan 27.

Nonbacterial osteitis of the clavicle: longitudinal imaging series from initial diagnosis to clinical improvement.

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Nonbacterial osteitis is a rare autoinflammatory disease. Often it is mistaken for a tumor or osteomyelitis. We present a case of a twelve-year-old girl referred to our hospital because of a lesion of the right clavicle. The differential diagnoses were sarcoma, osteitis, and Langerhans cell histiocytosis. After biopsy the diagnosis nonbacterial osteitis (NBO) was established. Treatment of choice is a nonsteroidal anti-inflammatory drug. This case report gives a complete follow-up of the disease, showing the pitfalls of the diagnosis.

DOI: 10.1155/2015/182731

PMCID: PMC4322822

PMID: 25692064

1736. J Eur Acad Dermatol Venereol. 2016 Feb;30(2):302-5. doi: 10.1111/jdv.13034. Epub 2015 Feb 16.

A novel mutation in IL36RN underpins childhood pustular dermatosis.

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**BACKGROUND:** Chronic pustular dermatoses are severe and debilitating autoinflammatory conditions that can have a monogenic basis. Their clinical features are, however, complex with considerable overlap. Null and missense mutations in the genes encoding interleukin (IL)-1 family (IL-1 and IL-36) anti-inflammatory receptor antagonist (Ra) cytokines can underlie the development of severe pustular dermatoses.

**OBJECTIVE:** We present a clinical and genetic study of four children of Pakistani descent with similar clinical presentations and treatment course, each of whom suffers from a severe pustular dermatosis, initially described as a pustular variant of psoriasis. We use DNA sequencing to refine the diagnosis of two of the children studied.

**METHODS:** Bidirectional Sanger sequencing was performed on the coding regions of the IL-1Ra and IL-36Ra genes (IL1RN and IL36RN, respectively), for the four affected children and their parents.

**RESULTS:** We identified a novel homozygous missense mutation in IL36RN in two siblings, and showed the molecular basis of the condition to be both distinct from psoriasis and distinct between the two families studied.

**CONCLUSIONS:** We describe a novel mutation which underpins the diagnosis of childhood pustular dermatosis. Molecular diagnostics can be used to aid the clinical diagnosis and potential treatment of autoinflammatory conditions.

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DOI: 10.1111/jdv.13034

PMCID: PMC4973684

PMID: 25688670 [Indexed for MEDLINE]

1737. Nat Rev Rheumatol. 2015 Mar;11(3):125. doi: 10.1038/nrrheum.2015.15. Epub 2015 Feb 17.

Inflammation: New classification criteria for autoinflammatory periodic fevers.

Bernard NJ.

Comment on

Ann Rheum Dis. 2015 May;74(5):799-805.

DOI: 10.1038/nrrheum.2015.15

PMID: 25687178 [Indexed for MEDLINE]

1738. Nat Med. 2015 Mar;21(3):263-9. doi: 10.1038/nm.3804. Epub 2015 Feb 16.

The ketone metabolite  $\beta$ -hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease.

Youm YH(1), Nguyen KY(1), Grant RW(2), Goldberg EL(1), Bodogai M(3), Kim D(4), D'Agostino D(5), Planavsky N(6), Lupfer C(7), Kanneganti TD(7), Kang S(8), Horvath TL(1), Fahmy TM(4), Crawford PA(9), Biragyn A(3), Alnemri E(8), Dixit VD(10).

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Comment in

Trends Immunol. 2015 Jun;36(6):323-4.

Nat Rev Immunol. 2015 Apr;15(4):199.

Cell Metab. 2015 Apr 7;21(4):513-4.

The ketone bodies  $\beta$ -hydroxybutyrate (BHB) and acetoacetate (AcAc) support mammalian survival during states of energy deficit by serving as alternative sources of ATP. BHB levels are elevated by starvation, caloric restriction, high-intensity exercise, or the low-carbohydrate ketogenic diet. Prolonged fasting reduces inflammation; however, the impact that ketones and other alternative metabolic fuels produced during energy deficits have on the innate immune response is unknown. We report that BHB, but neither AcAc nor the structurally related short-chain fatty acids butyrate and acetate, suppresses activation of the NLRP3 inflammasome in response to urate crystals, ATP and lipotoxic fatty acids. BHB did not inhibit caspase-1 activation in response to pathogens that activate the NLR family, CARD domain containing 4 (NLRC4) or absent in melanoma 2 (AIM2) inflammasome and did not affect non-canonical caspase-11, inflammasome activation. Mechanistically, BHB inhibits the NLRP3 inflammasome by preventing K<sup>+</sup> efflux and reducing ASC oligomerization and speck formation. The inhibitory effects of BHB on NLRP3 are not dependent on chirality or starvation-regulated mechanisms like AMP-activated protein kinase (AMPK), reactive oxygen species (ROS), autophagy or glycolytic inhibition. BHB blocks the NLRP3 inflammasome without undergoing oxidation in the TCA cycle, and independently of uncoupling protein-2 (UCP2), sirtuin-2 (SIRT2), the G protein-coupled receptor GPR109A or hydrocaboxylic acid receptor 2 (HCAR2). BHB reduces NLRP3 inflammasome-mediated interleukin (IL)-1 $\beta$  and IL-18 production in human monocytes. In vivo, BHB or a ketogenic diet attenuates caspase-1 activation and IL-1 $\beta$  secretion in mouse models of NLRP3-mediated diseases such as Muckle-Wells syndrome, familial cold autoinflammatory syndrome and urate crystal-induced peritonitis. Our findings suggest that the anti-inflammatory effects of caloric restriction or ketogenic diets may be linked to BHB-mediated inhibition of the NLRP3 inflammasome.

DOI: 10.1038/nm.3804

PMCID: PMC4352123

PMID: 25686106 [Indexed for MEDLINE]

A small-molecule inhibitor of the NLRP3 inflammasome for the treatment of inflammatory diseases.

Coll RC(1), Robertson AA(2), Chae JJ(3), Higgins SC(4), Muñoz-Planillo R(5), Inserra MC(6), Vetter I(6), Dungan LS(4), Monks BG(7), Stutz A(7), Croker DE(2), Butler MS(2), Haneklaus M(4), Sutton CE(4), Núñez G(5), Latz E(8), Kastner DL(3), Mills KH(4), Masters SL(9), Schroder K(2), Cooper MA(2), O'Neill LA(4).

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Comment in

Nat Rev Immunol. 2015 Apr;15(4):199.

Cell Metab. 2015 Apr 7;21(4):513-4.

Trends Immunol. 2015 Jun;36(6):323-4.

Nat Rev Rheumatol. 2015 Apr;11(4):198.

The NOD-like receptor (NLR) family, pyrin domain-containing protein 3 (NLRP3) inflammasome is a component of the inflammatory process, and its aberrant

activation is pathogenic in inherited disorders such as cryopyrin-associated periodic syndrome (CAPS) and complex diseases such as multiple sclerosis, type 2 diabetes, Alzheimer's disease and atherosclerosis. We describe the development of MCC950, a potent, selective, small-molecule inhibitor of NLRP3. MCC950 blocked canonical and noncanonical NLRP3 activation at nanomolar concentrations. MCC950 specifically inhibited activation of NLRP3 but not the AIM2, NLRC4 or NLRP1 inflammasomes. MCC950 reduced interleukin-1 $\beta$  (IL-1 $\beta$ ) production in vivo and attenuated the severity of experimental autoimmune encephalomyelitis (EAE), a disease model of multiple sclerosis. Furthermore, MCC950 treatment rescued neonatal lethality in a mouse model of CAPS and was active in ex vivo samples from individuals with Muckle-Wells syndrome. MCC950 is thus a potential therapeutic for NLRP3-associated syndromes, including autoinflammatory and autoimmune diseases, and a tool for further study of the NLRP3 inflammasome in human health and disease.

DOI: 10.1038/nm.3806

PMCID: PMC4392179

PMID: 25686105 [Indexed for MEDLINE]

1740. Springerplus. 2014 Dec 22;3:759. doi: 10.1186/2193-1801-3-759. eCollection 2014.

Simple clinical indicators for early psoriatic arthritis detection.

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**BACKGROUND:** Diagnosis of psoriatic arthritis (PsA), in a period of 12 months from the onset of the first articular episode, permits of identifying the early form defined as "early PsA". The recognition of the disease in this phase leads to better outcome. The aim of this study was to identify peculiar clinical and/or laboratory findings that could be useful for the diagnosis of "early PsA".

**FINDINGS:** Thirty-five patients with early onset of arthritis were observed. The following data were collected for each patient: family and personal history, physical examination, tender and swollen joint counts (TJC, SJC), tender enthesal count, presence of dactylitis and low back pain (LBP), and laboratory tests. Among the 35 total patients, 24 showed skin and/or nail psoriasis or a family history of psoriasis. The remaining 11 patients showed absence of concomitant or previous psoriasis and/or familiarity for psoriasis. The comparison between the two groups showed that patients with psoriasis had a significant presence of LBP, dactylitis and enthesitis than patients with psoriasis.

**CONCLUSIONS:** The study confirms that the distinctive clinical findings of PsA is psoriasis, but also LBP, dactylitis and enthesitis have a relevant role in early identification. A low number of SJC and TJC are frequently observed in early phases of PsA than in other forms of early arthritis. These aspects could be mostly helpful when psoriasis is not detected or can follow arthritis in absence of familiar positivity, making difficult PsA diagnosis. In conclusion, careful medical history, clinical examination and first-level laboratory investigations are useful to characterize early phases of PsA.

DOI: 10.1186/2193-1801-3-759

PMCID: PMC4320171

PMID: 25674484

1741. Rheumatol Int. 2015 Aug;35(8):1393-8. doi: 10.1007/s00296-015-3227-z. Epub 2015 Feb 11.

Risk factors for subclinical inflammation in children with Familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is the most common autosomal recessive inherited inflammatory disease characterized by attacks of painful inflammation. Some patients with FMF have subclinical inflammation persisting between the attacks. We aimed to identify the demographic, clinical and genetic risk factors for subclinical inflammation in children with FMF. The medical records of the children with FMF were evaluated retrospectively for acute-phase response along with gender, age at the onset of symptoms and at the time of diagnosis, clinical signs and symptoms, the presence of amyloidosis and MEFV genotype. Patients with persistently elevated acute-phase response between the attacks were considered to have subclinical inflammation. Patients with or without subclinical inflammation (Group 1 and Group 2, respectively) were compared for the parameters defined above. Independent risk factors for subclinical inflammation were identified by multivariate logistic regression analysis. There were 105 children (male/female: 52/53) who were compliant on colchicine treatment. Subclinical inflammation was detected in 22 (20 %) patients. Group 1 had significantly higher rate of myalgia, arthritis/arthralgia, erysipelas like erythema, amyloidosis, protracted febrile myalgia and M694V mutation compared with Group 2. However, only the presence of myalgia and erysipelas like erythema were found to be independent risk factors for subclinical inflammation (OR 9.8 and 5.9, respectively). Children with FMF who have myalgia and erysipelas like erythema during the attacks are particularly at risk of ongoing inflammation and should be closely monitored for subclinical inflammation even during attack-free periods.

DOI: 10.1007/s00296-015-3227-z

PMID: 25669438 [Indexed for MEDLINE]

1742. Rheumatology (Oxford). 2015 Aug;54(8):1369-79. doi: 10.1093/rheumatology/keu456. Epub 2015 Feb 9.

Reliability, validity and responsiveness to change of the Saint George's Respiratory Questionnaire in early diffuse cutaneous systemic sclerosis.

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**OBJECTIVE:** Dyspnoea is a common, multifactorial source of functional impairment among patients with dcSSc. Our objective was to assess the reliability, construct validity and responsiveness to change of the Saint George's Respiratory Questionnaire (SGRQ) in patients with early dcSSc participating in a multicentre prospective study.

**METHODS:** At enrolment and 1 year, patients completed the SGRQ (a multi-item instrument with four scales: symptoms, activity, impact and total), a visual analogue scale (VAS) for breathing and the HAQ Disability Index (HAQ-DI) and underwent 6 min walk distance and pulmonary function tests, physician and patient global health assessments and high-resolution CT (HRCT). We assessed internal consistency reliability using Cronbach's  $\alpha$ . For validity we examined the ability of the SGRQ to differentiate the presence vs absence of interstitial lung disease (ILD) on HRCT or restrictive lung disease and evaluated the 1 year responsiveness to change using pulmonary function tests and patient- and physician-reported anchors. Correlation coefficients of 0.24-0.36 were considered moderate and  $>0.37$  was considered large.

**RESULTS:** A total of 177 patients were evaluated. Reliability was satisfactory for all SGRQ scales (0.70-0.93). All scales showed large correlations with the VAS for breathing and diffusing capacity of the lung for carbon monoxide in the overall cohort and in the subgroup with ILD. Three of the four scales in the overall cohort and the total scale in the ILD subgroup showed moderate to large correlation with the HAQ-DI and the predicted forced vital capacity ( $r = 0.33-0.44$ ). Each scale discriminated between the presence and absence of ILD and restrictive lung disease ( $P \leq 0.0001-0.03$ ). At follow-up, all scales were responsive to change using different anchors.

CONCLUSION: The SGRQ has acceptable reliability, construct validity and responsiveness to change for use in a dcSSc population and differentiates between patients with and without ILD.

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DOI: 10.1093/rheumatology/keu456

PMCID: PMC4502336

PMID: 25667436 [Indexed for MEDLINE]

1743. EMBO J. 2015 Apr 1;34(7):881-95. doi: 10.15252/emboj.201490296. Epub 2015 Feb 9.

SIGNR3-dependent immune regulation by *Lactobacillus acidophilus* surface layer protein A in colitis.

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Comment in

EMBO J. 2015 Apr 1;34(7):829-31.

Intestinal immune regulatory signals govern gut homeostasis. Breakdown of such regulatory mechanisms may result in inflammatory bowel disease (IBD). *Lactobacillus acidophilus* contains unique surface layer proteins (Slps), including SlpA, SlpB, SlpX, and lipoteichoic acid (LTA), which interact with pattern recognition receptors to mobilize immune responses. Here, to elucidate the role of SlpA in protective immune regulation, the NCK2187 strain, which solely expresses SlpA, was generated. NCK2187 and its purified SlpA bind to the C-type lectin SIGNR3 to exert regulatory signals that result in mitigation of colitis, maintenance of healthy gastrointestinal microbiota, and protected gut mucosal barrier function. However, such protection was not observed in Signr3(-/-) mice, suggesting that the SlpA/SIGNR3 interaction plays a key regulatory role in colitis. Our work presents critical insights into SlpA/SIGNR3-induced responses that are integral to the potential development of novel biological therapies for autoinflammatory diseases, including IBD.

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DOI: 10.15252/emboj.201490296

PMCID: PMC4388597

PMID: 25666591 [Indexed for MEDLINE]

1744. Clin Rheumatol. 2016 Feb;35(2):501-5. doi: 10.1007/s10067-015-2890-5. Epub 2015 Feb 10.

PFAPA syndrome and Behçet's disease: a comparison of two medical entities based on the clinical interviews performed by three different specialists.

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The pediatric syndrome characterized by periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) and adult Behçet's disease share some clinical manifestations and are both polygenic autoinflammatory disorders with interleukin-1 $\beta$  showing to play a pivotal role. However, the diagnosis is mostly clinical and we hypothesize that specific criteria may be addressed differently by different physicians. To determine the diagnostic variability, we compared the answers of 80 patients with a definite diagnosis of Behçet's disease (age  $42.1 \pm 13.7$  years) obtained by separate telephone interviews conducted by a rheumatologist, a pediatrician, and an internist working largely in the field of autoinflammatory disorders. Questions were related to the age of symptom onset, the occurrence of recurrent fevers during childhood, and the association with oral aphthosis, cervical adenitis and/or pharyngitis, previous treatments, possible growth impairment, the time lapse between PFAPA-like symptoms and the onset of Behçet's disease, and the occurrence of Behçet-related manifestation during childhood. The rheumatologist identified 30 % of patients with Behçet's disease fulfilling PFAPA syndrome diagnostic criteria, compared to the

pediatrician and the internist identifying 10 and 7.5 %, respectively. Most of the patients suffered from recurrent oral aphthosis in childhood also without fever (50, 39, and 48 % with each interviewer), yet no patient fulfilled the Behçet's disease diagnostic criteria. Our data suggest that physician awareness and expertise are central to the diagnosis of autoinflammatory disorders through an accurate collection of the medical history.

DOI: 10.1007/s10067-015-2890-5

PMID: 25665824 [Indexed for MEDLINE]

1745. J Inflamm (Lond). 2015 Jan 31;12:7. doi: 10.1186/s12950-015-0048-5. eCollection 2015.

Knockdown of MVK does not lead to changes in NALP3 expression or activation.

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**BACKGROUND:** Mutations in the Mevalonate Kinase gene (MVK) are causes of a rare autoinflammatory disease: Mevalonate Kinase Deficiency and its more acute manifestation, Mevalonic Aciduria. The latter is characterized, among other features, by neuroinflammation, developmental delay and ataxia, due to failed cerebellar development or neuronal death through chronic inflammation. Pathogenesis of neuroinflammation in Mevalonate Kinase Deficiency and Mevalonic Aciduria has not yet been completely clarified, however different research groups have been suggesting the inflammasome complex as the key factor in the disease development. A strategy to mimic this disease is blocking the mevalonate pathway, using HMG-CoA reductase inhibitors (Statins), while knock-out mice for Mevalonate Kinase are non-vital and their hemizygous (i.e only one copy of gene preserved) littermate display almost no pathological features.

**FINDINGS:** We sought to generate a murine cellular model closely resembling the pathogenic conditions found in vivo, by direct silencing of Mevalonate Kinase gene. Knockdown of Mevalonate Kinase in a murine microglial cellular model (BV-2 cells) results in neither augmented NALP3 expression nor increase of apoptosis.

On the contrary, statin treatment of BV-2 cells produces an increase both in Mevalonate Kinase and NALP3 expression.

**CONCLUSIONS:** MKD deficiency could be due or affected by protein accumulation leading to NALP3 activation, opening novel questions about strategies to tackle this disease.

DOI: 10.1186/s12950-015-0048-5

PMCID: PMC4320511

PMID: 25663823

1746. Dtsch Med Wochenschr. 2015 Feb;140(3):191-3. doi: 10.1055/s-0041-100067. Epub 2015 Feb 6.

[News about autoinflammatory syndromes].

[Article in German]

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DOI: 10.1055/s-0041-100067

PMID: 25658407 [Indexed for MEDLINE]

1747. Mol Immunol. 2015 May;65(1):139-47. doi: 10.1016/j.molimm.2015.01.004. Epub 2015 Feb 3.

Polyclonal, newly derived T cells with low expression of inhibitory molecule PD-1 in tonsils define the phenotype of lymphocytes in children with Periodic Fever, Aphthous Stomatitis, Pharyngitis and Adenitis (PFAPA) syndrome.

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Erratum in

Mol Immunol. 2015 Aug;66(2):428. Petra, Dytrych; Petra, Krol; Michaela, Kotrova; Daniela, Kuzilkova; Petr, Hubacek; Ladislav, Krol; Rami, Katra; Ondrej, Hrusak; Zdenek, Kabelka; Pavla, Dolezalova; Tomas, Kalina; Eva, Fronkova [Corrected to Dytrych, Petra; Krol, Petra; Kotrova, Michaela; K.

**PURPOSE:** PFAPA syndrome is a benign, recurrent inflammatory disease of childhood. Tonsillectomy is one of the therapeutic options with a yet unexplained biological mechanism. We tested whether specific lymphocyte subsets recruited from blood to human tonsils participate in PFAPA pathogenesis.

**METHODS:** Paired tonsils/peripheral blood (PB) samples were investigated (a) from children with PFAPA that successfully resolved after tonsillectomy (n=10) (b) from children with obstructive sleep apnoea syndrome as controls (n=10). The lymphocyte profiles were analysed using 8-colour flow cytometry, immunoglobulin (IGH) and T-cell receptor (TCR) gene rearrangements via PCR and next generation sequencing; a TREC/KREC analysis was performed using qPCR.

**RESULTS:** The PFAPA tonsils in the asymptomatic phase had a lower percentage of B-lymphocytes than controls; T-lymphocyte counts were significantly higher in PB. The percentages of cytotoxic CD8pos T-lymphocytes were approximately 2-fold higher in PFAPA tonsils; the transitional B cells and naïve stages of both the CD4pos and CD8pos T-lymphocytes with a low expression of PD-1 molecule and high



numbers of TREC were also increased. With the exception of elevated plasmablasts, no other differences were significant in PB. The expression levels of CXCL10, CXCL9 and CCL19 genes were significantly higher in PFAPA tonsils. The IGH/TCR pattern showed no clonal/oligoclonal expansion. DNA from the Epstein-Barr virus, Human Herpesvirus-6 or adenovirus was detected in 7 of 10 PFAPA tonsils but also in 7 of 9 controls.

**CONCLUSIONS:** Our findings suggest that the uninhibited, polyclonal response of newly derived lymphocytes participate in the pathogenesis of PFAPA. Because most of the observed changes were restricted to tonsils and were not present in PB, they partly explain the therapeutic success of tonsillectomy in PFAPA syndrome.

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DOI: 10.1016/j.molimm.2015.01.004

PMID: 25656804 [Indexed for MEDLINE]

1748. J Inflamm Res. 2015 Jan 16;8:15-27. doi: 10.2147/JIR.S51250. eCollection 2015.

Targeting the NLRP3 inflammasome in chronic inflammatory diseases: current perspectives.

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The inflammasome is a molecular platform formed by activation of an innate immune pattern recognition receptor seed, such as NLRP3. Once activated, NLRP3 recruits the adapter ASC (apoptosis-related speck-like protein containing a caspase recruitment domain), which in turn recruits procaspase-1. Procaspase-1 autocatalyzes its cleavage and activation, resulting in maturation of the precursor forms of interleukin (IL)-1 $\beta$  and IL-18 into active proinflammatory cytokines and initiation of pyroptotic cell death. The NLRP3 inflammasome has been implicated in the pathogenesis of a wide variety of diseases, including genetically inherited autoinflammatory conditions as well as chronic diseases in

which NLRP3 is abnormally activated. The NLRP3 inflammasome has been linked to diseases such as Alzheimer's disease, atherosclerosis, metabolic syndrome, and age-related macular degeneration. In this review, we describe the NLRP3 inflammasome complex and its activation in disease, and detail the current therapies that modulate either the NLRP3 inflammasome complex itself or the two cytokines it is responsible for activating, ie, IL-1 $\beta$  and IL-18.

DOI: 10.2147/JIR.S51250

PMCID: PMC4303395

PMID: 25653548

1749. Ther Clin Risk Manag. 2014 Dec 22;11:33-43. doi: 10.2147/TCRM.S64951. eCollection 2015.

Treatment of adult-onset Still's disease: a review.

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Adult-onset Still's disease (AOSD) is a rare inflammatory disorder that has been recently classified as a polygenic autoinflammatory disorder. The former classification, based on the disease course, seems to be quite dated. Indeed, there is accumulating evidence that AOSD can be divided into two distinct phenotypes based on cytokine profile, clinical presentation, and outcome, ie, a "systemic" pattern and an "articular" pattern. The first part of this review deals with the treatments that are currently available for AOSD. We then present the different strategies based on the characteristics of the disease according to clinical presentation. To do so, we focus on the two subsets of the disease. Finally, we discuss the management of life-threatening complications of AOSD,

along with the therapeutic options during pregnancy.

DOI: 10.2147/TCRM.S64951

PMCID: PMC4278737

PMID: 25653531

1750. Arch Pediatr. 2015 Mar;22(3):279-82. doi: 10.1016/j.arcped.2014.11.021. Epub 2015 Jan 30.

[Value of whole-body MRI in vertebral fractures].

[Article in French]

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Chronic recurrent multifocal osteomyelitis (CRMO) is a rare autoinflammatory disease in children. Pathological vertebral fracture may be the first symptom revealing this disease. We describe the case of a 14-year-old boy, with no significant past medical history, who had a sudden dorsal pain after carrying a friend on his back. Plain radiographs and MRI showed fractures of the superior endplate of T5 and T6 associated with a mild degree of kyphosis. MRI allowed ruling out discitis. The diagnostic hypotheses raised were cancer (lymphoma,

leukemia), Langerhans cell histiocytosis, osteogenesis imperfecta, and CRMO. A whole-body MRI (wbMRI) was performed and disclosed several clinically silent signal abnormalities in key sites of CRMO (pelvic bone and tibial metaphyses). We point out that CRMO should be systematically added to the list of possible diseases in case of vertebral fracture. In this perspective, wbMRI is a major noninvasive tool to assess the diagnosis of CRMO, and allows avoiding a bone biopsy in most cases.

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DOI: 10.1016/j.arcped.2014.11.021

PMID: 25650082 [Indexed for MEDLINE]

1751. Acta Medica (Hradec Kralove). 2014;57(3):97-104. doi: 10.14712/18059694.2014.47.

Familial Mediterranean Fever.

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Familial Mediterranean Fever is an autosomal recessive inherited disease with a course of autoinflammation, which is characterized by the episodes of fever and serositis. It affects the populations from Mediterranean basin. Genetic mutation of the disease is on MEFV gene located on short arm of Chromosome 16. The disease is diagnosed based on clinical evaluation. Amyloidosis is the most important complication. The only agent that decreases the development of amyloidosis and the frequency and severity of the episodes is colchicine, which has been used for about 40 years. In this review, we aimed to discuss especially the most recent advances about Familial Mediterranean Fever which is commonly seen in our population.

DOI: 10.14712/18059694.2014.47

1752. Iran J Med Sci. 2015 Jan;40(1):68-72.

MEFV Gene Profile in Northwest of Iran, Twelve Common MEFV Gene Mutations Analysis in 216 Patients with Familial Mediterranean Fever.

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Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory disease with autosomal recessive inheritance pattern often seen around the Mediterranean Sea. It is characterized by recurrent episodes of fever and polyserositis and rash. Recently, MEFV gene analysis determines the definitive diagnosis of FMF. In this study, we analyzed 12 MEFV gene mutations in more than 200 FMF patients, previously diagnosed by Tel-Hashomer clinical criteria, in northwest of Iran, located in the proximity of the Mediterranean Sea. In the northwest of Iran (Ardabil), 216 patients with FMF diagnosis, based on Tel-Hashomer criteria, referred to the genetic laboratory to be tested for the following mutations; P369S, F479L, M680I(G/C), M680I(G/A), I692del, M694V, M694I, K695R, V726A, A744S, R761H, E148Q. All patients were screened for MEFV gene mutations by a reverse hybridization assay (FMF Strip Assay, Vienna lab, Vienna, Austria) according to manufacturer's instructions. Among these FMF patients, no mutation was detected in 51 (23/62%) patients, but 165 (76/38%) patients had one or two mutations, 33 patients (15/28%) homozygous, 86 patients (39/81%) compound heterozygous and 46 patients (21/29%) were heterozygous. The most common mutations were M694V (23/61%), V726A (11/11%) and E148Q (9/95%) respectively. MEFV gene mutations showed similarities and dissimilarities in different ethnic groups, while it is common among Arabs and Armenians genotype. Since common 12 MEFV gene analysis could not detect up to 50% of our patients, who had FMF on the basis of clinical

Tel-Hashomer criteria, clinical criteria is still the best way in the diagnosis of FMF in this area. The abstract of this article has been presented in the 7th Congress of International Society of Systemic Auto-Inflammatory Diseases in Lausanne, Switzerland, 22-26 May 2013.

PMCID: PMC4300484

PMID: 25648235

1753. Breastfeed Med. 2015 Mar;10(2):92-5. doi: 10.1089/bfm.2014.0086. Epub 2015 Feb 3.

Colchicine use during breastfeeding.

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**OBJECTIVE:** This study evaluated the outcome of infants exposed to colchicine during lactation.

**SUBJECTS AND METHODS:** A prospective observational cohort study design was used. Mothers who contacted Beilinson Teratology Information Service (BELTIS) regarding use of colchicine while breastfeeding were followed up by phone interview. Data on lactation, neonatal symptoms, and outcome 1-3 years after initial consultation were obtained. Mothers breastfeeding while taking colchicine (n=37) and their infants (n=38) were compared with a matched control group of mothers using a drug known to be safe during lactation (n=75) and their infants (n=76).

**RESULTS:** Follow-up was obtained for 59 of 76 (78%) women who contacted BELTIS regarding use of colchicine. Of the 59 women, 37 breastfed while taking colchicine, five did not take colchicine, 16 did not breastfeed, and one declined to participate. The mean duration of breastfeeding was similar in both groups. Adverse neonatal symptoms were seen in three of 38 colchicine-exposed infants versus four of 76 of control group infants (p=0.68). Delayed development or neurological abnormalities were seen in two infants in both study groups (p=0.60). None of the colchicine-exposed infants showed abnormal growth.

**CONCLUSIONS:** No increase in adverse long-term outcomes was found in colchicine-exposed breastfed infants. Our data support continuation of

breastfeeding in women treated with colchicine.

DOI: 10.1089/bfm.2014.0086

PMID: 25646562 [Indexed for MEDLINE]

1754. J Neuroinflammation. 2015 Feb 3;12:21. doi: 10.1186/s12974-015-0239-2.

Danger- and pathogen-associated molecular patterns recognition by pattern-recognition receptors and ion channels of the transient receptor potential family triggers the inflammasome activation in immune cells and sensory neurons.

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An increasing number of studies show that the activation of the innate immune system and inflammatory mechanisms play an important role in the pathogenesis of numerous diseases. The innate immune system is present in almost all multicellular organisms and its activation occurs in response to pathogens or tissue injury via pattern-recognition receptors (PRRs) that recognize

pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs). Intracellular pathways, linking immune and inflammatory response to ion channel expression and function, have been recently identified. Among ion channels, the transient receptor potential (TRP) channels are a major family of non-selective cation-permeable channels that function as polymodal cellular sensors involved in many physiological and pathological processes. In this review, we summarize current knowledge of interactions between immune cells and PRRs and ion channels of TRP families with PAMPs and DAMPs to provide new insights into the pathogenesis of inflammatory diseases. TRP channels have been found to interfere with innate immunity via both nuclear factor- $\kappa$ B and procaspase-1 activation to generate the mature caspase-1 that cleaves pro-interleukin-1 $\beta$  cytokine into the mature interleukin-1 $\beta$ . Sensory neurons are also adapted to recognize dangers by virtue of their sensitivity to intense mechanical, thermal and irritant chemical stimuli. As immune cells, they possess many of the same molecular recognition pathways for danger. Thus, they express PRRs including Toll-like receptors 3, 4, 7, and 9, and stimulation by Toll-like receptor ligands leads to induction of inward currents and sensitization in TRPs. In addition, the expression of inflammasomes in neurons and the involvement of TRPs in central nervous system diseases strongly support a role of TRPs in inflammasome-mediated neurodegenerative pathologies. This field is still at its beginning and further studies may be required. Overall, these studies highlight the therapeutic potential of targeting the inflammasomes in proinflammatory, autoinflammatory and metabolic disorders associated with undesirable activation of the inflammasome by using specific TRP antagonists, anti-human TRP monoclonal antibody or different molecules able to abrogate the TRP channel-mediated inflammatory signals.

DOI: 10.1186/s12974-015-0239-2

PMCID: PMC4322456

PMID: 25644504 [Indexed for MEDLINE]

1755. Microbiol Immunol. 2015 Mar;59(3):160-5. doi: 10.1111/1348-0421.12229.

Mediterranean fever gene mutations: correlation with cytotoxic  
T-lymphocyte-associated antigen 4 gene polymorphism.

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Mutations in the Mediterranean fever (MEFV) gene lead to familial Mediterranean fever (FMF), a pro-inflammatory state characterized by outbursts of inflammatory cytokines. The aims of this study were to identify the common mutations of MEFV gene in Egyptian patients with FMF, to study cytotoxic T lymphocyte associated antigen 4 (CTLA-4) gene polymorphism and to evaluate correlations between CTLA4-1661 polymorphisms and MEFV mutations and clinical symptoms. Four hundred and twenty-four patients with clinical pictures suspicious of FMF were enrolled in this study. Mutations in MEFV gene were confirmed by reversed hybridization. Patients with homozygous and compound heterozygous mutations and 120 healthy controls were investigated for polymorphism of -1661 CTLA4 gene and the findings correlated with disease incidence and clinical symptoms of the disease. Ninety-seven patients had single heterozygous mutations and 78 had compound heterozygous or homozygous MEFV gene mutations. M694I/V726A was the most common genotype (14.1%), followed by homozygous M694I. There was no statistically significant difference between patients and controls in incidence of -1661 A/G single nucleotide polymorphism CTLA4 ( $P = 0.189$ ), nor any significant correlation with any of the clinical symptoms of FMF and MEFV gene mutations.

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DOI: 10.1111/1348-0421.12229

PMID: 25643856 [Indexed for MEDLINE]

1756. J Immunol. 2015 Mar 1;194(5):2358-68. doi: 10.4049/jimmunol.1401992. Epub 2015 Jan 30.

A novel model for IFN- $\gamma$ -mediated autoinflammatory syndromes.

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Autoinflammatory disease and hyperinflammatory syndromes represent a growing number of diseases associated with inappropriately controlled inflammation in multiple organs. Systemic inflammation commonly results from dysregulated activation of innate immune cells, and therapeutic targeting of the IL-1 $\beta$  pathway has been used to ameliorate some of these diseases. Some hyperinflammatory syndromes, however, such as hemophagocytic lymphohistiocytosis and the newly classified proteasome disability syndromes, are refractory to such treatments, suggesting that other factors or environmental stressors may be contributing. In comparing two cytokine reporter mouse strains, we identify IFN- $\gamma$  as a mediator of systemic autoinflammatory disease. Chronically elevated levels of IFN- $\gamma$  resulted in progressive multiorgan inflammation and two copies of the mutant allele resulted in increased mortality accompanied by myeloproliferative disease. Disease was alleviated by genetic deletion of T-bet. These studies raise the possibility that therapeutics targeting the IFN- $\gamma$  pathway might be effective in hyperinflammatory conditions refractory to IL-1 $\beta$ -targeted therapies.

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DOI: 10.4049/jimmunol.1401992

PMCID: PMC4337485

PMID: 25637019 [Indexed for MEDLINE]

1757. Ann Rheum Dis. 2015 May;74(5):799-805. doi: 10.1136/annrheumdis-2014-206580.  
Epub  
2015 Jan 30.

Evidence-based provisional clinical classification criteria for autoinflammatory  
periodic fevers.

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Comment in

Nat Rev Rheumatol. 2015 Mar;11(3):125.

The objective of this work was to develop and validate a set of clinical criteria for the classification of patients affected by periodic fevers. Patients with inherited periodic fevers (familial Mediterranean fever (FMF); mevalonate kinase deficiency (MKD); tumour necrosis factor receptor-associated periodic fever syndrome (TRAPS); cryopyrin-associated periodic syndromes (CAPS)) enrolled in the Eurofever Registry up until March 2013 were evaluated. Patients with periodic fever, aphthosis, pharyngitis and adenitis (PFAPA) syndrome were used as negative controls. For each genetic disease, patients were considered to be 'gold standard' on the basis of the presence of a confirmatory genetic analysis. Clinical criteria were formulated on the basis of univariate and multivariate

analysis in an initial group of patients (training set) and validated in an independent set of patients (validation set). A total of 1215 consecutive patients with periodic fevers were identified, and 518 gold standard patients (291 FMF, 74 MKD, 86 TRAPS, 67 CAPS) and 199 patients with PFAPA as disease controls were evaluated. The univariate and multivariate analyses identified a number of clinical variables that correlated independently with each disease, and four provisional classification scores were created. Cut-off values of the classification scores were chosen using receiver operating characteristic curve analysis as those giving the highest sensitivity and specificity. The classification scores were then tested in an independent set of patients (validation set) with an area under the curve of 0.98 for FMF, 0.95 for TRAPS, 0.96 for MKD, and 0.99 for CAPS. In conclusion, evidence-based provisional clinical criteria with high sensitivity and specificity for the clinical classification of patients with inherited periodic fevers have been developed.

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DOI: 10.1136/annrheumdis-2014-206580

PMID: 25637003 [Indexed for MEDLINE]

1758. Ann Rheum Dis. 2015 Apr;74(4):635-41. doi: 10.1136/annrheumdis-2014-206844. Epub 2015 Jan 27.

Evidence-based recommendations for genetic diagnosis of familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is a disease of early onset which can lead to significant morbidity. In 2012, Single Hub and Access point for pediatric Rheumatology in Europe (SHARE) was launched with the aim of optimising and disseminating diagnostic and management regimens for children and young adults with rheumatic diseases. The objective was to establish recommendations for FMF focusing on provision of diagnostic tools for inexperienced clinicians

particularly regarding interpretation of MEFV mutations. Evidence-based recommendations were developed using the European League against Rheumatism standard operating procedure. An expert committee of paediatric rheumatologists defined search terms for the systematic literature review. Two independent experts scored articles for validity and level of evidence. Recommendations derived from the literature were evaluated by an online survey and statements with less than 80% agreement were reformulated. Subsequently, all recommendations were discussed at a consensus meeting using the nominal group technique and were accepted if more than 80% agreement was reached. The literature search yielded 3386 articles, of which 25 were considered relevant and scored for validity and level of evidence. In total, 17 articles were scored valid and used to formulate the recommendations. Eight recommendations were accepted with 100% agreement after the consensus meeting. Topics covered were clinical versus genetic diagnosis of FMF, genotype-phenotype correlation, genotype-age at onset correlation, silent carriers and risk of amyloid A (AA) amyloidosis, and role of the specialist in FMF diagnosis. The SHARE initiative provides recommendations for diagnosing FMF aimed at facilitating improved and uniform care throughout Europe.

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DOI: 10.1136/annrheumdis-2014-206844  
PMID: 25628446 [Indexed for MEDLINE]

1759. Rev Bras Reumatol. 2014 Sep-Oct;54(5):356-9. doi: 10.1016/j.rbr.2014.03.022. Epub 2014 Jul 6.

[Evaluation of frequency and the attacks features of patients with colchicine resistance in FMF].

[Article in Portuguese]

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**INTRODUCTION:** Colchicine is the mainstay for the treatment of FMF, which is an auto-inflammatory disease mainly with relapsing polyserositis. Despite daily doses of 2mg or more each day, approximately 5% to 10% of the patients continue to suffer from its attacks. In this study, we aimed to investigate the depression and attack features in patients with FMF who have colchicine resistance (CR).

**PATIENTS E METHODS:** CR was defined for FMF patients with 2 or more attacks within the last 6 months period while using 2mg/day colchicine. Eighteen patients (9 Female/9 Male) were enrolled into the CR group and 41 patients were enrolled into the control group (12 Male/29 Female). Demographic, clinical e laboratory findings, treatment adherence, and the Beck Depression Inventory (BDI) scores were evaluated.

**RESULTS:** The age of onset of FMF was significantly lower in the CR group (12.3 yrs vs. 16.9 yrs,  $P=0.03$ ). Disease duration was longer in the CR group ( $P=0.01$ ). Abdominal and leg pain due to exercise were significantly more frequent in the CR group versus controls (83% vs. 51%;  $P=0.02$  e 88% vs. 60%;  $P=0.04$ , respectively). Patients with BDI scores over 17 points were more frequent in the CR group compared to controls (50% vs. 34.1%;  $P<0.001$ ).

**DISCUSSION:** We found that: (1) the age of disease onset was lower and (2) the disease duration was longer in CR group. Pleuritic attacks, hematuria e proteinuria were more frequent in CR patients. We propose that depression is an important factor to consider in the susceptibility to CR.

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DOI: 10.1016/j.rbr.2014.03.022

PMID: 25627298 [Indexed for MEDLINE]



1760. Prague Med Rep. 2014;115(3-4):128-33. doi: 10.14712/23362936.2014.43.

Acute hepatitis in a child heterozygous for the I259V MEFV gene variant.

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Familial Mediterranean Fever (FMF) is a systemic auto-inflammatory disease characterized by recurrent episodes of fever accompanied by synovial, serosal and/or cutaneous inflammation. Liver involvement has been described mainly in patients with paired FMF gene mutations, i.e. involving both alleles, and rarely in patients heterozygous for FMF mutations. These patients may present with acute or chronic hepatitis, with or without liver failure. Non-alcoholic hepatitis, mild hyperbilirubinemia, and elevation of liver enzymes of unknown etiology should also raise suspicion of FMF. Patients with FMF and liver involvement usually respond to colchicine medication. The mutation I259V (c.775A MEFV gene has not been reported in FMF patients with liver involvement. Furthermore, among several MEFV gene variants, it has been reported so far in only one heterozygous FMF patient of Turkish ancestry presenting with abdominal pain without any hepatic complication. Herein, the second case of a FMF patient heterozygous for the above mentioned mutation is discussed. It is a male child with FMF clinical phenotype which presented two consecutively episodes of acute hepatitis during fever attacks, that spontaneously resolved. Therapeutic trial with colchicine was successful, since no other fever attacks and acute hepatitis episodes were noticed.

DOI: 10.14712/23362936.2014.43

PMID: 25626331 [Indexed for MEDLINE]

1761. Redox Biol. 2015;4:296-307. doi: 10.1016/j.redox.2015.01.008. Epub 2015 Jan 14.

NLRP3 inflammasome: from a danger signal sensor to a regulatory node of oxidative

stress and inflammatory diseases.

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IL-1 $\beta$  production is critically regulated by cytosolic molecular complexes, termed inflammasomes. Different inflammasome complexes have been described to date. While all inflammasomes recognize certain pathogens, it is the distinctive feature of NLRP3 inflammasome to be activated by many and diverse stimuli making NLRP3 the most versatile, and importantly also the most clinically implicated inflammasome. However, NLRP3 activation has remained the most enigmatic. It is not plausible that the intracellular NLRP3 receptor is able to detect all of its many and diverse triggers through direct interactions; instead, it is discussed that NLRP3 is responding to certain generic cellular stress-signals induced by the multitude of molecules that trigger its activation. An ever increasing number of studies link the sensing of cellular stress signals to a direct pathophysiological role of NLRP3 activation in a wide range of autoinflammatory and autoimmune disorders, and thus provide a novel mechanistic rationale, on how molecules trigger and support sterile inflammatory diseases. A vast interest has created to unravel how NLRP3 becomes activated, since mechanistic insight is the prerequisite for a knowledge-based development of therapeutic intervention strategies that specifically target the NLRP3 triggered IL-1 $\beta$  production. In this review, we have updated knowledge on NLRP3 inflammasome assembly and activation and on the pyrin domain in NLRP3 that could represent a drug target to treat sterile inflammatory diseases. We have reported mutations in NLRP3 that were found to be associated with certain diseases. In addition, we have reviewed the functional link between NLRP3 inflammasome, the regulator of cellular redox status Trx/TXNIP complex, endoplasmic reticulum stress and the pathogenesis of diseases such as type 2 diabetes. Finally, we have provided data on NLRP3

inflammasome, as a critical regulator involved in the pathogenesis of obesity and cardiovascular diseases.

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DOI: 10.1016/j.redox.2015.01.008

PMCID: PMC4315937

PMID: 25625584 [Indexed for MEDLINE]

1762. Zhonghua Er Ke Za Zhi. 2014 Dec;52(12):896-901.

[Mutations of NOD2 gene and clinical features in Chinese Blau syndrome patients].

[Article in Chinese]

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**OBJECTIVE:** Blau syndrome (BS), an autosomal dominant inherited autoinflammatory disease, is caused by NOD2 mutations. This study aimed to analyze NOD2 gene of suspected BS patients to make definite diagnosis, find NOD2 mutation types and clinical features of Chinese BS cases, and find some clinical indications to identify BS by comparing BS and non-BS cases.

**METHOD:** Eighteen suspected BS children (7 boys and 11 girls, age of first visit was from 1 y 8 m to 9 y 6 m) who visited Peking Union Medical College Hospital from 2006 to 2014 and their parents's DNA were extracted from 4 ml blood specimens. PCR was performed for exon 4 of NOD2 and PCR products were purified by 2% gel electrophoresis and sequenced directly. Role of novel missense mutations in pathogenicity was analyzed by SIFT and sequencing NOD 2 of fifty normal controls. Clinical data of BS children diagnosed by NOD2 analysis were summarized and compared with the data of non-BS group.

**RESULT:** (1) Twelve of eighteen suspected BS children were diagnosed as BS by NOD2

analysis, and the remaining 6 were excluded. Seven missense mutations were detected, 4 were reported before: c.1000C>T, p. Arg 334Trp; c.1001G>A, p. Arg334Gln; c.1538T>C, p. Met513Thr; c.1759C>T, p. Arg587Cys. Three novel mutations were found: c. 1147 G>C, p.Glu383Gln; c.1471A>T, p. Met491Leu; c.2006A>G, p.His669Arg. (2) Chronic symmetric arthritis and multi-joints periarticular hydatoncus, which were painless with fluctuation, were found in all 12 BS children with NOD2 mutations. Skin rash, chronic symmetric arthritis, and recurrent uveitis were identified in 7 patients. Three patients had no skin rash, while 1 had no uveitis, 1 only had symmetric arthritis and multi-joints periarticular hydatoncus. Four children inherited the disease from father. (3) Compared with other 6 non-BS children, BS children had such different clinical characteristic ( $P < 0.05$ ): All the BS cases had multiple periarticular hydatoncus, which always had no persistent fever, most had no elevated CRP, while non-BS group always had no hydatoncus, most had persistent fever, all had elevated CRP.

CONCLUSION: The 12 BS children were diagnosed by NOD2 analysis; 7 missense mutations were detected, 3 were novel mutations, adding new findings to human NOD2 mutations. Although classic BS was characterized by skin rash, arthritis, and eye involvement, some presented with less than 3 of the classic features. Chronic symmetric arthritis and multi-joints periarticular hydatoncus were the most comment fetures. Comparing with non-BS group, all BS cases had multi hydatoncus surrounding multi-joints, always had no persistent fever, most had no elevated CRP. Those features may distinguish BS in clinical settings.

PMID: 25619344 [Indexed for MEDLINE]

1763. Zhonghua Er Ke Za Zhi. 2014 Dec;52(12):885-9.

[New interpretation of autoinflammatory diseases].

[Article in Chinese]

Song H.

PMID: 25619342 [Indexed for MEDLINE]

1764. *Mod Rheumatol*. 2016 Jul;26(4):610-3. doi: 10.3109/14397595.2014.908810. Epub 2015 Jan 25.

Successful treatment with humanized anti-interleukin-6 receptor antibody (tocilizumab) in a case of AA amyloidosis complicated by familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is a well-known cause of secondary AA amyloidosis. Colchicine is generally considered to be the most effective treatment for FMF and FMF-associated amyloidosis, but the management of patients who are refractory to colchicine remains controversial. We encountered a 51-year-old Japanese man with suspected FMF, who had periodic fever with abdominal pain, polyarthritis, and nephropathy (serum creatinine of 1.9 mg/dL and 24-h protein excretion of 3.8 g). FMF was diagnosed by mutation analysis of the Mediterranean fever (MEFV) gene, which revealed that the patient was compound heterozygous for the marenostirin/pyrin variant E148Q/M694I. AA amyloidosis was diagnosed by renal and gastric biopsy. Colchicine was administered, but his arthritis persisted, and serum creatinine increased to 2.4 mg/dL. Therefore, a humanized anti-interleukin-6 receptor antibody (tocilizumab) was administered at a dose of 8 mg/kg on a monthly basis. Both arthritis and abdominal pain subsided rapidly, and C-reactive protein (CRP) decreased from 2.5 to 0.0 mg/dL. After 2 years, his serum creatinine was decreased to 1.5 mg/dL and proteinuria was improved to 0.3 g daily. In addition, repeat gastric biopsy showed a marked decrease of AA amyloidosis. This case suggests that tocilizumab could be a new therapeutic option for patients with FMF-associated AA amyloidosis if colchicine is not effective.

DOI: 10.3109/14397595.2014.908810  
PMID: 25619282 [Indexed for MEDLINE]

1765. Georgian Med News. 2014 Dec;(237):99-102.

[Familial Mediterranean Fever in children and adolescents in Georgia].

[Article in Russian]

Pagava Ki, Sarkisian TF, Shonvadze DN, Korniteli IA, Airapetian AS, Egiazarian AR.

There are presented preliminary results of the analysis of the materials of the register of children and adolescents suffering from Familial Mediterranean Fever in Georgia. The register was created by the "snow ball" method. For today it contains data on 138 patients, 56 (40.6%) males, 82 (59.4%) females, 86 (62.3%) less than 10 year old, 52 (37.7%) 10-18 year old. Almost in all patients the Armenian roots were revealed, both from maternal and paternal sides. Among the MEFV gene mutations M694V (mainly) and also V726A and M680I were the most common ones.

PMID: 25617110 [Indexed for MEDLINE]

1766. Med Sci Monit. 2015 Jan 23;21:298-303. doi: 10.12659/MSM.892289.

Simple markers for subclinical inflammation in patients with Familial Mediterranean Fever.

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**BACKGROUND:** In this study we investigated the potential of neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), mean platelet volume (MPV), and red cell width distribution (RDW) as new inflammatory markers to identify chronic inflammations during symptom-free periods in children diagnosed with Familial Mediterranean Fever (FMF).

**MATERIAL/METHODS:** The study included 153 children diagnosed with FMF based on the Tel-Hashomer Criteria, and 90 healthy volunteers. Hospital records were obtained to collect NLR, PLR, MPV, RDW, and FMF scores and the FMF mutation analyses of the patients enrolled in the study. Data on proteinuria were also collected and defined as a protein/creatinine ratio >0.2.

**RESULTS:** NLR, PLR, MPV, and RDW were significantly higher in symptom-free FMF patients than in the control group. C-reactive protein values also weakly correlated with NLR, PLR, MPV, and RDW, but the correlation was not statistically significant. NLR had the strongest correlation with CRP. The NLR cut-off point to indicate subclinical inflammation in symptom-free FMF patients was calculated to be 1.65.

**CONCLUSIONS:** NLR, PLR, MPV, and RDW are potential subclinical inflammation markers in patients with FMF. NLR, PLR, MPV, and RDW values are higher in patients with FMF during symptom-free periods. NLR was found to be the most reliable marker for subclinical inflammation when compared to PLR, MPV, and RDW. We also found that these markers are not significantly higher in proteinuric patients when compared with levels in non-proteinuric patients.

DOI: 10.12659/MSM.892289

PMCID: PMC4315639

PMID: 25615955 [Indexed for MEDLINE]

1767. Ophthalmologe. 2015 Sep;112(9):778-82. doi: 10.1007/s00347-014-3221-y.

[Papillary edema in Muckle-Wells syndrome].

[Article in German]

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Papillary edema may occur isolated without functional impairment or secondary related to various syndromes, increased intracerebral pressure or associated with medicinal treatment. The Muckle-Wells syndrome is a rare disease, which among many other symptoms can lead to optic disc swelling and recurrent increase in intracerebral pressure. Besides familial cold-induced autoinflammatory syndrome (FCAS) and neonatal onset multisystem inflammatory disease (NOMID), the Muckle-Wells syndrome also belongs to the cryopyrin-associated periodic syndromes (CAPS). In most cases of CAP syndromes there is an underlying genetic disorder that leads to overproduction of interleukin-1 $\beta$  (IL-1 $\beta$ ); therefore, typical symptoms include inflammation reactions, such as repeated skin rash, fatigue, fever, joint pain and conjunctivitis.

DOI: 10.1007/s00347-014-3221-y

PMID: 25614348 [Indexed for MEDLINE]

1768. Hepatology. 2015 Jul;62(1):40-6. doi: 10.1002/hep.27716. Epub 2015 Feb 24.

Safety of long-term biologic therapy in rheumatologic patients with a previously resolved hepatitis B viral infection.

Barone M(1), Notarnicola A(2), Lopalco G(2), Viggiani MT(3), Sebastiani F(3), Covelli M(2), Iannone F(2), Avolio AW(4), Di Leo A(3), Cantarini L(5), Lapadula G(2).

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Comment in

Hepatology. 2015 Jul;62(1):16-8.

European and Asian studies report conflicting data on the risk of hepatitis B virus (HBV) reactivation in rheumatologic patients with a previously resolved HBV (prHBV) infection undergoing long-term biologic therapies. In this patient category, the safety of different immunosuppressive biologic therapies, including rituximab, was assessed. A total of 1218 Caucasian rheumatologic patients, admitted consecutively as outpatients between 2001 and 2012 and taking biologic therapies, underwent evaluation of anti-HCV and HBV markers as well as liver amino transferases every 3 months. Starting from January 2009, HBV DNA monitoring was performed in patients with a prHBV infection who had started immunosuppressive biologic therapy both before and after 2009. Patients were considered to have elevated aminotransferase levels if values were  $>1\times$  upper normal limit at least once during follow-up. We found 179 patients with a prHBV infection (14 treated with rituximab, 146 with anti-tumor necrosis factor- $\alpha$ , and 19 with other biologic therapies) and 959 patients without a prHBV infection or other liver disease (controls). The mean age in the former group was significantly higher than the controls. Patients with a prHBV infection never showed detectable HBV DNA serum levels or antibody to hepatitis B surface antigen/hepatitis B surface antigen seroreversion. However, when the prevalence of elevated amino transferases in patients with prHBV infection was compared to controls, it was significantly higher in the former group only for aminotransferase levels  $>1\times$  upper normal limit but not when aminotransferase levels  $>2\times$  upper normal limit were considered. **CONCLUSION:** Among patients with a prHBV infection and rheumatologic indications for long-term biologic therapies, HBV reactivation was not seen; this suggests that universal prophylaxis is not justified and is not cost-effective in this clinical setting.

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DOI: 10.1002/hep.27716

PMID: 25613809 [Indexed for MEDLINE]

1769. Immunology. 2015 Jul;145(3):347-56. doi: 10.1111/imm.12444. Epub 2015 Apr 3.

## In vivo regulation of gene expression and T helper type 17 differentiation by ROR $\gamma$ t inverse agonists.

Skepner J(1), Trocha M(1), Ramesh R(1), Qu XA(2), Schmidt D(1), Baloglu E(1), Lobera M(1), Davis S(1), Nolan MA(1), Carlson TJ(1), Hill J(1), Ghosh S(1), Sundrud MS(1)(3), Yang J(1).

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The orphan nuclear receptor, retinoic acid receptor-related orphan nuclear receptor  $\gamma$ t (ROR $\gamma$ t), is required for the development and pathogenic function of interleukin-17A-secreting CD4(+) T helper type 17 (Th17) cells. Whereas small molecule ROR $\gamma$ t antagonists impair Th17 cell development and attenuate autoimmune inflammation in vivo, the broader effects of these inhibitors on ROR $\gamma$ t-dependent gene expression in vivo has yet to be characterized. We show that the ROR $\gamma$ t inverse agonist TMP778 acts potently and selectively to block mouse Th17 cell differentiation in vitro and to impair Th17 cell development in vivo upon immunization with the myelin antigen MOG35-55 plus complete Freund's adjuvant. Importantly, we show that TMP778 acts in vivo to repress the expression of more than 150 genes, most of which fall outside the canonical Th17 transcriptional signature and are linked to a variety of inflammatory pathologies in humans. Interestingly, more than 30 genes are related with SMAD3, a transcription factor involved in the Th17 cell differentiation. These results reveal novel disease-associated genes regulated by ROR $\gamma$ t during inflammation in vivo, and provide an early read on potential disease indications and safety concerns associated with pharmacological targeting of ROR $\gamma$ t.

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DOI: 10.1111/imm.12444

PMCID: PMC4479534

PMID: 25604624 [Indexed for MEDLINE]

1770. Z Rheumatol. 2015 Aug;74(6):533-9. doi: 10.1007/s00393-014-1518-5.

[Heterozygote forms of familial Mediterranean fever can be manifested in adults as myofascial pain syndrome].

[Article in German]

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**BACKGROUND:** Familial Mediterranean fever (FMF) is a disease characterized by recurrent fever, serositis, arthritis and unspecific myalgia. It is prevalent among Mediterranean people and has been shown to be associated with mutations in the Mediterranean fever (MEFV) gene which, encodes pyrin a regulatory protein of the inflammasome. As heterozygous mutations in MEFV can be associated with only mild inflammatory symptoms, such as arthralgia or chronic fibromyalgic pain, FMF may be underdiagnosed in the current diagnostic work-up of musculoskeletal diseases.

**METHODS:** The selection of patients was carried out according to the following criteria: myofascial pain syndrome, seronegative oligoarthritis, a slight inflammatory constellation and ethnic origin from the Mediterranean area. When these criteria were fulfilled a molecular genetic investigation was carried out

**RESULTS:** This article presents evidence that 9 out of 12 Mediterranean patients with recurrent myofascial pain syndrome and mild inflammation revealed heterozygote mutations in the MEFV gene and 7 of these patients benefitted from treatment with colchicine.

**DISCUSSION:** As colchicine treatment not only improved the myofascial pain but also prevented FMF-associated amyloidosis and nephropathy, differential diagnosis of fibromyalgia in patients of Mediterranean origin should include FMF and a genetic screening of the MEFV locus.

DOI: 10.1007/s00393-014-1518-5

PMID: 25604326 [Indexed for MEDLINE]

1771. Rheumatology (Oxford). 2015 Jul;54(7):1317-26. doi: 10.1093/rheumatology/keu481.

Epub 2015 Jan 18.

Increased neutrophil infiltration, IL-1 production and a SAPHO syndrome-like phenotype in PSTPIP2-deficient mice.

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**OBJECTIVE:** Proline-serine-threonine-phosphatase-interacting protein 2 (PSTPIP2) is involved in macrophage activation, neutrophil motility and osteoclast differentiation. However, the role of PSTPIP2 in inflammation and autoinflammatory diseases is still not clear. In this study, we generated PSTPIP2 knockout (*Pstpip2*(-/-)) mice to investigate its phenotype and role in autoinflammatory diseases.

**METHODS:** We constructed a *Pstpip2*-targeting vector and generated *Pstpip2*(-/-) mice. The phenotype and immunopathology of *Pstpip2*(-/-) mice were analysed.

**RESULTS:** All *Pstpip2*(-/-) mice developed paw swelling, synovitis, hyperostosis and osteitis, resembling SAPHO syndrome, an inflammatory disorder of the bone, skin and joints. Multifocal osteomyelitis was found in inflamed paws, with increased macrophage and marked neutrophil infiltrations in the bone, joint and skin. Profound osteolytic lesions with markedly decreased bone volume density developed in paws and limbs. Neutrophil-attracting chemokines and IL-1 $\beta$  were markedly elevated in inflamed tissues.

**CONCLUSION:** Our study suggests that PSTPIP2 could play a role in innate immunity and development of autoinflammatory bone disorders, and may be associated with the pathogenesis of human SAPHO syndrome.

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DOI: 10.1093/rheumatology/keu481

PMID: 25602062 [Indexed for MEDLINE]

1772. Iran J Kidney Dis. 2015 Jan;9(1):71.

Familial Mediterranean fever E148Q mutation, episodic fever and kidney allograft dysfunction.

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PMID: 25599741 [Indexed for MEDLINE]

1773. Rev Med Interne. 2015 Jul;36(7):457-66. doi: 10.1016/j.revmed.2014.11.010. Epub 2015 Jan 13.

[Diagnostic approach of recurrent fevers of unknown origin in adults].

[Article in French]

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Recurrent fever of unknown origin is probably the most difficult to diagnose subtype of fever of unknown origin. It represents between 18 and 42% of the cases in large series of patients with fever of unknown origin. The limited literature data do not allow one to construct a diagnostic algorithm. However, the diagnostic strategy is different from classic fever of unknown origin. The spectrum of causative disorders is different from continuous fever with less infections and tumors. Among systemic inflammatory diseases, adult-onset Still's disease is the most common cause. More than 50% of the cases remain unexplained. Hereditary recurrent fevers, the prototype of autoinflammatory diseases, are now

more easily discuss in a young adult.

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DOI: 10.1016/j.revmed.2014.11.010

PMID: 25595877 [Indexed for MEDLINE]

1774. G Ital Dermatol Venereol. 2015 Feb;150(1):41-50. Epub 2015 Jan 14.

Urticarial vasculitis and urticarial autoinflammatory syndromes.

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Urticaria is a frequent disorder classified as acute and chronic forms, which presents with wheals that can be associated with angioedema. Several entities may manifest with urticarial skin lesions, encompassing a heterogeneous group of conditions that have to be differentiated from ordinary urticaria. This review is focused on two of these urticarial syndromes: urticarial vasculitis (UV), which represents the most important differential diagnosis with common urticaria, and autoinflammatory diseases such as cryopyrin-associated periodic syndromes (CAPS) and Schnitzler's Syndrome, both rare multisystem forms that may masquerade as common urticaria. UV is a small-vessel vasculitis with predominant skin involvement, characterized by wheals persisting for more than 24 hours, burning rather than itching and resolving with hyperpigmentation as well as by other cutaneous manifestations including purpura, papules, vesicles, bullae and necrotic-ulcerative lesions. Histology shows a classic pattern of leukocytoclastic vasculitis, with possible presence of upper dermal edema. CAPS are classified as three distinct entities: familial cold autoinflammatory syndrome, Muckle-Wells Syndrome and chronic infantile neurological cutaneous and articular syndrome, which represent a spectrum of disorders caused by different mutations in a single gene, NLRP3 (NOD-like receptor 3). This gene encodes for

cryopyrin, an inflammasome protein that activates interleukin-1 $\beta$ , leading to an overproduction of this pivotal proinflammatory cytokine. Histologically, urticarial lesions are generally characterized by a perivascular neutrophilic infiltrate. Unlike urticaria, neither UV nor urticarial autoinflammatory syndromes do respond to antihistamines: thus, it is important not to misdiagnose such conditions in order to give the patients specific treatments, potentially preventing serious systemic complications.

PMID: 25586657 [Indexed for MEDLINE]

1775. Rheumatol Int. 2015 Jul;35(7):1257-61. doi: 10.1007/s00296-014-3205-x. Epub 2015 Jan 14.

Predictors of AA amyloidosis in familial Mediterranean fever.

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The aim of the study was to evaluate the clinical and genetic predictors of AA amyloidosis in patients with familial Mediterranean fever (FMF). We retrospectively studied 170 Armenian patients who were admitted to the two tertiary centers in 2003-2014. The diagnosis of amyloidosis that was suspected clinically (new proteinuria or nephrotic syndrome) was confirmed histologically. Screening for MEFV gene mutations was performed in 70 patients. The most common genotype was M694V/M694V (in 36 % of patients). Biopsy-proven AA amyloidosis was found in 102 (60 %) of 170 patients. AA amyloidosis was diagnosed in 17 (68 %) of 25 patients with homozygous M694V mutation, 17 (53 %) of 32 patients with heterozygous M694V allele and 4 (31 %) of 13 patients with other MEFV gene mutations. The M694V homozygosity and heterozygosity were associated with increased risk of AA amyloidosis, but this association did not reach statistical significance (odds ratio 2.43; 95 % CI 0.87-6.76, and 3.33; 0.91-12.1, respectively). Male gender, early onset of disease, severity of FMF, frequent attacks, peritonitis, pleuritis and erysipelas-like erythema also did not predict



AA amyloidosis development. Recurrent arthritis was the only clinical finding that was significantly associated with AA amyloidosis (odds ratio 2.28; 95 % CI 1.17-4.42). Involvement of the joint synovial membrane, that is capable of active serum amyloid A production, is the main predictor of renal amyloidosis in FMF.

DOI: 10.1007/s00296-014-3205-x

PMID: 25586652 [Indexed for MEDLINE]

1776. Rev Bras Reumatol. 2015 Jul-Aug;55(4):325-9. doi: 10.1016/j.rbr.2014.10.008. Epub 2014 Nov 26.

[Is there a relationship between gouty arthritis and Mediterranean fever gene mutations?].

[Article in Portuguese]

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**OBJECTIVE:** Gouty arthritis and familial Mediterranean fever (FMF) share some clinical and pathological features such as being classified as auto inflammatory disease, association with inflammasome, short-lived intermittent arthritis, and good response to colchicine and anti-interleukin-1 treatments. As Mediterranean fever (MEFV) gene is the causative factor of FMF, we aimed to investigate the prevalence of MEFV gene mutations and their effect on disease manifestations in Turkish gouty arthritis patients.

**METHODS:** Ninety-seven patients diagnosed with primary gouty arthritis (93M and 4 F, 54 [37-84] years) and 100 healthy controls (94M and 6 F, 57 [37-86] years) included in the study. All subjects were genotyped for the MEFV variations. Number of gout attacks, diuretic use, and history of nephrolithiasis and presence of tophus were also recorded.

**RESULTS:** The carriage rate of MEFV mutations for patients and controls were 22.7% (n=22) and 24% (n=24) respectively. The comparison of the patient and control groups yielded no significant difference in terms of the MEFV mutations carriage rate (p=0.87). The allelic frequencies of the MEFV mutations in patients were 11.9% (n=23) and 14% (n=28) in controls (p=0.55). The presence of MEFV variants did not show any association with clinical features of gouty arthritis. The subgroup analysis of patients revealed that gouty arthritis patients with mutations had similar frequencies of tophus, history of nephrolithiasis and podagra compared to the ones without mutations (p>0.05).

**CONCLUSIONS:** This study does not provide support for a major role of MEFV mutations in Turkish gouty arthritis patients.

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DOI: 10.1016/j.rbr.2014.10.008

PMID: 25582998 [Indexed for MEDLINE]

1777. Scand J Gastroenterol. 2015 Mar;50(3):378. doi: 10.3109/00365521.2014.999115. Epub 2015 Jan 12.

Comment on: small bowel mucosal damage in familial Mediterranean fever: results of capsule endoscopy screening.

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Comment on

Scand J Gastroenterol. 2014 Dec;49(12):1414-8.

DOI: 10.3109/00365521.2014.999115

PMID: 25578081 [Indexed for MEDLINE]

1778. Int J Immunopathol Pharmacol. 2014 Oct-Dec;27(4):491-8.

Current advances in the understanding and treatment of mevalonate kinase deficiency.

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Mevalonate kinase deficiency (MKD) is a rare autosomal recessive autoinflammatory metabolic disease that is caused by mutations in the MVK gene. Patients with MKD typically have an early onset in infancy. MKD is characterized by recurrent episodes of high fever, abdominal distress, diffuse joint pain, and skin rashes. In a subset of patients, MKD is also associated with elevated serum immunoglobulin D (IgD) levels (hyperimmunoglobulinemia D syndrome, HIDS). The clinical phenotype of MKD varies widely and depends on the severity of the impaired mevalonate kinase activity. Complete impairment results in the severe metabolic disease, mevalonic aciduria, while a partial deficiency results in a broad spectrum of clinical presentation, including HIDS. The precise molecular mechanisms behind the elevated serum IgD levels and inflammation that occurs in MKD remain unknown. Children who exhibit symptoms of MKD should be tested for mutations in the MKD gene. However, the complexity of MKD often results in delays in its definitive diagnosis and the outcome in adult age is not completely known. Therapeutic options for MKD are based on limited data and include non-steroidal anti-inflammatory drugs, corticosteroids, and biological agents that target specific cytokine pathways. In recent years, some studies have reported promising results for new biological drugs; however, these cases have failed to achieve satisfactory remission. Therefore, further studies are needed to understand the

pathogenesis of MKD and identify innovative therapeutic tools for its management.

DOI: 10.1177/039463201402700404

PMID: 25572728 [Indexed for MEDLINE]

1779. Clin Exp Rheumatol. 2015 Nov-Dec;33(6 Suppl 94):S169. Epub 2015 Jan 9.

Remission of nephrotic syndrome due to AA-amyloidosis, complicating familial Mediterranean fever, with tocilizumab.

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PMID: 25572486 [Indexed for MEDLINE]

1780. Iran J Pediatr. 2014 Jun;24(3):229-40.

Periodic Fever: A Review on Clinical, Management and Guideline for Iranian Patients - Part II.

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Periodic fever syndromes are a group of diseases characterized by episodes of fever with healthy intervals between febrile episodes. In the first part of this paper, we presented a guideline for approaching patients with periodic fever and reviewed two common disorders with periodic fever in Iranian patients including familial Mediterranean fever (FMF) and periodic fever syndromes except for periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA). In this part, we review other autoinflammatory disorders including hyper IgD, tumor necrosis factor receptor-associated periodic syndrome (TRAPS), cryopyrin associated periodic syndromes, autoinflammatory bone disorders and some other rare autoinflammatory disorders such as Sweet's and Blau syndromes. In cryopyrin associated periodic syndromes group, we discussed chronic infantile neurologic cutaneous and articular (CINCA) syndrome, Muckle-Wells syndrome and familial cold autoinflammatory syndrome. Autoinflammatory bone disorders are categorized to monogenic disorders such as pyogenic arthritis, pyoderma gangraenosa and acne (PAPA) syndrome, the deficiency of interleukin-1 receptor antagonist (DIRA) and Majeed syndrome and polygenic background or sporadic group such as chronic recurrent multifocal osteomyelitis (CRMO) or synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome are classified in sporadic group. Other autoinflammatory syndromes are rare causes of periodic fever in Iranian system registry.

PMCID: PMC4276575

PMID: 25562014

1781. Arch Rheumatol. 2015 Jan 6;31(2):192-193. doi: 10.5606/ArchRheumatol.2016.5819. eCollection 2016 Jun.

The Frequency of Ankylosing Spondylitis Among Patients With Familial Mediterranean Fever and the Relationship With M694V Mutation.

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DOI: 10.5606/ArchRheumatol.2016.5819

PMCID: PMC5827839

PMID: 29900951

Conflict of interest statement: Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

1782. Am J Med. 2015 May;128(5):461-70. doi: 10.1016/j.amjmed.2014.12.010. Epub 2014 Dec 30.

Colchicine: old and new.

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Comment in

Am J Med. 2015 Aug;128(8):e11.

Am J Med. 2015 Aug;128(8):e13.

Although colchicine has been a focus of research, debate, and controversy for thousands of years, the US Food and Drug Administration just approved it in 2009. Over the past decade, advances in the knowledge of colchicine pharmacology, drug safety, and mechanisms of action have led to changes in colchicine dosing and to potential new uses for this very old drug. In this review, we discuss the pharmacologic properties of colchicine and summarize what is currently known about its mechanisms of action. We then discuss and update the use of colchicine in a variety of illnesses, including rheumatic and, most recently, cardiovascular diseases.

Published by Elsevier Inc.

DOI: 10.1016/j.amjmed.2014.12.010

PMCID: PMC4684410

PMID: 25554368 [Indexed for MEDLINE]

1783. Anatol J Cardiol. 2015 Aug;15(8):663-8. doi: 10.5152/akd.2014.5544. Epub 2014 Aug 19.

Assessment of left ventricular functions with tissue Doppler, strain, and strain rate echocardiography in patients with familial Mediterranean fever.

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Comment in

Anatol J Cardiol. 2015 Aug;15(8):669-70.

**OBJECTIVE:** This study assessed the early changes in regional and global systolic and diastolic myocardial functions in patients with familial Mediterranean fever without any cardiovascular symptoms using tissue Doppler and strain and strain rate echocardiography and compared them to the results of a control group.

**METHODS:** This study has a cross-sectional and observational design. FMF patients with normal left ventricular function were included in the study. We excluded

patients who had arrhythmia, acquired/congenital heart disease, pericarditis, or acute attack. We compared 45 children with familial Mediterranean fever on colchicine therapy and 45 age- and sex-matched healthy children.

**RESULTS:** The 45 patients with familial Mediterranean fever included 24 (55.3%) girls and 21 (46.7%) boys with a mean age of  $11.3 \pm 3.7$  (range 2-18) years. The mean disease duration was  $4.6 \pm 2.4$  (range 0.5-10) years. In the patient group, the homozygous M694V mutation was the most common (64.4%) mutation. The patients with familial Mediterranean fever had statistically lower longitudinal global strain, radial global strain, and strain rates ( $-14.44 \pm 4.77\%$ ,  $14.80 \pm 6.29\%$ , and  $0.59 \pm 0.24$  s, respectively) than the controls ( $-17.40 \pm 1.79\%$ ,  $17.53 \pm 4.63\%$ , and  $0.83 \pm 0.51$  s) ( $p < 0.05$ ). The circumferential global strain did not differ significantly between the groups.

**CONCLUSION:** Patients with familial Mediterranean fever who are subclinical from a cardiac aspect might have normal left ventricular function as measured by conventional echocardiography. However, the disease affects their myocardial tissue, and these patients should be followed with conventional, strain, and strain rate echocardiography techniques regularly.

DOI: 10.5152/akd.2014.5544

PMCID: PMC5336868

PMID: 25550179 [Indexed for MEDLINE]

1784. Immunol Res. 2015 Mar;61(3):326-37. doi: 10.1007/s12026-014-8615-z.

Intravenous immunoglobulins (IVIG) in systemic sclerosis: a challenging yet promising future.

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The etiology and pathogenesis of systemic sclerosis are still largely unknown, but a variety of humoral and cellular autoimmune phenomena have been documented. In addition, the rarity of the disease, the broad spectrum of clinical



manifestations, and the relevant risk of severe complications as well as the highly variable disease course render its management a major challenge. Some immunomodulatory agents have been used, but no single agent has given a convincing proof of effectiveness, and treatment has remained largely symptomatic through recent years. Novel therapies are currently being tested and may have the potential of modifying the disease process and overall clinical outcome. Efficacy of intravenous immunoglobulins (IVIG) in different regimens (1-2 g/kg of body weight, administered over 2-5 consecutive days) has been described in a limited number of trials and small case series, showing benefits in skin, articular, and lung interstitial disease symptoms. However, studies on IVIG in systemic sclerosis still remain few, and further randomized controlled trials should be undertaken to assess their clinical effectiveness or define the optimal dosage and times of administration.

DOI: 10.1007/s12026-014-8615-z

PMID: 25550086 [Indexed for MEDLINE]

1785. Iran J Immunol. 2014 Dec;11(4):282-91. doi: IJlv11i4A7.

Distribution of primary immunodeficiency disorders diagnosed in a tertiary referral center, Tehran, Iran (2006-2013).

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**BACKGROUND:** Primary immunodeficiency disorders (PID) are a group of hereditary disorders characterized by an increased susceptibility to severe and recurrent infections, autoimmunity, lymphoproliferative disorders, and malignancy.

**OBJECTIVE:** To evaluate the demographic and clinical data of PID patients diagnosed in a referral pediatric hospital.

**METHOD:** All PID cases with a confirmed diagnosis, according to the criteria of International Union of Immunological Societies, who were referred to the Children's Medical Center in Tehran, Iran, between March 2006 and March 2013 were enrolled in this retrospective cohort study.

RESULTS: Three-hundred and seven PID patients were investigated. Predominantly antibody deficiencies were the most common group of PID observed in 118 cases (38.4%), followed by the well-defined syndromes with immunodeficiency in 52 (16.9%), congenital defects of phagocyte in 45 (14.7%), combined immunodeficiencies in 36 (11.7%), autoinflammatory disorders in 34 (11.4%), immune dysregulation in 11 (3.6%), complement deficiencies in 7 (2.3%), and defects in innate immunity in 3 (1%). Selective IgA deficiency was the most prevalent disorder which affected 46 individuals (14.9%). The median diagnostic delay was 15 months.

CONCLUSION: Increased awareness and availability of diagnostic tests could result in the better recognition of more undiagnosed PID cases and a decrease in diagnostic delay.

DOI: IJlv11i4A7

PMID: 25549596 [Indexed for MEDLINE]

1786. J Nephropharmacol. 2015 Jan 1;4(1):5-8. eCollection 2015.

Familial Mediterranean fever; diagnosis, treatment, and complications.

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PMCID: PMC5297479

PMID: 28197466

1787. Temperature (Austin). 2015 Feb 3;2(1):1-7. doi: 10.1080/23328940.2014.995569. eCollection 2015 Jan-Mar.

30 years hids-Travels between bedside and bench.

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In this paper I describe more than 30 years of investigations of the autoinflammatory syndrome hyper-IgD syndrome (HIDS). In the first paper after the recognition of the syndrome published in 1984, we described the characteristics of this periodic fever syndrome. The hypotheses regarding the pathogenesis of the fever and the acute phase response in these patients prompted us to study interleukin-1 (IL-1), the cytokine formerly described as endogenous pyrogen and lymphocyte activating factor. Although we were unable to find elevated concentrations of IL-1 in the circulation, we discovered that white blood cells spontaneously produced elevated amounts of IL-1 $\beta$ . A major next discovery was the identification of the gene defect by us and others in 1999: quite unexpectedly the mevalonate kinase, an enzyme in the cholesterol synthesis pathway was found to be mutated. We were able to describe a founder effect and a phenotypic continuum with the classical mevalonate aciduria in the years to follow. A major step forward was the finding that recombinant interleukin-1 receptor antagonist (anakinra) was an effective treatment for the majority of patients. Thus, research over a period of three decades after the first recognition of the syndrome, has yielded much insight into the pathogenesis as well as an effective therapy for HIDS.

DOI: 10.1080/23328940.2014.995569

PMCID: PMC4843863

PMID: 27226995

1788. F1000Res. 2015 Nov 19;4. pii: F1000 Faculty Rev-1297. doi: 10.12688/f1000research.7046.1. eCollection 2015.

Post-translational control of RIPK3 and MLKL mediated necroptotic cell death.

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Several programmed lytic and necrotic-like cell death mechanisms have now been uncovered, including the recently described receptor interacting protein kinase-3 (RIPK3)-mixed lineage kinase domain-like (MLKL)-dependent necroptosis pathway. Genetic experiments have shown that programmed necrosis, including necroptosis, can play a pivotal role in regulating host-resistance against microbial infections. Alternatively, excess or unwarranted necroptosis may be pathological in autoimmune and autoinflammatory diseases. This review highlights the recent advances in our understanding of the post-translational control of RIPK3-MLKL necroptotic signaling. We discuss the critical function of phosphorylation in the execution of necroptosis, and highlight the emerging regulatory roles for several ubiquitin ligases and deubiquitinating enzymes. Finally, based on current evidence, we discuss the potential mechanisms by which the essential, and possibly terminal, necroptotic effector, MLKL, triggers the disruption of cellular membranes to cause cell lysis.

DOI: 10.12688/f1000research.7046.1

PMCID: PMC4851234

PMID: 27158445

1789. Mol Med. 2014 Dec 16;20 Suppl 1:S7-9. doi: 10.2119/molmed.2014.00168.

TNF antagonists opened the way to personalized medicine in rheumatoid arthritis.

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Rheumatoid arthritis (RA) is an autoimmune disease resulting from a largely unknown interaction between genetically determined and environmental factors. Progress in the understanding of this chronic inflammation in the synovial lining of joints has led to the insight that one cytokine, tumor necrosis factor (TNF), has an important role. This insight started the development of a series of targeted and highly effective therapeutics for RA and a range of other autoinflammatory diseases. RA has changed from a severely debilitating disease into a disease where progression can be stopped in most of the patients.

DOI: 10.2119/molmed.2014.00168

PMCID: PMC4374517

PMID: 25549234 [Indexed for MEDLINE]

1790. Mol Med. 2014 Dec 16;20 Suppl 1:S43-58. doi: 10.2119/molmed.2014.00232.

An expanding role for interleukin-1 blockade from gout to cancer.

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There is an expanding role for interleukin (IL)-1 in diseases from gout to cancer. More than any other cytokine family, the IL-1 family is closely linked to innate inflammatory and immune responses. This linkage is because the cytoplasmic segment of all members of the IL-1 family of receptors contains a domain, which is highly homologous to the cytoplasmic domains of all toll-like receptors (TLRs). This domain, termed "toll IL-1 receptor (TIR) domain," signals as does the IL-1 receptors; therefore, inflammation due to the TLR and the IL-1 families is nearly the same. Fundamental responses such as the induction of cyclo-oxygenase type 2, increased surface expression of cellular adhesion molecules and increased gene expression of a broad number of inflammatory molecules characterizes IL-1 signal transduction as it does for TLR agonists. IL-1 $\beta$  is the most studied member of the IL-1 family because of its role in mediating autoinflammatory disease. However, a role for IL-1 $\alpha$  in disease is being validated because of the availability of a neutralizing monoclonal antibody to human IL-1 $\alpha$ . There are presently three approved therapies for blocking IL-1 activity. Anakinra is a recombinant form of the naturally occurring IL-1 receptor antagonist, which binds to the IL-1 receptor and prevents the binding of IL-1 $\beta$  as well as IL-1 $\alpha$ . Rilonacept is a soluble decoy receptor that neutralizes primarily IL-1 $\beta$  but also IL-1 $\alpha$ . Canakinumab is a human monoclonal antibody that neutralizes only IL-1 $\beta$ . Thus, a causal or significant contributing role can be established for IL-1 $\beta$  and IL-1 $\alpha$  in human disease.

DOI: 10.2119/molmed.2014.00232  
PMCID: PMC4374514  
PMID: 25549233 [Indexed for MEDLINE]

1791. Medicine (Baltimore). 2014 Dec;93(29):e351. doi: 10.1097/MD.0000000000000351.

Lupus erythematosus and neutrophilic urticarial dermatosis: a retrospective study of 7 patients.

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Neutrophilic urticarial dermatosis (NUD) resembles urticaria clinically but is a neutrophilic dermatosis histopathologically. The majority of patients with NUD have an underlying systemic condition, mainly, autoinflammatory disorders such as cryopyrin-associated periodic syndromes, Schnitzler syndrome, and adult-onset Still disease, but a few also have systemic lupus erythematosus (LE). Here, we confirm these data and we report relevant clinical and histopathological data of 7 patients with LE and NUD. We retrospectively retrieved the medical records of all patients with LE in whom skin biopsy showed NUD in registers of Strasbourg and Montpellier University hospitals since 2000. All were female and aged between 13 and 45 years. Skin lesions were typically rose or red macules or slightly elevated papules occurring in a wide distribution. Individual lesions resolved within 24 hours and were not or only slightly itchy. Every patient had associated signs, most of the time polyarthritis and/or fever. NUD was the presenting mode of LE in 2 patients. NUD was misdiagnosed as a classic lupus flare and led to therapeutic intensification with the introduction of immunosuppressive drugs in 4 patients. Histopathological findings consisted of intense neutrophilic interstitial and perivascular infiltrate with leukocytoclasia and without fibrinoid necrosis of vessel walls. Direct immunofluorescence testing showed a lupus band in 4 patients. Antinuclear antibodies were always positive, anti-dsDNA antibodies were positive in 5 patients, and anti-Ro/SSA antibodies in 6 patients.

Immunosuppressive drugs such as prednisone, hydroxychloroquine, mycophenolate mofetil, and methotrexate were never effective to treat NUD. Antihistamines were effective in 1 patient and dapsone or colchicine was effective in 5 patients. NUD is not exceptional in patients with systemic LE and is easily misdiagnosed as an acute LE flare. Furthermore, we show that conventional immunosuppressive LE treatments are not efficient and we underline the major interest of dapsone and colchicine, classic neutrophil migration inhibitors, in those patients.

DOI: 10.1097/MD.0000000000000351

PMCID: PMC4602611

PMID: 25546692 [Indexed for MEDLINE]

1792. Medicine (Baltimore). 2014 Dec;93(29):e346. doi: 10.1097/MD.0000000000000346.

Neutrophilic skin lesions in autoimmune connective tissue diseases: nine cases and a literature review.

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The pathophysiology of neutrophilic dermatoses (NDs) and autoimmune connective tissue diseases (AICTDs) is incompletely understood. The association between NDs and AICTDs is rare; recently, however, a distinctive subset of cutaneous lupus erythematosus (LE, the prototypical AICTD) with neutrophilic histological features has been proposed to be included in the spectrum of lupus. The aim of our study was to test the validity of such a classification. We conducted a monocentric retrospective study of 7028 AICTDs patients. Among these 7028 patients, a skin biopsy was performed in 932 cases with mainly neutrophilic infiltrate on histology in 9 cases. Combining our 9 cases and an exhaustive literature review, pyoderma gangrenosum, Sweet syndrome (n = 49), Sweet-like ND (n = 13), neutrophilic urticarial dermatosis (n = 6), palisaded neutrophilic granulomatous dermatitis (n = 12), and histiocytoid neutrophilic dermatitis (n = 2) were likely to occur both in AICTDs and autoinflammatory diseases. Other NDs

were specifically encountered in AICTDs: bullous LE (n = 71), amicrobial pustulosis of the folds (n = 28), autoimmunity-related ND (n = 24), ND resembling erythema gyratum repens (n = 1), and neutrophilic annular erythema (n = 1). The improvement of AICTDS neutrophilic lesions under neutrophil targeting therapy suggests possible common physiopathological pathways between NDs and AICTDs.

DOI: 10.1097/MD.0000000000000346

PMCID: PMC4602621

PMID: 25546688 [Indexed for MEDLINE]

1793. Medicina (Kaunas). 2014;50(6):329-33. doi: 10.1016/j.medici.2014.11.009. Epub 2014 Nov 28.

Atherogenic index as a predictor of atherosclerosis in subjects with familial Mediterranean fever.

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**BACKGROUND AND OBJECTIVE:** Numerous inflammatory and innate immune pathways are involved in atherogenesis. We aimed to investigate the atherogenic index and other lipid parameters in individuals with familial Mediterranean fever (FMF), as a predictor of atherosclerosis.

**MATERIALS AND METHODS:** A total of 60 patients with FMF and 60 healthy age- and



sex-matched controls were included in this study. The patients with acute infection, chronic metabolic and rheumatic diseases, use of drugs other than colchicine and smoking history were excluded. CRP, ESR, total cholesterol, triglycerides, LDL-C, and HDL-C levels of patients and the control group were measured. Atherogenic index (TG/HDL-C) was calculated.

RESULTS: We found that the atherogenic index values of the patients were significantly higher than those of the control group. HDL-C levels were lower and ESR and TG levels were higher in patients. Total cholesterol, LDL-C and CRP levels did not differ significantly between the two groups. There was no significant difference in the values of total cholesterol, LDL-C, triglycerides (TG), HDL-C, and atherogenic indexes between the groups of patients with and without M694V mutation.

CONCLUSIONS: Elaboration of clinical models of inflammation-induced atherogenesis may further advance our knowledge of multiple inflammatory pathways implicated in atherogenesis and provide a useful tool for cardiovascular prevention. We believe that the atherogenic index also be used as a preliminary indication of accelerated atherosclerosis in FMF. However, large-scale prospective studies on this issue are needed.

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DOI: 10.1016/j.medici.2014.11.009

PMID: 25541265 [Indexed for MEDLINE]

1794. Ann Dermatol Venereol. 2014 Nov;141 Suppl 3:S580-5. doi: 10.1016/S0151-9638(14)70161-9.

[Systemic urticaria in 2014].

[Article in French]

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Systemic urticaria are defined as urticaria, most often chronic, associated with systemic diseases. At present time, urticarial vasculitis and neutrophilic urticarial dermatosis associated to autoinflammatory syndromes are not considered to be subtypes of chronic spontaneous urticaria due to their distinctly clinical and histological characteristics as well different pathomechanisms. Sometimes, chronic urticaria is associated to thyroid autoimmunity. However, the majority of cases of chronic spontaneous urticaria have no discernible cause and further investigations are not necessary, as already suggested by some authors and French consensus conference more than 10 years ago.

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DOI: 10.1016/S0151-9638(14)70161-9

PMID: 25539679 [Indexed for MEDLINE]

1795. J Res Med Sci. 2014 Oct;19(10):1009-11.

Vasculitis and long standing ankylosing spondylitis in a patient with familial Mediterranean fever.

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Coexistence of familial Mediterranean fever (FMF) and other inflammatory disorders has been frequently reported, but no specific underlying factor has been identified. We report a patient with FMF who is presented with long-standing ankylosing spondylitis (AS) and cutaneous leukocytoclastic vasculitis (LV) of the lower limbs. It is the first report on combination of FMF with AS and LV. The Mediterranean Fever (MEFV) gene mutation of heterozygote (R202Q/R726A) and HLA-B27 are detected in this case, and are believed to form genetic susceptibility to LV.

PMCID: PMC4274560

PMID: 25538787

1796. Turk J Med Sci. 2014;44(2):203-7.

MEFV mutation frequency and effect on disease severity in ankylosing spondylitis.

Maraş Y, Akdoğan A, Kisacik B, Kiliç L, Yilmaz E, Tufan A, Kalyoncu U, Apraş Bilgen ŞŞ, Kiraz S, Ertenli Aİ, Çalgüneri M.

**BACKGROUND/AIM:** To define the frequency of familial Mediterranean fever gene (MEFV) mutations in ankylosing spondylitis (AS) and describe different clinical aspects of MEFV mutation carrier and noncarrier AS patients.

**MATERIALS AND METHODS:** In 112 AS patients, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) scores were calculated. The frequencies of 12 different MEFV mutations were studied by multiplex polymerase chain reaction/reverse hybridization method and were compared to those of previously studied healthy controls for 5 common MEFV mutations.

**RESULTS:** MEFV mutations were identified in 46 of 224 (20%) alleles and in 39 (35%) of AS patients. The distribution of mutations was: M694V, 30% (14); E148Q, 30% (14); P369S, 17% (8); V726A, 13% (6); A744S, 8% (4); and K695R, 2% (1). There were no significant differences between MEFV mutation carriers and noncarriers with respect to sex, age of symptom onset, disease duration, peripheral joint involvement, acute phase reactant levels, and BASDAI and BASFI scores ( $P > 0.05$  all). MEFV mutation allelic frequency was not different between AS patients and healthy controls after adjusting for mutations studied (34/224 versus 22/200;  $P > 0.05$ ).

**CONCLUSION:** Although we did not find significant clinical and laboratory differences between MEFV mutation carrier and noncarrier AS patients, further investigations are needed to define the impact of MEFV mutations on AS disease course.

PMID: 25536725 [Indexed for MEDLINE]

1797. Pediatrics. 2015 Jan;135(1):e211-5. doi: 10.1542/peds.2014-2553. Epub 2014 Dec 22.

Long-term outcome of a successful cord blood stem cell transplant in mevalonate kinase deficiency.

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Mevalonate kinase deficiency (MKD) is a rare autosomal recessive inborn error of metabolism with an autoinflammatory phenotype that may be expressed as a spectrum of disease phenotypes, from those with prevailing autoinflammatory syndrome and variable response to anti-inflammatory therapies, to mevalonic aciduria, which is associated with dysmorphic features, severe neurologic involvement, and the worst prognosis. We describe a boy, aged 2 years, 10 months, with severe phenotype of mevalonate kinase deficiency who underwent allogeneic hematopoietic stem cell transplantation (HSCT) from HLA-identical unrelated cord blood because his condition had failed to improve with antiinflammatory treatment as first-line therapy and an anticytokine drug as second-line therapy. The child had a sustained remission of febrile attacks and inflammation after transplant, and during a 5-year follow-up period, psychomotor and neurologic development were normal, without signs of underlying disease or late transplant-related effects. This case confirms that allogeneic HSCT is a safe and effective cure for patients affected by MKD in whom anticytokine drugs alone are insufficient for the management of autoinflammatory syndrome and for the unfavorable outcome of the disease.

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DOI: 10.1542/peds.2014-2553

PMID: 25535259 [Indexed for MEDLINE]

1798. Mod Rheumatol. 2015 Jul;25(4):621-4. doi: 10.3109/14397595.2014.987437. Epub 2014 Dec 22.

Interleukin-1 targeting treatment in familial Mediterranean fever: an experience of pediatric patients.

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**OBJECTIVES:** The aim of this report was to evaluate and discuss treatment of pediatric familial Mediterranean fever (FMF) patients with anti-interleukin1 (IL-1) agents.

**METHODS:** Refractory or colchicine unresponsive FMF was described as severe and frequent attacks and/or having high acute phase reactance levels despite having a maximum dose of colchicine (2 mg/day). Disease course, adverse effects, duration of follow-up, treatment protocols, responses to the therapies were discussed.

**RESULTS:** Eight patients (6 male, 2 female) having refractory FMF were identified. Mediterranean fever (MEFV) gene analyses revealed homozygous M694V mutations in six patients and heterozygote M694V mutations in one patient and no mutation in one patient. They were all treated with anakinra and/or canakinumab. The use of anti-IL-1 drugs was beneficial to all patients. None of them had any severe adverse effects due to the therapy.

**CONCLUSIONS:** Anakinra and canakinumab were effective in patient refractory to colchicine treatment as shown both in our series and in the literature.

Therefore, controlled trials are needed to evaluate the safety and long-term efficacy of IL-1 targeting agents in colchicine resistant patients.

DOI: 10.3109/14397595.2014.987437

PMID: 25528863 [Indexed for MEDLINE]

1799. Mod Rheumatol. 2016;26(2):315-7. doi: 10.3109/14397595.2014.988861. Epub 2014 Dec 22.

IL-18 serum concentration is markedly elevated in typical familial Mediterranean fever with M694I mutation and can distinguish it from atypical type.

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DOI: 10.3109/14397595.2014.988861

PMID: 25528861

1800. Int J Rheum Dis. 2015 May;18(4):473-5. doi: 10.1111/1756-185X.12521. Epub 2014 Dec 18.

Delights and let-downs in the management of tumor necrosis factor receptor-associated periodic syndrome: the canakinumab experience in a patient with a high-penetrance T50M TNFRSF1A variant.

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DOI: 10.1111/1756-185X.12521

PMID: 25522898 [Indexed for MEDLINE]

1801. Int J Dermatol. 2015 Feb;54(2):121-9. doi: 10.1111/ijd.12695. Epub 2014 Dec 18.

Proteasome-associated autoinflammatory syndromes: advances in pathogeneses, clinical presentations, diagnosis, and management.

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The disease spectrum currently known as the proteasome-associated autoinflammatory syndromes (PRAAS) was first described in 1939 in patients who presented with recurrent fevers beginning in infancy or early childhood, which were accompanied by nodular erythema, a pernio-like rash, and joint contractures. Since then, several syndromes, such as chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome, Nakajo-Nishimura syndrome (NNS), joint contractures, muscle atrophy, microcytic anemia and panniculitis-induced lipodystrophy (JMP) syndrome, and Japanese autoinflammatory syndrome with lipodystrophy (JASL), have been used to categorize patients with diseases within the same spectrum. Recently, independent studies have identified mutations in the human proteasome subunit  $\beta$  type 8 (PSMB8) gene, which result in a sustained inflammatory response in all syndromes. Further functional studies not only suggest a causative role of PSMB8 mutations but also imply that they represent one disease spectrum, referred to as PRAAS. In this paper, we review the clinical presentations and laboratory findings of PRAAS, as well as the most

recent advances in pathogenesis, diagnosis, and treatment options for patients with diseases in this spectrum.

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DOI: 10.1111/ijd.12695

PMID: 25521013 [Indexed for MEDLINE]

1802. Int J Dermatol. 2015 Jun;54(6):715-22. doi: 10.1111/ijd.12645. Epub 2014 Dec 16.

The Worst Itch Numeric Rating Scale for patients with moderate to severe plaque psoriasis or psoriatic arthritis.

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Plaque psoriasis (PP) and psoriatic arthritis (PsA) are autoinflammatory chronic conditions associated with skin involvement. Pruritus, or itching, is a prevalent and bothersome symptom in patients with PP and is associated with reduced health-related quality of life. The Worst Itch Numeric Rating Scale (WI-NRS) has been developed as a simple, single item with which to assess the patient-reported severity of this symptom at its most intense during the previous 24-hour period. Qualitative research was undertaken to assess the content validity of the WI-NRS. Patients with moderate to severe PP and patients with PsA were recruited from clinical sites in the USA. The qualitative research entailed two-part interviews, which began with concept elicitation to gain understanding of patients' experiences of itching, followed by cognitive debriefing of the WI-NRS to assess the instrument's understandability, clarity, and degree of appropriateness from the patient's perspective. Twelve patients with PP and 22 with PsA participated in the study. Patients reported that itching was an important and relevant symptom of their psoriatic disease. The WI-NRS was reported to be complete and easy to understand; the recall period was considered appropriate, the response scale was familiar, and, overall, the instrument was found to be appropriate for assessing itching severity. Patient responses support the content validity of the WI-NRS. The psychometric properties of the tool will be evaluated in future



studies.

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DOI: 10.1111/ijd.12645

PMID: 25515935 [Indexed for MEDLINE]

1803. J Am Podiatr Med Assoc. 2014 Nov;104(6):583-7. doi: 10.7547/8750-7315-104.6.583.

Chronic recurrent multifocal osteomyelitis: the prevalence of lower-limb and foot involvement.

Ferrari J, Pilkington C.

**BACKGROUND:** Chronic recurrent multifocal osteomyelitis (CRMO) is an autoinflammatory condition. The lesions are reported to present most frequently in the long bones. This study aimed to review the presenting features of CRMO in a cohort of children diagnosed as having CRMO and to compare the level of agreement between the clinical and published diagnostic criteria.

**METHODS:** A case notes review was undertaken of patients with a clinical diagnosis of CRMO. Patients were younger than 16 years at the time of diagnosis. Features were identified in each patient that agreed or disagreed with the published diagnostic criteria. The location of bone lesions in the lower limb at onset and disease progression was recorded.

**RESULTS:** A total of 37 patients were included. There was a high prevalence in white individuals. Agreement with the diagnostic criteria of Jansson et al and El-Shanti and Ferguson was poor, with levels of agreement of 40.5% and 43%, respectively, and low kappa scores ( $\kappa = 0.07$  and  $0.09$ , respectively). The lower limb was affected in 49% of patients at onset and in 72% overall.

**CONCLUSIONS:** This study presents one of the largest published cohorts of pediatric patients with CRMO and also presents racial/ethnic group data that have not previously been reported in other studies. Despite being a condition considered to affect the metaphysis of long bones, the ankle area and foot bones were also frequently affected. The agreement between the clinical diagnosis and the published diagnostic criteria was weak.

DOI: 10.7547/8750-7315-104.6.583

PMID: 25514269 [Indexed for MEDLINE]

1804. Reumatizam. 2014;61(1):23-31.

[Genetic predisposition for various forms of spondyloarthritis].

[Article in Croatian]

Lamot L, Vidović M, Perica M, Bukovac LT, Harjaček M.

In addition to the long-established association of HLA-B27 antigen and spondyloarthritis, several studies have shown a similar association with HLA-B7 antigen. But since the whole MHC region carries less than half of the risk for the development of the disease, the main goal of many recently performed researches, which implemented various high-throughput methods, was to discover the influence of genes outside the MHC region on disease development. The results showed that genes closely linked to spondyloarthritis participate in antigen processing and coding of various cytokines. This can lead to the conclusion that diseases from the spondyloarthritis group are polygenic, affected by both autoinflammatory and autoimmune mechanisms.

PMID: 25509833 [Indexed for MEDLINE]

1805. Rheumatology (Oxford). 2015 Mar;54(3):564-5. doi: 10.1093/rheumatology/keu474. Epub 2014 Dec 11.

Tocilizumab in the treatment of patients with AA amyloidosis secondary to familial Mediterranean fever.

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DOI: 10.1093/rheumatology/keu474

1806. Sports Med. 2015 May;45(5):625-40. doi: 10.1007/s40279-014-0296-1.

Neutrophil extracellular traps: a walk on the wild side of exercise immunology.

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Intense exercise evokes a rapid and transient increase in circulating cell-free DNA (cf-DNA), a phenomenon that is commonly observed in a variety of acute and chronic inflammatory conditions. While the potential value of cf-DNA for the prediction of disease outcome and therapeutic response is well documented, the release mechanisms and biological relevance of cf-DNA have long remained enigmatic. The discovery of neutrophil extracellular traps (NETs) provided a novel mechanistic explanation for increased cf-DNA levels. Now there is increasing evidence that NETs may contribute to cf-DNA in diverse infectious, non-infectious and autoinflammatory conditions, as well as in response to acute exercise. NETs have now been firmly established as a fundamental immune mechanism used by neutrophils to respond to infection and tissue injury. On the other side, aberrant formation of NETs appears to be a driving force in the pathogenesis of autoimmunity and cardiovascular disease. Thus, the emergence of NETs in the 'exercising vasculature' raises important questions considering beneficial effects, as well as occasional adverse effects, of exercise on immune homeostasis. This review gives an overview of the current state of research into the mechanisms of how NETs are released, contribute to host defence and participate in inflammatory disorders. We discuss the impact of exercise-induced NETs, considering a potentially beneficial role in the prevention of lifestyle-related diseases, as well as putative detrimental effects that may arise in elite sports. Finally, we propose that exercise-induced cf-DNA responses could be exploited for diagnostic/prognostic purposes to identify individuals who are at increased risk of cardiovascular events or autoimmunity.

1807. Medicine (Baltimore). 2014 Dec;93(27):e187. doi: 10.1097/MD.0000000000000187.

Association of pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH) shares genetic and cytokine profiles with other autoinflammatory diseases.

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Erratum in

Medicine (Baltimore). 2015 Feb;94(8):1.

Medicine (Baltimore). 2015 Apr;94(15):1.

The association of pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH) has recently been described and suggested to be a new entity within the spectrum of autoinflammatory syndromes, which are characterized by recurrent episodes of sterile inflammation, without circulating autoantibodies and autoreactive T-cells. We conducted an observational study on 5 patients with PASH syndrome, analyzing their clinical features, genetic profile of 10 genes already known to be involved in autoinflammatory diseases (AIDs), and cytokine expression pattern both in lesional skin and serum. In tissue skin samples, the expressions of interleukin (IL)-1 $\beta$  and its receptors I and II were significantly higher in PASH ( $P = 0.028$ ,  $0.047$ , and  $0.050$ , respectively) than in controls. In PASH patients, chemokines such as IL-8 ( $P = 0.004$ ), C-X-C motif ligand (CXCL) 1/2/3 ( $P$

= 0.028), CXCL 16 (P = 0.008), and regulated on activation, normal T cell expressed and secreted (RANTES) (P = 0.005) were overexpressed. Fas/Fas ligand and cluster of differentiation (CD)40/CD40 ligand systems were also overexpressed (P = 0.016 for Fas, P = 0.006 for Fas ligand, P = 0.005 for CD40, and P = 0.004 for CD40 ligand), contributing to tissue damage and inflammation. In peripheral blood, serum levels of the main proinflammatory cytokines, that is, IL-1 $\beta$ , tumor necrosis factor- $\alpha$ , and IL-17, were within the normal range, suggesting that in PASH syndrome, the inflammatory process is mainly localized into the skin. Four out of our 5 PASH patients presented genetic alterations typical of well-known AIDs, including inflammatory bowel diseases, and the only patient lacking genetic changes had clinically evident Crohn disease. In conclusion, overexpression of cytokines/chemokines and molecules amplifying the inflammatory network, along with the genetic changes, supports the view that PASH syndrome is autoinflammatory in origin.

DOI: 10.1097/MD.0000000000000187

PMCID: PMC4602806

PMID: 25501066 [Indexed for MEDLINE]

1808. Intern Med. 2014;53(24):2817-9. Epub 2014 Dec 15.

Protracted febrile myalgia syndrome in a Japanese patient with fasciitis detected on MRI.

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Protracted febrile myalgia syndrome (PFMS) is a rare manifestation of familial Mediterranean fever characterized by prolonged severe myalgia. We herein describe a case of PFMS with fasciitis on magnetic resonance imaging. The response to corticosteroid therapy was prompt, as is typical for PFMS. An MEFV gene analysis revealed the patient to be homozygous for E148Q and compound heterozygous for P369S-R408Q. This is the first case report of a Japanese patient with PFMS. MRI findings may help to diagnose such cases.

PMID: 25500445 [Indexed for MEDLINE]

1809. Autoimmun Rev. 2015 Apr;14(4):332-40. doi: 10.1016/j.autrev.2014.12.003. Epub 2014 Dec 12.

Why treatments do(n't) work in vitiligo: An autoinflammatory perspective.

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Vitiligo is a recalcitrant depigmentary skin disorder with significant effects on the quality of life and a frequent association with other autoimmune disorders. The results of the current therapeutic options remain variable and treatment resistance is often encountered. The mainstay of treatment remains topical corticosteroids, topical calcineurin inhibitors and UVB therapy. In more extensive or progressive cases, systemic corticosteroids are effective although their prolonged use is hampered due to safety concerns. A lot of topical and systemic treatments have been investigated during the last decades. Given the elevated TNF- $\alpha$  levels in vitiligo lesions, the failure and even paradoxal effects of TNF- $\alpha$  inhibitors were highly remarkable. Nonetheless, a lot of progress has been made to unravel the pathophysiology of vitiligo. In this review, we provide an overview of the currently known underlying mechanisms leading to vitiligo and link this to the success or failure of treatments that have been used in clinical trials. We believe that this overview can direct future vitiligo research and rationalise the treatment options.

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DOI: 10.1016/j.autrev.2014.12.003

PMID: 25500433 [Indexed for MEDLINE]

1810. Trends Mol Med. 2015 Mar;21(3):193-201. doi: 10.1016/j.molmed.2014.11.008. Epub 2014 Nov 27.

Mitochondria: diversity in the regulation of the NLRP3 inflammasome.

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Recent studies have identified new roles for mitochondria in the regulation of autoinflammatory processes. Emerging data suggests that the release of danger signals from mitochondria in response to stress and infection promotes the formation of the inflammatory signaling platform known as inflammasomes. Activation of inflammasomes by damaged mitochondria results in caspase-1-dependent secretion of the inflammatory cytokines interleukin-1 $\beta$  (IL-1 $\beta$ ) and IL-18, and an inflammatory form of cell death referred to as pyroptosis. Here, we review recently described mechanisms that have been proposed to be involved in mitochondria-mediated regulation of inflammasome activation and inflammation. In addition, we highlight how aberrant regulation of mitochondria-induced inflammasome activation centrally contributes to the inflammatory process that is responsible for obesity and associated metabolic diseases.

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DOI: 10.1016/j.molmed.2014.11.008

PMCID: PMC4352396

PMID: 25500014 [Indexed for MEDLINE]

1811. Pflugers Arch. 2015 May;467(5):959-72. doi: 10.1007/s00424-014-1664-2. Epub 2014 Dec 9.

## The CNS under pathophysiologic attack--examining the role of K<sub>2</sub>p channels.

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Members of the two-pore domain K(+) channel (K2P) family are increasingly recognized as being potential targets for therapeutic drugs and could play a role in the diagnosis and treatment of neurologic disorders. Their broad and diverse expression pattern in pleiotropic cell types, importance in cellular function, unique biophysical properties, and sensitivity toward pathophysiologic parameters represent the basis for their involvement in disorders of the central nervous system (CNS). This review will focus on multiple sclerosis (MS) and stroke, as there is growing evidence for the involvement of K2P channels in these two major CNS disorders. In MS, TASK1-3 channels are expressed on T lymphocytes and are part of a signaling network regulating Ca(2+)- dependent pathways that are mandatory for T cell activation, differentiation, and effector functions. In addition, TASK1 channels are involved in neurodegeneration, resulting in autoimmune attack of CNS cells. On the blood-brain barrier, TREK1 channels regulate immune cell trafficking under autoinflammatory conditions. Cerebral ischemia shares some pathophysiologic similarities with MS, including hypoxia and extracellular acidosis. On a cellular level, K2P channels can have both proapoptotic and antiapoptotic effects, either promoting neurodegeneration or protecting neurons from ischemic cell death. TASK1 and TREK1 channels have a neuroprotective effect on stroke development, whereas TASK2 channels have a detrimental effect on neuronal survival under ischemic conditions. Future research in preclinical models is needed to provide a more detailed understanding of the contribution of K2P channel family members to neurologic disorders, before translation to the clinic is an option.

DOI: 10.1007/s00424-014-1664-2

PMID: 25482672 [Indexed for MEDLINE]



Increased proteasome activator 28 gamma (PA28 $\gamma$ ) levels are unspecific but correlate with disease activity in rheumatoid arthritis.

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**BACKGROUND:** PA28 $\gamma$  (also known as Ki, REG gamma, PMSE3), a member of the ubiquitin-and ATP-independent proteasome activator family 11S, has been proved to show proteasome-dependent and -independent effects on several proteins including tumor suppressor p53, cyclin-dependent kinase inhibitor p21 and steroid receptor co-activator 3 (SCR-3). Interestingly, PA28 $\gamma$  is overexpressed in pathological tissue of various cancers affecting e. g. breast, bowel and thyroids. Furthermore, anti-PA28 $\gamma$  autoantibodies have been linked to several autoimmune disorders. The aim of this study was to develop and evaluate a novel and sensitive PA28 $\gamma$  sandwich ELISA for the quantification of PA28 $\gamma$  serum levels in patients with cancer and autoimmune diseases for diagnostic and prognostic purposes.

**METHODS:** PA28 $\gamma$ -specific polyclonal antibodies and recombinant His-tagged PA28 $\gamma$  were purified and used to develop a sandwich ELISA for the detection of circulating PA28 $\gamma$ . With this new assay, PA28 $\gamma$  serum levels of patients with various cancers, rheumatoid arthritis (RA), Sjögren's syndrome (SS), adult-onset Still's disease (AOSD) and different connective-tissue diseases (CTD) were compared with healthy control subjects. Anti-PA28 $\gamma$  autoantibodies were additionally confirmed using a newly developed microbead assay.

**RESULTS:** The developed PA28 $\gamma$  sandwich ELISA showed a high specificity with a detection limit of 3 ng/ml. A significant up-regulation of circulating PA28 $\gamma$  was detected in the sera of patients with cancer, RA, SS and CTD. A significant correlation was observed dependent on age as well as anti-PA28 $\gamma$  autoantibody levels with circulating PA28 $\gamma$  protein levels. Furthermore, PA28 $\gamma$  serum levels showed a correlation with disease activity in patients with RA under treatment with the T-cell directed biological compound abatacept according to disease activity score 28 (DAS28) and erythrocyte sedimentation rate (ESR).

**CONCLUSION:** The application of PA28 $\gamma$  as a novel biomarker for diagnostic purposes of a specific disease is limited, since elevated levels were observed in different disorders. However, the correlation with disease activity in patients with RA suggests a prognostic value, which needs to be addressed by further

studies. Therefore our results show that PA28γ is a useful marker which should be included in studies related to novel treatments, e.g. abatacept.

DOI: 10.1186/1471-2474-15-414

PMCID: PMC4295294

PMID: 25482151 [Indexed for MEDLINE]

1813. J Craniofac Surg. 2015 Jan;26(1):186-90. doi: 10.1097/SCS.0000000000001202.

Prevalence of chronic rhinosinusitis in the setting of Behçet disease.

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Behçet disease (BD) is a systemic autoimmune/autoinflammatory, T helper 1-mediated condition. It is well known that the prevalence of a T helper 1-mediated disease increases in the presence of another T helper 1-mediated comorbidity. The purpose of this study was to investigate the prevalence of T helper 1-mediated chronic rhinosinusitis without nasal polyposis (CRSsNP) and T helper 2-mediated chronic rhinosinusitis with polyposis in the presence of comorbid BD. Sixty-nine patients and 74 healthy controls were included in the study. Participants were asked to complete a questionnaire for symptoms of rhinosinusitis. Nasal cavities were scored using the Lund-Kennedy endoscopy scores. Paranasal sinus computed tomography imagings were scored according to Lund-Mackay radiology scores. Skin prick tests were carried out for all participants to determine the predisposing role of allergy (T helper 2 disease) in the etiopathogenesis of rhinosinusitis among patients and controls. Patients' endoscopy, radiology, and skin prick testing scores were evaluated with regard to BD activity. The prevalence of CRSsNP was 23.2 % in BD and 2.7% in normal population. The CRSsNP was more frequently seen in patients than in the healthy

controls ( $P = 0.002$ ). The BD patients displayed worse scores on their left sinonasal endoscopy. No statistically significant difference was seen between BD and control groups with regard to Lund-Mackay radiology scores of both sides. The presence of an allergic response to a specific allergen in skin-prick testing were confirmed in 25 patients (36.2%) and 17 controls (23.0%). However, the difference was not statistically significant. There were positive responses to more allergens when BD activity was reduced. The CRSsNP thought to be of T helper 1-mediated origin was more frequently seen in the presence of comorbid BD.

DOI: 10.1097/SCS.0000000000001202

PMID: 25469896 [Indexed for MEDLINE]

1814. Cytokine Growth Factor Rev. 2015 Jun;26(3):263-80. doi: 10.1016/j.cytogfr.2014.10.001. Epub 2014 Oct 28.

Hemophagocytic lymphohistiocytosis (HLH): A heterogeneous spectrum of cytokine-driven immune disorders.

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Hemophagocytic lymphohistiocytosis (HLH) comprises a group of life-threatening immune disorders classified into primary or secondary HLH. The former is caused by mutations in genes involved in granule-mediated cytotoxicity, the latter occurs in a context of infections, malignancies or autoimmune/autoinflammatory disorders. Both are characterized by systemic inflammation, severe cytokine storms and immune-mediated organ damage. Despite recent advances, the pathogenesis of HLH remains incompletely understood. Animal models resembling

different subtypes of HLH are therefore of great value to study this disease and to uncover novel treatment strategies. In this review, all known animal models of HLH will be discussed, highlighting findings on cell types, cytokines and signaling pathways involved in disease pathogenesis and extrapolating therapeutic implications for the human situation.

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DOI: 10.1016/j.cytogfr.2014.10.001

PMID: 25466631 [Indexed for MEDLINE]

1815. Rev Med Interne. 2015 May;36(5):319-27. doi: 10.1016/j.revmed.2014.10.365. Epub 2014 Nov 5.

[Pathophysiology, subtypes, and treatments of adult-onset Still's disease: An update].

[Article in French]

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Adult-onset Still's disease is a rare and difficult to diagnose multisystemic

disorder considered as a multigenic autoinflammatory syndrome. Its immunopathogenesis seems to be at the crossroads between inflammasomopathies and hemophagocytic lymphohistiocytosis, the most severe manifestation of the disease. According to recent insights in the pathophysiology and thanks to cohort studies and therapeutic trials, two phenotypes of adult-onset Still's disease may be distinguished: a systemic pattern, initially highly symptomatic and with a higher risk to exhibit life-threatening complications such as reactive hemophagocytic lymphohistiocytosis, where interleukin-1 blockade seems to be very effective, a chronic articular pattern, more indolent with arthritis in the foreground and less severe systemic manifestations, which would threat functional outcome and where interleukin-6 blockade seems to be more effective. This review focuses on these data.

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DOI: 10.1016/j.revmed.2014.10.365  
PMID: 25466605 [Indexed for MEDLINE]

1816. Clin Neurol Neurosurg. 2014 Dec;127:158-60. doi: 10.1016/j.clineuro.2014.10.010.  
Epub 2014 Oct 18.

A rare coincidence of torticollis in Familial Mediterranean Fever: atlanto-axial rotatory subluxation.

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DOI: 10.1016/j.clineuro.2014.10.010  
PMID: 25459264 [Indexed for MEDLINE]

1817. Curr Opin Immunol. 2014 Dec;31:121-6. doi: 10.1016/j.coi.2014.10.009. Epub 2014 Nov 4.

Self-DNA, STING-dependent signaling and the origins of autoinflammatory disease.

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Self-DNA has long been considered a key cause of inflammatory and autoimmune disease, although the exact origin and general mechanisms of action have remained to be elucidated. Recently, new insight has been gained into our understanding of those innate immune pathways and sensors that are responsible for instigating self-DNA triggered autoinflammatory events in the cell. One such sensor referred to as STING (for stimulator of interferon genes) has been found to be seminal for controlling cytosolic-DNA induced cytokine production, and may be responsible for a wide variety of inflammatory diseases including systemic lupus erythematosus (SLE), Aicardi-Goutieres syndrome (AGS) and STING-associated vasculopathy with onset of infancy (SAVI). STING may also be involved with augmenting certain types of carcinogen induced cancer. Aside from generating valuable information into mechanisms underlining innate immune gene regulation, these findings offer new opportunities to generate innovative therapeutics which may help treat such diseases.

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DOI: 10.1016/j.coi.2014.10.009

PMID: 25459004 [Indexed for MEDLINE]

1818. J Allergy Clin Immunol. 2015 Apr;135(4):1067-70.e9. doi: 10.1016/j.jaci.2014.09.043. Epub 2014 Nov 12.

IL36RN mutations define a severe autoinflammatory phenotype of generalized pustular psoriasis.

Hussain S(1), Berki DM(1), Choon SE(2), Burden AD(3), Allen MH(1), Arostegui JI(4), Chaves A(5), Duckworth M(1), Irvine AD(6), Mockenhaupt M(7), Navarini AA(8), Seyger MM(9), Soler-Palacin P(10), Prins C(11), Valeyrie-Allanore L(12), Vicente MA(13), Trembath RC(14), Smith CH(1), Barker JN(15), Capon F(16).

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DOI: 10.1016/j.jaci.2014.09.043

PMID: 25458002 [Indexed for MEDLINE]

1819. Immunol Lett. 2014 Dec;162(2 Pt B):150-62. doi: 10.1016/j.imlet.2014.10.013. Epub 2014 Oct 19.

Autoimmunity: break-through in the diagnosis and treatment of immune-mediated inflammatory diseases.

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The study of fundamental mechanisms of autoimmunity has been instrumental to clinical progress in the diagnosis and treatment of a range of immune-mediated inflammatory disorders. Dutch immunology has made major contributions to these developments, ranging from fundamental studies on immune cells, antibodies and cytokines to translational and clinical studies with targeted therapies in patients. In this paper we illustrate the progress made in our understanding of autoimmunity and the translational implications for human disease management by focusing on three areas: the autoantibody response in rheumatoid arthritis (RA), T-B cell interactions in Sjögren's syndrome (SS), and cytokine targeting in spondylarthritis (SpA).

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DOI: 10.1016/j.imlet.2014.10.013

PMID: 25455603 [Indexed for MEDLINE]

1820. Trends Cardiovasc Med. 2015 Feb;25(2):129-36. doi: 10.1016/j.tcm.2014.09.011. Epub 2014 Oct 2.



Colchicine for pericarditis.

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Comment in

Trends Cardiovasc Med. 2015 Feb;25(2):137-9.

Colchicine is one of the oldest available drugs. It has been used for centuries to treat and prevent gouty attacks and more recently to prevent attacks of autoinflammatory diseases such as Familial Mediterranean Fever. Its main mechanism of action is the capability to block the polymerization of tubulin, thus affecting the function of microtubules. The capability to concentrate in white blood cells, especially granulocytes, and interfere with their function explains its potentiality as an anti-inflammatory drug. Colchicine (0.5mg twice daily for patients >70kg or once daily for those weighing less) in addition to standard anti-inflammatory therapy, in either acute or recurrent pericarditis, may hasten the response to anti-inflammatory therapy and reduce the subsequent risk of recurrences. After exclusion of contraindication and appropriate dose adjustment, the drug is safe and well tolerated. The more common side effect is gastrointestinal intolerance occurring in 5-10% of cases and may be controlled by dose reduction or temporary discontinuation.

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DOI: 10.1016/j.tcm.2014.09.011

PMID: 25454379 [Indexed for MEDLINE]

1821. Gastroenterology. 2015 Jan;148(1):24-5. doi: 10.1053/j.gastro.2014.08.006. Epub 2014 Nov 21.

Recurrent abdominal pain accompanied by small intestinal lesions.

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DOI: 10.1053/j.gastro.2014.08.006

PMID: 25450071 [Indexed for MEDLINE]

1822. *Microbes Infect.* 2014 Dec;16(12):998-1001. doi: 10.1016/j.micinf.2014.10.002. Epub 2014 Oct 18.

The STING controlled cytosolic-DNA activated innate immune pathway and microbial disease.

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The innate immune system is critically important for the primary sensing of invading pathogens. Over the past decade, the cellular sensors important for recognizing microbial entry into the host cell have been largely elucidated. These sensors, some of which are evolutionarily conserved, include the Toll-like receptor (TLR) and RIG-I-like helicase family (RLH) pathway that can recognize bacterial and viral non-self nucleic acid. In addition, a cellular sensor referred to as STING (for stimulator of interferon genes) has been shown to be critical for triggering host defense countermeasures, including stimulation of the adaptive immune response, following the detection of cytosolic DNA species. The STING pathway has now been shown to be critical for activating innate immune gene transcription in response to infection by DNA pathogens such as herpes simplex virus 1 (HSV1) as well as retroviruses. In addition, it is clear that chronic STING activation can also cause autoinflammatory disease manifested by self-DNA. Here we review recent developments in our understanding of STING function, including importance in the control of microbial disease.

DOI: 10.1016/j.micinf.2014.10.002

PMCID: PMC4845094

PMID: 25449752 [Indexed for MEDLINE]

1823. Eur J Med Genet. 2015 Jan;58(1):31-4. doi: 10.1016/j.ejmg.2014.10.005. Epub 2014 Nov 4.

A study of familial Mediterranean Fever (MEFV) gene mutations in Egyptian children with type 1 diabetes mellitus.

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**BACKGROUND/AIMS:** An association of type 1 DM and familial Mediterranean fever (FMF) has been newly reported in the medical literature. The aim of the present work was to investigate frequency of MEFV gene mutations in Egyptian children with type 1 diabetes mellitus.

**METHODS:** Forty five children with type 1 DM were screened for Mediterranean Fever (MEFV) gene mutation. Forty one healthy control subjects were included.

Identification of FMF gene mutation was done based on polymerase chain reaction (PCR) and reverse hybridization. The assay covers 12 mutations in the FMF gene: E148Q - P369S - F479L - M680I (G/C) - M680I (G/A) - I692del - M694V - M694I - K695R-V726A - A744S and R761H.

**RESULTS:** Among the screened diabetics, the overall frequency of MEFV gene mutations was 42.2% and among the control group it was 34.1% with no significant difference. Fourteen out of 45 diabetic children (31.1%) were heterozygous (E148Q

in 7 children, A744S in 3 children, V726A in 2 children, M680I (G/C) in 1 child and P369S in 1 child), while 5 children (11.1%) were compound heterozygous (M694V/M694I in 2 children, E148Q/K695R mutations in 1 child, E148Q/M694I in 1 child and E148Q/V726A in 1 child). The control group showed heterozygous mutation in 34.1% of cases (E148Q mutation in 14.6%, V726A in 12.2%, M680I (G/C) in 4.9% and M694V in 2.4%).

CONCLUSION: No significant difference in mutation frequency between diabetic and non-diabetic children. We have high carrier rate of MEFV gene mutations among Egyptian population probably due to high consanguinity.

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DOI: 10.1016/j.ejmg.2014.10.005

PMID: 25449140 [Indexed for MEDLINE]

1824. Curr Allergy Asthma Rep. 2015 Jan;15(1):489. doi: 10.1007/s11882-014-0489-6.

Update on ankylosing spondylitis: current concepts in pathogenesis.

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Ankylosing spondylitis is an insidiously progressive and debilitating form of arthritis involving the axial skeleton. The long delay in diagnosis and insufficient response to currently available therapeutics both advocate for a greater understanding of disease pathogenesis. Genome-wide association studies of this highly genetic disease have implicated specific immune pathways, including the interleukin (IL)-17/IL-23 pathway, control of nuclear factor kappa B (NF- $\kappa$ B) activation, amino acid trimming for major histocompatibility complex (MHC) antigen presentation, and other genes controlling CD8 and CD4 T cell subsets. The relevance of these pathways has borne out in animal and human subject studies, in particular, the response to novel therapeutic agents. Genetics and the findings of autoantibodies in ankylosing spondylitis revisit the question of autoimmune

vs. autoinflammatory etiology. As environmental partners to genetics, recent attention has focused on the roles of microbiota and biomechanical stress in initiating and perpetuating inflammation. Herein, we review these current developments in the investigation of ankylosing spondylitis pathogenesis.

DOI: 10.1007/s11882-014-0489-6

PMID: 25447326 [Indexed for MEDLINE]

1825. Isr Med Assoc J. 2014 Oct;16(10):659-61.

Cryopyrin-associated periodic syndrome.

Giat E, Lidar M.

CAPS is a rare autoinflammatory disease associated with mutations in the NLRP3 gene that result in overactivation of the inflammasome, increased secretion of IL-1 $\beta$  and IL-18, and systemic inflammation. Genetic testing has allowed for grouping of the three, previously distinct clinical syndromes of FCAS, MWS and NOMID, into a single syndrome termed CAPS. The clinical features include urticarial rash and fever, CNS and musculoskeletal involvement, ocular disorders and progressive deafness. Onset, severity and complications (mainly retardation, seizures, destructive arthropathy and amyloidosis) depend on the specific mutation. Diagnosis is determined by genetic tests but is often delayed due to lack of awareness. In Israel, the relative abundance of other autoinflammatory disorders (FMF, Behçet's disease) may result in misdiagnosis. Treatment is based on IL-1 antagonism, which usually results in prompt clinical response and may prevent amyloidosis.

PMID: 25438464 [Indexed for MEDLINE]

1826. Isr Med Assoc J. 2014 Oct;16(10):608-10.

The body against self: autoinflammation and autoimmunity.

Borella E, Palma L, Zen M, Bettio S, Nalotto L, Gatto M, Domeneghetti M, Laccarino L, Punzi L, Doria A.

PMID: 25438443 [Indexed for MEDLINE]

1827. Cell Rep. 2014 Nov 6;9(3):910-7. doi: 10.1016/j.celrep.2014.10.003. Epub 2014 Oct 30.

Granzyme A produces bioactive IL-1 $\beta$  through a nonapoptotic inflammasome-independent pathway.

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Bacterial components are recognized by the immune system through activation of the inflammasome, eventually causing processing of the proinflammatory cytokine interleukin-1 $\beta$  (IL-1 $\beta$ ), a pleiotropic cytokine and one of the most important mediators of inflammation, through the protease caspase-1. Synthesis of the precursor protein and processing into its bioactive form are tightly regulated, given that disturbed control of IL-1 $\beta$  release can cause severe autoinflammatory diseases or contribute to cancer development. We show that the bacterial *Pasteurella multocida* toxin (PMT) triggers IL1 $\beta$  gene transcription in macrophages independently of Toll-like receptor signaling through RhoA/Rho-kinase-mediated

NF- $\kappa$ B activation. Furthermore, PMT mediates signal transducer and activator of transcription (STAT) protein-controlled granzyme A (a serine protease) expression in macrophages. The exocytosed granzyme A enters target cells and mediates IL-1 $\beta$  maturation independently of caspase-1 and without inducing cytotoxicity. These findings show that macrophages can induce an IL-1 $\beta$ -initiated immune response independently of inflammasome activity.

DOI: 10.1016/j.celrep.2014.10.003

PMID: 25437548 [Indexed for MEDLINE]

1828. Med Clin (Barc). 2015 Jun 8;144(11):525. doi: 10.1016/j.medcli.2014.07.033. Epub 2014 Nov 26.

[Fibromyalgia as a comorbid phenomenon in autoinflammatory diseases].

[Article in Spanish]

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Comment in

Med Clin (Barc). 2015 Jun 8;144(11):525-6.

Comment on

Med Clin (Barc). 2014 Jun 16;142(12):538-9.

DOI: 10.1016/j.medcli.2014.07.033

PMID: 25433788 [Indexed for MEDLINE]

1829. Eur J Rheumatol. 2014 Dec;1(4):172-173. Epub 2014 Dec 1.

Familial Mediterranean fever and demyelinating plaques in the central nervous system.

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DOI: 10.5152/eurjrheumatol.2014.030

PMCID: PMC5042252

PMID: 27708909

1830. Eur J Rheumatol. 2014 Dec;1(4):140-143. Epub 2014 Dec 1.

Serum lipid changes and insulin resistance in familial Mediterranean fever.

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**OBJECTIVE:** Inflammation is known to alter lipid profiles and to induce insulin resistance. This study was planned to test the hypothesis that familial Mediterranean fever (FMF) patients and their first-degree asymptomatic relatives may have lipid profile changes and/or insulin resistance, similar to other inflammatory diseases.

**MATERIAL AND METHODS:** We studied 72 FMF patients, 30 asymptomatic first-degree relatives, and 75 healthy controls. Fasting and 2-hour postprandial glucose, insulin, apolipoprotein (Apo) A1, Apo B, acute phase reactants, and lipid profiles of all subjects were studied. Insulin resistance was determined by the



HOMA (Homeostasis Model Assessment) index.

RESULTS: There was no difference between the groups with regard to sex, mean systolic and diastolic blood pressure, body mass index, smoking status, fasting and postprandial 2-hour glucose, insulin, acute phase reactants, and HOMA index levels. High-density lipoprotein cholesterol (HDL-C) levels were similar between FMF patients and FMF relatives ( $48.9 \pm 12.4$  mg/dL vs  $49.3 \pm 13.8$  mg/dL;  $p = \text{NS}$ ), and both were lower than controls ( $48.9 \pm 12.4$  mg/dL vs  $59.6 \pm 15.1$  mg/dL;  $p < 0.001$  and  $49.3 \pm 13.8$  mg/dL vs  $59.8 \pm 15.1$  mg/dL;  $p = 0.001$ , respectively). Apo A1 levels in FMF patients and asymptomatic first-degree FMF relatives were both lower than in controls, similar to the HDL-C levels ( $126.1 \pm 25.7$  mg/dL vs  $151.2 \pm 31.4$  mg/dL;  $p < 0.001$  and  $129.5 \pm 29.0$  mg/dL vs  $151.2 \pm 31.4$  mg/dL;  $p = 0.002$ , respectively). TG levels were significantly higher in FMF relatives as compared to controls ( $113.4 \pm 53.6$  mg/dL vs  $97.1 \pm 54.9$  mg/dL;  $p = 0.025$ ).

CONCLUSION: Low HDL-C and low Apo A1 levels are found in FMF patients and their first-degree asymptomatic relatives. Low-grade inflammation caused by MEFV mutations may be responsible for these lipid profile changes.

DOI: 10.5152/eurjrheumatol.2014.140045

PMCID: PMC5042242

PMID: 27708899

1831. Annu Rev Pathol. 2015;10:395-424. doi: 10.1146/annurev-pathol-012414-040431. Epub 2014 Nov 19.

The inflammasomes and autoinflammatory syndromes.

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Inflammation, a vital response of the immune system to infection and damage to tissues, can be initiated by various germline-encoded innate immune-signaling receptors. Among these, the inflammasomes are critical for activation of the potent proinflammatory interleukin-1 cytokine family. Additionally, inflammasomes can trigger and maintain inflammatory responses aimed toward excess nutrients and the numerous danger signals that appear in a variety of chronic inflammatory diseases. We discuss our understanding of how inflammasomes assemble to trigger

caspase-1 activation and subsequent cytokine release, describe how genetic mutations in inflammasome-related genes lead to autoinflammatory syndromes, and review the contribution of inflammasome activation to various pathologies arising from metabolic dysfunction. Insights into the mechanisms that govern inflammasome activation will help in the development of novel therapeutic strategies, not only for managing genetic diseases associated with overactive inflammasomes, but also for treating common metabolic diseases for which effective therapies are currently lacking.

DOI: 10.1146/annurev-pathol-012414-040431

PMID: 25423351 [Indexed for MEDLINE]

1832. Arthritis Rheumatol. 2015 Feb;67(2):563-7.

Connecting two pathways through Ca<sup>2+</sup> signaling: NLRP3 inflammasome activation induced by a hypermorphic PLCG2 mutation.

Chae JJ, Park YH, Park C, Hwang IY, Hoffmann P, Kehrl JH, Aksentijevich I, Kastner DL.

**OBJECTIVE:** We previously reported that p.Ser707Tyr, a novel variant in phospholipase C $\gamma$ 2 (PLC $\gamma$ 2), is the cause of a dominantly inherited autoinflammatory disease, autoinflammation and PLC $\gamma$ 2-associated antibody deficiency and immune dysregulation (APLAID). The hypermorphic mutation enhances PLC $\gamma$ 2 activity and causes an increase in intracellular Ca<sup>2+</sup> release from endoplasmic reticulum stores. Because increased intracellular Ca<sup>2+</sup> signaling has been associated with NLRP3 inflammasome activation, we studied the role of the NLRP3 inflammasome in the pathogenesis of APLAID.

**METHODS:** Human peripheral blood mononuclear cells (PBMCs) were isolated from healthy control subjects and 2 patients with APLAID. Inflammasome activation was analyzed by Western blotting. Intracellular Ca<sup>2+</sup> levels were measured with a FLIPR Calcium 4 assay kit.

**RESULTS:** Cells from the patients had elevated basal levels of intracellular Ca<sup>2+</sup>, and the intracellular Ca<sup>2+</sup> flux triggered by extracellular CaCl<sub>2</sub> was substantially enhanced. Patient PBMCs secreted interleukin-1 $\beta$  in response to lipopolysaccharide priming alone, and this effect was attenuated by treatment with a PLC inhibitor, intracellular Ca<sup>2+</sup> blockers, or an adenylate cyclase activator.

**CONCLUSION:** Our findings suggest that the inflammation in patients with APLAID is partially driven by activation of the NLRP3 inflammasome. These data link 2 seemingly distinct molecular pathways and provide new insights into the pathogenesis of APLAID and autoinflammation.

DOI: 10.1002/art.38961

PMCID: PMC4369162

PMID: 25418813 [Indexed for MEDLINE]

1833. J Med Chem. 2014 Dec 26;57(24):10366-82. doi: 10.1021/jm501072b. Epub 2014 Dec 4.

Electrophilic warhead-based design of compounds preventing NLRP3 inflammasome-dependent pyroptosis.

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Pyroptosis is a caspase-1-dependent pro-inflammatory form of programmed cell death implicated in the pathogenesis of autoinflammatory diseases as well as in disorders characterized by excessive cell death and inflammation. Activation of NLRP3 inflammasome is a key event in the pyroptotic cascade. In this study, we describe the synthesis and chemical tuning of  $\alpha,\beta$ -unsaturated electrophilic warheads toward the development of antipyroptotic compounds. Their pharmacological evaluation and structure-activity relationships are also described. Compound 9 was selected as a model of this series, and it proved to be a reactive Michael acceptor, irreversibly trapping thiol nucleophiles, which prevented both ATP- and nigericin-triggered pyroptosis of human THP-1 cells in a time- and concentration-dependent manner. Moreover, 9 and other structurally related compounds, inhibited caspase-1 and NLRP3 ATPase activities. Our findings can contribute to the development of covalent, multitarget antipyroptotic compounds targeting molecular components of the NLRP3 inflammasome regulatory pathway.

DOI: 10.1021/jm501072b

PMID: 25418070 [Indexed for MEDLINE]

1834. Lupus. 2015 Mar;24(3):343-4.

Coexistence of systemic lupus erythematosus and familial Mediterranean fever.

Devrimsel G, Beyazal MS, Turkeyilmaz AK.

Comment in

Lupus. 2015 Aug;24(9):1006.

DOI: 10.1177/0961203314560425

PMID: 25416696 [Indexed for MEDLINE]

1835. Lupus. 2015 Jun;24(7):705-11. doi: 10.1177/0961203314560203. Epub 2014 Nov 20.

Familial Mediterranean fever gene (MEFV) mutations and disease severity in systemic lupus erythematosus (SLE): implications for the role of the E148Q MEFV allele in inflammation.

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OBJECTIVE: Observed low prevalence of SLE among familial Mediterranean fever (FMF) patients in several large cohorts suggests a possible protective effect of the MEFV mutations from SLE. In contrast, SLE patient carriers for the common MEFV mutations had rather complex disease expression with an increased frequency of febrile episodes and pleurisy and a decreased renal complication rate. Our aim

was to investigate the prevalence of MEFV gene mutations in patients with SLE and their effect on organ involvement in a well-defined group of biopsy-proven SLE nephritis patients.

**MATERIAL AND METHOD:** The prevalence of four MEFV gene mutations (M694V, M680I, V726A and E148Q) was investigated in 114 SLE patients and effect on disease severity was analyzed in patients with biopsy-proven SLE nephritis.

**RESULTS:** None of the SLE patients fulfilled the revised Tel-Hashomer criteria. Fourteen of 114 SLE patients (12.2%) were found to carry at least one MEFV mutation. A single patient in the SLE-Nephritis group was compound heterozygous for M694V/M680I mutations and only one patient in the SLE-Mild group was homozygous for E148Q mutation. Carrier frequency was similar to controls in SLE patients (12.2 vs 18.8%,  $p = 0.34$ ). After the exclusion of the less penetrant E148Q mutation, re-analysis revealed an association between exon 10 mutations and SLE nephritis ( $p = 0.050$ , odds ratio (OR) = 4.16, 95% confidence interval (CI) = 1.04-16.6). Carrier rate for the E148Q mutation decreased in the SLE group (controls vs. SLE = 20/186 vs. 3/114,  $p = 0.08$ ) and E148Q mutation was absent in SLE nephritis (controls vs. SLE nephritis = 20/186 vs. 0/47,  $p = 0.016$ , OR = 11.69, 95% CI = 0.69-197.13).

**CONCLUSIONS:** Carrier rate for the studied MEFV mutations was slightly lower in the SLE group, which is in agreement with previous observations that FMF may confer some protection from SLE. Exon 10 mutations were associated with SLE nephritis after the exclusion of the E148Q mutation. The significance of the E148Q as a disease-causing mutation is controversial, and whether E148Q substitution is a polymorphism generally affecting inflammatory pathways is not addressed in the current literature. In this regard, absence of the E148Q mutation in SLE nephritis may serve as a clue for further investigation into its role as a general modulatory polymorphism for inflammation. This clarification is necessary to conclude whether other more penetrant MEFV gene mutations confer susceptibility to nephritis in SLE.

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DOI: 10.1177/0961203314560203

PMID: 25413357 [Indexed for MEDLINE]

Evidence of Crohn's disease-related anti-glycoprotein 2 antibodies in patients with celiac disease.

Roggenbuck D, Vermeire S, Hoffman I, Reinhold D, Schierack P, Goihl A, von Arnim U, De Hertogh G, Polymeros D, Bogdanos DP, Bossuyt X.

**BACKGROUND:** Autoantibodies to exocrine-pancreatic glycoprotein 2 (anti-GP2) are Crohn's disease (CD) markers. However, CD-specific antibodies have also been found in celiac-disease (CeD) patients, in which type 1 diabetes-specific autoantibodies against endocrine pancreatic targets can be present. We investigated whether anti-GP2 are also present in CeD, a disease like CD which is also characterised by intestinal mucosal inflammation with barrier impairment.

**METHODS:** Antibodies against GP2, tissue transglutaminase (tTG), deamidated gliadin (dGD), glutamic decarboxylase (GAD), and islet antigen-2 (IA2) were tested in sera from 73 CD patients, 90 blood donors (BD), and 79 (58 de novo) CeD patients (2 consecutive sera were available from 40 patients).

**RESULTS:** IgA and/or IgG anti-GP2 were found in 15/79 (19.0%) CeD patients on at least one occasion, in 25/73 (34.2%) CD patients, and in 4/90 (4.4%) BD (CeD vs. CD,  $p=0.042$ ; BD vs. CeD and CD,  $p<0.001$ , respectively). Amongst the 58 de novo CeD patients, anti-GP2 IgA and/or IgG were present in 11 (19.0%). Anti-GP2 IgA was significantly less prevalent in CeD compared with CD ( $p=0.004$ ). Anti-GP2 IgA and IgG in CD patients demonstrated a significantly higher median level compared to patients with CeD ( $p<0.001$ ,  $p=0.008$ , respectively). IgA anti-GP2 levels correlated significantly with IgA anti-tTG and anti-dGD levels in CeD Spearman's coefficient of rank correlation ( $\rho=0.42$ , confidence interval (CI): 0.26-0.56,  $p<0.001$ ;  $\rho=0.54$ , CI 0.39-0.65,  $p<0.001$ , respectively).

**CONCLUSIONS:** The presence of anti-GP2 in CeD patients supports the notion that loss of tolerance to GP2 can probably be a manifestation of an autoinflammatory process in this intestinal disorder.

DOI: 10.1515/cclm-2014-0238

PMID: 25411995 [Indexed for MEDLINE]

1837. Eur J Hum Genet. 2015 Aug;23(8). doi: 10.1038/ejhg.2014.257. Epub 2014 Nov 19.

Clinical utility gene card for: prototypic hereditary recurrent fever syndromes (monogenic autoinflammatory syndromes).

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DOI: 10.1038/ejhg.2014.257

PMCID: PMC4795104

PMID: 25407006 [Indexed for MEDLINE]

1838. BMC Immunol. 2014 Nov 19;15:55. doi: 10.1186/s12865-014-0055-y.

The discriminative capacity of soluble Toll-like receptor (sTLR)2 and sTLR4 in inflammatory diseases.

Ten Oever J, Kox M, van de Veerdonk FL, Mothapo KM, Slavcovici A, Jansen TL, Tweehuysen L, Giamarellos-Bourboulis EJ, Schneeberger PM, Wever PC, Stoffels M, Simon A, van der Meer JW, Johnson MD, Kullberg BJ, Pickkers P, Pachot A, Joosten LA, Netea MG.

**BACKGROUND:** The extracellular domains of cytokine receptors are released during inflammation, but little is known about the shedding of Toll-like receptors (TLR) and whether they can be used as diagnostic biomarkers.

**METHODS:** The release of sTLR2 and sTLR4 was studied in in-vitro stimulations, as well as in-vivo during experimental human endotoxemia (n = 11, 2 ng/kg LPS), and in plasma of 394 patients with infections (infectious mononucleosis, measles, respiratory tract infections, bacterial sepsis and candidemia) or non-infectious inflammation (Crohn's disease, gout, rheumatoid arthritis, autoinflammatory syndromes and pancreatitis). Using C-statistics, the value of sTLR2 and sTLR4 levels for discrimination between infections and non-infectious inflammatory diseases, as well as between viral and bacterial infections was analyzed.

**RESULTS:** In-vitro, peripheral blood mononuclear cells released sTLR2 and sTLR4 by exposure to microbial ligands. During experimental human endotoxemia, plasma concentrations peaked after 2 hours (sTLR4) and 4 hours (sTLR2). sTLR4 did not correlate with cytokines, but sTLR2 correlated positively with TNF $\alpha$  (rs = 0.80, P < 0.05), IL-6 (rs = 0.65, P < 0.05), and IL-1Ra (rs = 0.57, P = 0.06), and

negatively with IL-10 ( $r_s = -0.58$ ,  $P = 0.06$ ), respectively. sTLR4 had a similar area under the ROC curve [AUC] for differentiating infectious and non-infectious inflammation compared to CRP: 0.72 (95% CI 0.66-0.79) versus 0.74 (95% CI 0.69-0.80) [ $P = 0.80$ ], while sTLR2 had a lower AUC: 0.60 (95% CI 0.54-0.66) [ $P = 0.0004$ ]. CRP differentiated bacterial infections better from viral infections than sTLR2 and sTLR4: AUC 0.94 (95% CI 0.90-0.96) versus 0.58 (95% CI 0.51-0.64) and 0.75 (95% CI 0.70-0.80), respectively [ $P < 0.0001$  for both].

CONCLUSIONS: sTLRs are released into the circulation, and suggest the possibility to use sTLRs as diagnostic tool in inflammatory conditions.

DOI: 10.1186/s12865-014-0055-y

PMCID: PMC4240815

PMID: 25406630 [Indexed for MEDLINE]

1839. Autoimmune Dis. 2014;2014:473170. doi: 10.1155/2014/473170. Epub 2014 Oct 22.

Occurrence of Autoimmune Diseases Related to the Vaccine against Yellow Fever.

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Yellow fever is an infectious disease, endemic in South America and Africa. This is a potentially serious illness, with lethality between 5 and 40% of cases. The most effective preventive vaccine is constituted by the attenuated virus strain 17D, developed in 1937. It is considered safe and effective, conferring protection in more than 90% in 10 years. Adverse effects are known as mild reactions (allergies, transaminases transient elevation, fever, headache) and



severe (visceral and neurotropic disease related to vaccine). However, little is known about its potential to induce autoimmune responses. This systematic review aims to identify the occurrence of autoinflammatory diseases related to 17D vaccine administration. Six studies were identified describing 13 possible cases. The diseases were Guillain-Barré syndrome, multiple sclerosis, multiple points evanescent syndrome, acute disseminated encephalomyelitis, autoimmune hepatitis, and Kawasaki disease. The data suggest that 17D vaccination may play a role in the mechanism of loss of self-tolerance.

DOI: 10.1155/2014/473170

PMCID: PMC4227414

PMID: 25405025

1840. Wien Klin Wochenschr. 2015 Jan;127(1-2):68-70. doi: 10.1007/s00508-014-0631-4. Epub 2014 Nov 15.

Intrauterine device may trigger typical attacks of familial Mediterranean fever: a case report.

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Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by episodic, recurrent, self-limited attacks of fever and serositis (sterile peritonitis, pleuritis, arthritis, etc). The insufficiency in restriction of mild inflammation contributes this consequence in FMF. Intrauterine devices (IUDs) have been widely used in the world for contraception by gynecologists as an effective and safe method. Herein, we present a woman with FMF as the first case, whose attacks were triggered by copper-containing IUD. Our hypothesis in the present case was that sterile mild inflammation in the uterus caused by copper-containing IUD may be the initial source of systemic inflammatory response. In our opinion, clinicians should consider that the copper-containing IUDs may be another cause of FMF attacks in women using this contraceptive method.

DOI: 10.1007/s00508-014-0631-4  
PMID: 25398289 [Indexed for MEDLINE]

1841. Curr Opin Hematol. 2015 Jan;22(1):23-9. doi: 10.1097/MOH.0000000000000100.

Neutrophilic dermatosis: disease mechanism and treatment.

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**PURPOSE OF REVIEW:** The purpose of this review is to describe the physiopathological and therapeutic aspects of neutrophilic dermatosis, taking into account their most frequent associated conditions.

**RECENT FINDINGS:** In autoinflammatory syndromes featuring neutrophilic dermatosis, the role of interleukin-1 and tumor necrosis factor (TNF)- $\alpha$  cytokines in the immunopathogenesis of neutrophilic dermatosis has supported their classification as autoinflammatory diseases. In malignancy-associated neutrophilic dermatosis, the role of the malignant clone in myeloid neoplasms and the role of the monoclonal gammopathy and/or of the malignant plasmocyte clone in myeloma have been underlined.

**SUMMARY:** Recent insights into neutrophilic dermatosis' pathophysiology have encouraged the use of targeted biological therapies for their treatment. Although systemic glucocorticoids remain the mainstay of treatment for Sweet's syndrome and pyoderma gangrenosum, anti-TNF- $\alpha$  is becoming the preferred treatment when pyoderma gangrenosum is accompanied by inflammatory bowel disease or rheumatoid arthritis. Interleukin-1 receptor inhibitor anakinra is a promising therapeutic alternative for refractory Sweet's syndrome.

DOI: 10.1097/MOH.0000000000000100  
PMID: 25394310 [Indexed for MEDLINE]

1842. Ann Hum Genet. 2015 Jan;79(1):20-7. doi: 10.1111/ahg.12087. Epub 2014 Nov 13.

Familial Mediterranean fever associated with MEFV mutations in a large cohort of

Cypriot patients.

Neocleous V(1), Costi C, Kyriakou C, Kyriakides TC, Shamma C, Skordis N, Toumba M, Kyriakou S, Koliou M, Kousparou M, Onoufriou M, Hadjipanayis A, Iasonides M, Atamyan VN, Pierides A, Christophidou-Anastasiadou V, Tanteles GA, Phylactou LA.

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Familial Mediterranean fever (FMF) is caused by mutations in the MEFV gene and the spectrum of mutations among Greek-Cypriots with FMF-related symptoms was examined. Sequence analysis for exons 2, 3, 5, and 10 of the MEFV gene was performed in a cohort of 593 patients. A total of 70 patients carried mutations in the homozygote or compound heterozygote state, 128 were identified with one MEFV mutation and 395 had no mutations. Of the 268 identified alleles, p.Val726Ala (27.61%) was the most frequent followed by p.Met694Val (19.40%). The missense mutations p.Arg761His (3.73%) and p.Ala744Ser (2.24%) were identified as the rarest. An interesting finding is the high frequency (18.28%) of the complex p.Phe479Leu-p.Glu167Asp that was identified in 49 of the mutated alleles. The MEFV genotypes did not follow a binomial distribution and proved not to satisfy the HWE ( $P < 0.001$ ). The high percentage (66.61%) of patients with unidentified mutations could be due to mutations in the rest of the coding or noncoding MEFV gene or due to mutations in other genes that are also causing Hereditary Recurrent Fevers. Results from this work indicate the high incidence of FMF in Cyprus and describe the spectrum of the mutations which occur in the country.

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DOI: 10.1111/ahg.12087

PMID: 25393764 [Indexed for MEDLINE]

1843. Immunol Res. 2015 Feb;61(1-2):53-62. doi: 10.1007/s12026-014-8561-9.

Pathogenesis of adult-onset Still's disease: new insights from the juvenile counterpart.

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Adult-onset Still's disease (AOSD) is a rare inflammatory disease characterized by the classical triad of daily fever, arthritis, and typical salmon-colored rash. Recent accumulation of knowledge, mostly arising from hereditary autoinflammatory diseases and from the systemic-onset juvenile idiopathic arthritis (sJIA), has given rise to new hypotheses on the pathophysiology of AOSD. In this review, we first discuss on the continuum between AOSD and sJIA. Then, we summarize current hypotheses on the underlying pathogenesis: (1) an infectious hypothesis; (2) an autoinflammatory hypothesis; (3) a lymphohistiocytic hypothesis; and (4) a hyperferritinemic hypothesis. Finally, we present the recent data suggesting that patients with AOSD fall into two distinct subgroups with different courses, one with prominent systemic features and one with chronic arthritis.

DOI: 10.1007/s12026-014-8561-9

PMID: 25388963 [Indexed for MEDLINE]

1844. J Dermatol. 2014 Dec;41(12):1112-3. doi: 10.1111/1346-8138.12689. Epub 2014 Nov 12.

Inflammatory response to heparinoid and heparin in a patient with tumor necrosis factor receptor-associated periodic syndrome: the second case with a T61I mutation in the TNFRSF1A gene.

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DOI: 10.1111/1346-8138.12689

PMID: 25387410 [Indexed for MEDLINE]

1845. J Exp Med. 2014 Nov 17;211(12):2385-96. doi: 10.1084/jem.20141091. Epub 2014 Nov 10.

An inherited mutation in NLRC4 causes autoinflammation in human and mice.

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Comment in

J Exp Med. 2014 Nov 17;211(12):2329.

Autoinflammatory syndromes cause sterile inflammation in the absence of any signs of autoimmune responses. Familial cold autoinflammatory syndrome (FCAS) is characterized by intermittent episodes of rash, arthralgia, and fever after exposure to cold stimuli. We have identified a missense mutation in the NLRC4 gene in patients with FCAS. NLRC4 has been known as a crucial sensor for several Gram-negative intracellular bacteria. The mutation in NLRC4 in FCAS patients promoted the formation of NLRC4-containing inflammasomes that cleave procaspase-1 and increase production of IL-1 $\beta$ . Transgenic mice that expressed mutant Nlrc4 under the invariant chain promoter developed dermatitis and arthritis. Inflammation within tissues depended on IL-1 $\beta$ -mediated production of IL-17A from neutrophils but not from T cells. Our findings reveal a previously unrecognized link between NLRC4 and a hereditary autoinflammatory disease and highlight the importance of NLRC4 not only in the innate immune response to bacterial infections but also in the genesis of inflammatory diseases.

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DOI: 10.1084/jem.20141091

PMCID: PMC4235634

PMID: 25385754 [Indexed for MEDLINE]

1846. BMJ Case Rep. 2014 Nov 9;2014. pii: bcr2014204853. doi: 10.1136/bcr-2014-204853.

Pyoderma gangrenosum as a first presentation of inflammatory bowel disease.

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Up to 40% of patients with inflammatory bowel disease (IBD) develop an extraintestinal manifestation of the disease with the skin being the most commonly involved organ. Pyoderma gangrenosum (PG), an autoinflammatory non-infectious neutrophilic dermatosis, occurs in 1-2% of patients with IBD. PG can follow a course independent to that of the bowel disease, however, most reported cases describe PG occurring in patients with an established diagnosis of IBD. We present a case of a young patient who presented with axillary skin ulceration, which was subsequently diagnosed as PG. On further investigation for a possible underlying cause, she was found to have Crohn's disease. She had not developed any preceding change in her bowels and did not have abdominal pain; the IBD was diagnosed on endoscopic findings. This case is also unusual for the distribution of the PG lesions that typically occur in the lower limbs.

2014 BMJ Publishing Group Ltd.

DOI: 10.1136/bcr-2014-204853

PMCID: PMC4225318

PMID: 25385558 [Indexed for MEDLINE]

1847. Mod Rheumatol. 2017 Jan;27(1):169-173. doi: 10.3109/14397595.2014.964388. Epub 2014 Nov 10.

A long-term follow-up of Japanese mother and her daughter with Blau syndrome: Effective treatment of anti-TNF inhibitors and useful diagnostic tool of joint ultrasound examination.

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Blau syndrome (BS) is an autosomal dominant autoinflammatory disease associated with NOD2 gene mutations. It is characterized by arthritis, skin rash, and uveitis. Here, we report contrasting outcomes of a daughter and her mother with BS. Their long-term follow-up revealed the efficacy of anti-tumor necrosis factor inhibitor (TNF) with respect to BS. Joint findings of BS feature tenosynovitis over articular synovitis on ultrasonography. BS might be one of the differential diagnoses of juvenile idiopathic arthritis and rheumatoid arthritis.

DOI: 10.3109/14397595.2014.964388

PMID: 25381727 [Indexed for MEDLINE]

1848. Virchows Arch. 2015 Jan;466(1):77-83. doi: 10.1007/s00428-014-1681-8. Epub 2014 Nov 8.

Native kidney biopsies in Armenian and Swiss children: high prevalence of amyloidosis in Yerevan and of IgA nephropathy in Zurich.

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The spectrum of pathology in native kidney biopsies varies considerably between different countries. Based on similar biopsy policy and joint workup, biopsy data

of native kidneys of children in Yerevan (Armenia) and Zurich (Switzerland) were compared over a period of two decades (1993-2002 and 2003-2012). A total of 487 renal biopsies in Yerevan (EVN), n = 253; median age 11.2 years (range 0.8-18; 56 % males) and in Zurich (ZRH), n = 234; median age 8.7 years (range 0.1-18; 61 % males) were analyzed. Biopsies from EVN were locally analyzed by light microscopy (LM) and sent to ZRH for electron microscopy (EM) and immunohistochemistry. Biopsies from ZRH were evaluated by LM, EM, and immunofluorescence. The significant difference concerns the high frequency of amyloidosis in EVN (25.4 % in the first and 19.4 % in the second decade vs. 0 % in ZRH) and of IgA nephropathy in ZRH (30.2 % in the first and 26.1 % in the second decade vs. 8.1 in EVN). Certain forms of glomerulonephritis (membranoproliferative type I and membranous) and primary focal segmental glomerulosclerosis tended to be more frequent in EVN than in ZRH. Amyloid nephropathy due to familial Mediterranean fever is still highly frequent in Armenia with a slight decrease in the second decade. In Switzerland, the most common finding was IgA nephropathy.

DOI: 10.1007/s00428-014-1681-8

PMID: 25380969 [Indexed for MEDLINE]

1849. Amyloid. 2015 Mar;22(1):1-7. doi: 10.3109/13506129.2014.980942. Epub 2014 Nov 7.

Risk factors for AA amyloidosis in Germany.

Blank N(1), Hegenbart U, Lohse P, Beimler J, Röcken C, Ho AD, Lorenz HM, Schönland SO.

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**OBJECTIVE:** To identify risk factors for serum amyloid-A (AA) amyloidosis in patients living in Germany.

**METHODS:** Clinical and genetic data were obtained from 71 patients with AA amyloidosis. SAA1 genotypes were analyzed in 231 individuals. Control groups comprised 45 patients with long-standing inflammatory diseases without AA amyloidosis and 56 age-matched patients without any inflammatory disease.

**RESULTS:** The most frequent underlying diseases of AA amyloidosis were familial Mediterranean fever (FMF) (n = 24, 34%) and inflammatory rheumatic diseases



(n = 30, 42%). Patients without any known underlying disease (n = 11, 16%) were considered as having idiopathic AA amyloidosis. Patients with FMF were significantly younger at disease onset and younger at diagnosis of AA amyloidosis compared with patients with rheumatic diseases. Patients with idiopathic AA amyloidosis were older than patients with definite rheumatic diseases. Patients with FMF and high penetrance MEFV gene mutations had a relative risk of 1.73 for AA amyloidosis. Patients with FMF or a rheumatic disease and the SAA1  $\alpha/\alpha$  genotype had a relative risk of 4.86 and 2.53, respectively, for developing an AA amyloidosis. The prevalence of this risk genotype was 36% in German patients without an inflammatory disease, 92% in German patients with AA amyloidosis and 100% in German patients with idiopathic AA amyloidosis.

CONCLUSIONS: Risk factors for AA amyloidosis are the presence of a hereditary autoinflammatory or chronic rheumatic disease, elevated C-reactive protein and SAA serum levels, a long delay of a sufficient therapy, an advanced age and the SAA1 $\alpha/\alpha$  genotype.

DOI: 10.3109/13506129.2014.980942

PMID: 25376380 [Indexed for MEDLINE]

1850. Scand J Gastroenterol. 2014 Dec;49(12):1414-8. doi: 10.3109/00365521.2014.976838. Epub 2014 Nov 5.

Small bowel mucosal damage in familial Mediterranean fever: results of capsule endoscopy screening.

Demir A(1), Akyüz F, Göktürk S, Evirgen S, Akyüz U, Örmeci A, Soyer Ö, Karaca C, Demir K, Gundogdu G, Güllüoğlu M, Erer B, Kamalı S, Kaymakoglu S, Besisik F, Gül A.

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Comment in

Scand J Gastroenterol. 2015 Mar;50(3):378.

OBJECTIVE: Familial Mediterranean fever (FMF) is the most common form of autoinflammatory diseases. We aimed to evaluate the small bowel mucosa by capsule

endoscopy (CE) in FMF patients for investigation of other possible causes of abdominal pain.

**MATERIAL AND METHODS:** The study group consisted of 41 patients with FMF. A standard questionnaire was used to record the gastrointestinal symptoms, other clinical findings, Mediterranean fever gene (MEFV) mutations, and history of medications including non-steroidal anti-inflammatory drugs (NSAIDs).

Gastroscopy, colonoscopy and small bowel CE were performed in all patients, and biopsies were taken from terminal ileum and duodenum.

**RESULTS:** The mean age of the patients was  $34 \pm 11$  years, 63% of them were female, and 76.5% of them were carrying MEFV exon 10 mutations. Only one patient used NSAIDs in addition to colchicine. In endoscopic investigations, gastric erosion was detected in only one patient, and no significant findings were detected in colonoscopy. CE showed small bowel mucosal defects in 44% (erosions in 26.8%, ulcer in 17.1%) and edema in 29.3% of the patients. Most (64%) of the ulcer and erosions were localized to jejunum, and only 24% were in ileum. Mitotic changes as an indirect finding of colchicine toxicity were not different from the changes observed in samples of independent group of patients with irritable bowel syndrome.

**CONCLUSION:** Mucosal defect was observed in half of the FMF patients, which may be associated with underlying inflammation or chronic colchicine exposure. Detection of nonspecific chronic inflammation without mitotic changes supports that mucosal defects may be associated with the autoinflammatory process.

DOI: 10.3109/00365521.2014.976838

PMID: 25369738 [Indexed for MEDLINE]

1851. Semin Neurol. 2014 Sep;34(4):437-43. doi: 10.1055/s-0034-1390392. Epub 2014 Nov 4.

Neuro-Behçet disease and autoinflammatory disorders.

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Misregulation of innate immunity leads to autoinflammation. Behçet disease is an autoinflammatory condition involving recurrent attacks of inflammation in skin, eyes, joints, and even the nervous system. The etiology may involve vascular inflammation. Central nervous system involvement in neuro-Behçet disease (NBD) comes in the form of parenchymal NBD or nonparenchymal NBD. The parenchymal form has a predilection for the brainstem, diencephalon and cerebral hemispheres, and represents a meningoencephalitis thought to be related to small vessel vasculitis. Cerebral venous sinus thrombosis, arising from a vasculitic process of large veins, comprises the majority of vascular NBD cases. The rarer monogenetic autoinflammatory syndromes are characterized by periodic fever, and typically present in the pediatric population. Neurologic involvement in these syndromes typically presents in the form of an aseptic meningitis. Treatment of autoinflammatory disorders involves immune modulation with corticosteroids, disease-modifying antirheumatic medications, and increasingly antibodies targeting cytokines like tumor necrosis factor  $\alpha$  and interleukin 1.

Thieme Medical Publishers 333 Seventh Avenue, New York, NY 10001, USA.

DOI: 10.1055/s-0034-1390392

PMID: 25369439 [Indexed for MEDLINE]

1852. PLoS One. 2014 Nov 4;9(11):e111255. doi: 10.1371/journal.pone.0111255. eCollection 2014.

CARD14 expression in dermal endothelial cells in psoriasis.

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Mutations in the caspase recruitment domain, family member 14 (CARD14) gene have recently been described in psoriasis patients, and explain the psoriasis susceptibility locus 2 (PSORS2). CARD14 is a scaffolding protein that regulates NF- $\kappa$ B activation, and psoriasis-associated CARD14 mutations lead to enhanced NF- $\kappa$ B signaling. CARD14 is expressed mainly in epidermal keratinocytes, but also in unidentified dermal cells. In this manuscript, the identity of the dermal cell types expressing CARD14, as well the potential functional consequence of overactive CARD14 in these dermal cell types, was determined. Using two-color immunofluorescence, dermal CARD14 did not co-localize with T-cells, dendritic cells, or macrophages. However, dermal CARD14 did highly co-localize with CD31(+) endothelial cells (ECs). CARD14 was also expressed non-dermal endothelial cells, such as aortic endothelial cells, which may indicate a role of CARD14(+)ECs in the systemic inflammation and cardiovascular comorbidities associated with psoriasis. Additionally, phosphorylated NF- $\kappa$ B was found in psoriatic CARD14(+) CD31(+) ECs, demonstrating this pathway is active in dermal ECs in psoriasis. Transfection of dermal ECs with psoriasis-associated CARD14 mutations resulted in increased expression of several chemokines, including CXCL10, IL-8, and CCL2. These results provide preliminary evidence that CARD14 expression in ECs may contribute to psoriasis through increased expression of chemokines and facilitating recruitment of immune cells into skin.

DOI: 10.1371/journal.pone.0111255

PMCID: PMC4219711

PMID: 25369198 [Indexed for MEDLINE]

1853. Expert Opin Drug Deliv. 2015 Mar;12(3):393-414. doi: 10.1517/17425247.2015.972931. Epub 2014 Nov 4.

Targeted delivery systems for biological therapies of inflammatory diseases.

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**INTRODUCTION:** Inflammatory diseases, including autoimmune diseases and autoinflammatory diseases, are characterized by the imbalance of pro-inflammatory cytokines and anti-inflammatory cytokines. Targeted systems allow for specific delivery and sustained release of biological agents to inflamed tissues and macrophages, hence reducing their side effects.

**AREAS COVERED:** This review discusses various targeting strategies for biological therapies of inflammatory diseases, with a focus on modulating macrophage functional polarization from an M1 to M2 phenotype. Furthermore, recent advances in the development of targeted delivery systems for gene therapy against inflammatory diseases including liposomal therapeutics, polymeric nanoparticles and microspheres, and multi-compartmental delivery systems are summarized.

**EXPERT OPINION:** Molecular advances have uncovered various targets for biological therapies against inflammatory diseases. Despite substantial promise, the potential translation from the bench to the clinic is limited due to poor systemic stability of the delivery systems, low tissue distribution, and safety concerns. In order to develop clinically translatable targeted delivery systems, thorough evaluation of the efficacy and toxicity in relevant animal models and in different inflammatory diseases is needed. In addition, issues related to long-term storage stability, scale-up and manufacturing of the systems need to be addressed.

DOI: 10.1517/17425247.2015.972931

PMID: 25366552 [Indexed for MEDLINE]

1854. PLoS One. 2014 Nov 3;9(11):e111490. doi: 10.1371/journal.pone.0111490.  
eCollection 2014.

Autophagy, inflammation and innate immunity in inflammatory myopathies.

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Autophagy has a large range of physiological functions and its dysregulation contributes to several human disorders, including autoinflammatory/autoimmune diseases such as inflammatory myopathies (IIMs). In order to better understand the pathogenetic mechanisms of these muscular disorders, we sought to define the role of autophagic processes and their relation with the innate immune system in the three main subtypes of IIM, specifically sporadic inclusion body myositis (sIBM), polymyositis (PM), dermatomyositis (DM) and juvenile dermatomyositis (JDM). We found that although the mRNA transcript levels of the autophagy-related genes BECN1, ATG5 and FBXO32 were similar in IIM and controls, autophagy activation in all IIM subgroups was suggested by immunoblotting results and confirmed by immunofluorescence. TLR4 and TLR3, two potent inducers of autophagy, were highly increased in IIM, with TLR4 transcripts significantly more expressed in PM and DM than in JDM, sIBM and controls, and TLR3 transcripts highly up-regulated in all IIM subgroups compared to controls. Co-localization between autophagic marker, LC3, and TLR4 and TLR3 was observed not only in sIBM but also in PM, DM and JDM muscle tissues. Furthermore, a highly association with the autophagic processes was observed in all IIM subgroups also for some TLR4 ligands, endogenous and bacterial HSP60, other than the high-mobility group box 1 (HMGB1). These findings indicate that autophagic processes are active not only in sIBM but also in PM, DM and JDM, probably in response to an exogenous or endogenous 'danger signal'. However, autophagic activation and regulation, and also interaction with the innate immune system, differ in each type of IIM. Better understanding of these differences may lead to new therapies for the different IIM types.

DOI: 10.1371/journal.pone.0111490

PMCID: PMC4218755

PMID: 25365350 [Indexed for MEDLINE]

1855. J Res Med Sci. 2014 Jul;19(7):644-9.

Outcome of 121 patients with renal amyloid a amyloidosis.

Ahbap E(1), Kara E(1), Sahutoglu T(1), Basturk T(1), Koc Y(1), Sakaci T(1), Sevinc M(1), Akgol C(1), Ucar ZA(1), Kayalar AO(1), Bayraktar F(1), Ozagari AA(2), Unsal A(1).

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**BACKGROUND:** Amyloid A (AA) amyloidosis is a multisystem, progressive and fatal disease. Renal involvement occurs early in the course of AA. We aimed to investigate the etiology, clinical and laboratory features, and outcome of patients with biopsy-proven renal AA amyloidosis.

**MATERIALS AND METHODS:** A total of 121 patients (male/female: 84/37, mean age  $42.6 \pm 14.4$  years) were analyzed retrospectively between January of 2001 and May of 2013. Demographic, clinical and laboratory features and outcomes data were obtained from follow-up charts.

**RESULTS:** Familial Mediterranean fever (37.2%) and tuberculosis (24.8%) were the most frequent causes of amyloidosis. Mean serum creatinine and proteinuria at diagnosis were  $2.3 \pm 2.1$  mg/dL and  $6.7 \pm 5.3$  g/day, respectively. Sixty-eight (56.2%) patients were started dialysis treatment during the follow-up period. Mean duration of renal survival was  $64.7 \pm 6.3$  months. Age, serum creatinine and albumin levels were found as predictors of end-stage renal disease. Fifty patients (%41.3) died during the follow-up period. The mean survival of patients was  $88.7 \pm 7.8$  months (median:  $63 \pm 13.9$ ). 1, 2 and 5 years survival rates of patients were 80.7%, 68.2% and 51.3%, respectively. Older age, male gender, lower levels of body mass index, estimated glomerular filtration rate, serum albumin, calcium, and higher levels of phosphor, intact parathyroid hormone and proteinuria were associated with a higher mortality. Higher serum creatinine, lower albumin, dialysis requirement and short time to dialysis were predictors of mortality.

**CONCLUSION:** The outcome of patients with AA amyloidosis and renal involvement is poor, particularly in those who had massive proteinuria, severe hypoalbuminemia and dialysis requirement at the outset.

PMCID: PMC4214024

PMID: 25364365

1856. J Rheumatol. 2014 Nov;41(11):2271-2. doi: 10.3899/jrheum.140324.

Erysipelas-like erythema in a patient with familial Mediterranean fever.

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DOI: 10.3899/jrheum.140324

PMID: 25362709 [Indexed for MEDLINE]

1857. Iran J Kidney Dis. 2014 Nov;8(6):486-8.

Massive proteinuria and acute glomerulonephritis picture in a patient with Familial Mediterranean fever and E148Q mutation.

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Familial Mediterranean fever (FMF) is an inherited auto-inflammatory disorder. Secondary AA amyloidosis is the most devastating complication of FMF. Nonamyloid renal involvements have also been reported in association with FMF, including vasculitis, focal and diffuse glomerulonephritis, and IgA nephropathy. We describe a patient with FMF and E148Q mutation who presented with massive proteinuria, elevated serum creatinine level, and acute glomerulonephritis picture. Disease remission was achieved after treatment with corticosteroids and colchicine.



PMID: 25362225 [Indexed for MEDLINE]

1858. J Eur Acad Dermatol Venereol. 2015 Nov;29(11):2243-7. doi: 10.1111/jdv.12765. Epub 2014 Oct 28.

Successful treatment of PASH syndrome with infliximab, cyclosporine and dapsone.

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**BACKGROUND:** The group of autoinflammatory syndromes associated with Pyoderma gangrenosum, Acne, and Suppurative Hidradenitis are poorly defined and difficult to control with currently available treatment modalities.

**OBJECTIVES:** We describe a patient with PASH syndrome and report about the successful multimodal treatment with infliximab, cyclosporine, and dapsone.

**METHODS:** A review of the available literature to date about this group of autoinflammatory diseases was performed. We performed genetic analysis for PSTPIP1 mutations associated with PAPA syndrome.

**RESULTS:** A 22-year-old woman presented to our department with pyoderma gangrenosum, concomitant acne, and suppurative hidradenitis. She had previously been treated unsuccessfully with etanercept, adalimumab, fumaric acid and the IL-1 receptor antagonist (IL-1RA) anakinra without prolonged remission. Treatment with intravenous infliximab in combination with cyclosporine and dapsone lead to sudden and prolonged improvement of the clinical symptoms that we classified as PASH syndrome. We review the literature about this group of diseases and report the third case of PASH syndrome to date.

**CONCLUSION:** PASH syndrome and associated diseases should be considered whenever hidradenitis suppurativa is found in association with pyoderma gangrenosum. We

provide a systematic overview about PASH syndrome and suggest a novel multimodal therapeutic regimen beyond isolated inhibition of TNF or IL-1.

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DOI: 10.1111/jdv.12765

PMID: 25352307 [Indexed for MEDLINE]

1859. Pediatrics. 2014 Nov;134(5):e1468-73. doi: 10.1542/peds.2013-3185.

Successful management of cryopyrin-associated periodic syndrome with canakinumab in infancy.

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Neonatal onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic cutaneous and articular (CINCA) syndrome is a rare, early-onset autoinflammatory disorder and the most severe form of cryopyrin-associated periodic syndrome, which is associated with overproduction of interleukin (IL)-1 $\beta$ . This is a case report of a 70-day-old boy, who was diagnosed with NOMID/CINCA syndrome and who has been treated with anti-IL-1 $\beta$  monoclonal antibody (canakinumab) since then, despite his early infancy. The patient presented with fever, aseptic meningitis, and rash. The clinical manifestations combined with the elevated acute-phase reactants strengthened the suspicion of the diagnosis of NOMID/CINCA syndrome. Specific immunologic workup revealed high levels of serum amyloid A and IL-6. The clinical diagnosis was confirmed by the detection of a de novo mutation of the CIAS1/NLR3 gene (p.Thr348Met), and canakinumab was started

at a dose of 4 mg/kg, higher than the recommended dose for older age. White blood cell, serum amyloid A, C-reactive protein, and IL-6 levels quickly decreased and became normal within a month, and the clinical condition of the patient improved significantly. The infant remains without recurrence of disease or further complications and with satisfactory mental development with anti-IL-1 $\beta$  monoclonal antibody treatment for >2 years. This report indicates the importance of early diagnosis of NOMID/CINCA syndrome and medication with IL-1 blockers as soon as possible for the improvement of the prognosis of cryopyrin-associated periodic syndrome and of a better patient outcome.

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DOI: 10.1542/peds.2013-3185

PMID: 25349319 [Indexed for MEDLINE]

1860. Farm Hosp. 2014 Sep 16;38(5):446-8. doi: 10.7399/fh.2014.38.5.7555.

[Anakinra in a case of fever familial Mediterranean].

[Article in Spanish]

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DOI: 10.7399/fh.2014.38.5.7555

PMID: 25344140 [Indexed for MEDLINE]

1861. Curr Opin Allergy Clin Immunol. 2014 Dec;14(6):491-500. doi:  
10.1097/ACI.0000000000000117.

When less is more: primary immunodeficiency with an autoinflammatory kick.

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**PURPOSE OF REVIEW:** Next-generation sequencing is revolutionizing the molecular taxonomy of human disease. Recent studies of patients with unexplained autoinflammatory disorders reveal germline genetic mutations that target important regulators of innate immunity.

**RECENT FINDINGS:** Whole-exome analyses of previously undiagnosed patients have catalyzed the recognition of two new disease genes. First, a phenotypic spectrum, including livedo racemosa, fever with early-onset stroke, polyarteritis nodosa, and Sneddon syndrome, is caused by loss-of-function mutations in cat eye syndrome chromosome region, candidate 1 (CECR1), encoding adenosine deaminase 2. Adenosine deaminase 2 is a secreted protein expressed primarily in myeloid cells, and a regulator of macrophage differentiation and endothelial development.

Disease-associated mutations impair anti-inflammatory M2 macrophage differentiation. Second, patients presenting with cold-induced urticaria, granulomatous rash, autoantibodies, and common variable immunodeficiency, or with blistering skin lesions, bronchiolitis, enterocolitis, ocular inflammation, and mild immunodeficiency harbor distinct mutations in phospholipase  $Cy_2$ , encoding a signaling molecule expressed in natural killer cells, mast cells, and B lymphocytes. These mutations inhibit the function of a phospholipase  $Cy_2$  autoinhibitory domain, causing increased or constitutive signaling.

**SUMMARY:** These findings underscore the power of next-generation sequencing, demonstrating how the primary deficiency of key molecular regulators or even regulatory motifs may lead to autoinflammation, and suggesting a possible role for cat eye syndrome chromosome region, candidate 1 and phospholipase  $Cy_2$  in common diseases.

DOI: 10.1097/ACI.0000000000000117

PMCID: PMC4212813

PMID: 25337682 [Indexed for MEDLINE]

Amyloid goiter due to familial mediterranean Fever in a patient with byler syndrome: a case report.

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**BACKGROUND:** Familial Mediterranean Fever (FMF), also inherited with autosomal recessive trait, is characterized by recurrent episodes of fever, arthritis, and serositis. Congenital Byler Syndrome (Progressive Familial Intrahepatic Cholestasis) inherited with autosomal recessive trait and characterized by defective secretion of bile acids. FMF associated Amyloid A deposition occurs in many tissues and organs, but amyloid goiter is a rare entity that leads to enlargement and dysfunction of the thyroid.

**CASE REPORT:** We present a rare case of 24 year old male patient who had liver and kidney transplantation due to Byler Syndrome and secondary amyloidosis related to FMF, diagnosed as rapidly growing large amyloid goiter. Deposits of extracellular amyloid and dense adipose metaplasia diagnostic for amyloid goiter are determined upon histopathological examination of thyroidectomy material.

**CONCLUSION:** When goiter was detected in cases with history of systemic amyloidosis and rapidly growing goitre, amyloid goiter should be remembered at first. This case is unique since two autosomal genetic disorders are together in the same patient and important as it emphasizes the consequences of consanguineous marriage, early diagnosis and treatment compliance of FMF and the awareness of amyloid goiter in patients followed by primary care physicians and healthcare professionals.

DOI: 10.5152/balkanmedj.2014.13111

PMCID: PMC4204758

PMID: 25337425

1863. J Ultrasound Med. 2014 Nov;33(11):1991-7. doi: 10.7863/ultra.33.11.1991.

Sonographic assessment of spleen size in Turkish migrants with Familial Mediterranean fever in Germany.

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**OBJECTIVES:** Familial Mediterranean fever (FMF) can be associated with splenomegaly. Prospective quantitative data are lacking. We performed a sonographic assessment of spleen size in patients with FMF and healthy control participants to assess its diagnostic value.

**METHODS:** Patients with FMF according to the criteria of Livneh et al (Arthritis Rheum 1997; 40:1879-1885) who were in an asymptomatic interval and control participants were prospectively included in this study in Germany and underwent sonographic measurement of the spleen as well as a structured interview and a physical examination. Patients and controls were Turkish migrants.

**RESULTS:** Thirty-six patients and 27 controls were included. Patients and controls did not differ significantly in age (mean  $\pm$  SD,  $34.8 \pm 9.7$  versus  $33.3 \pm 10.0$  years, respectively;  $P = .56$ ), sex, height, weight, or body mass index ( $26.7 \pm 4.7$  versus  $26.1 \pm 4.3$  kg/m<sup>2</sup>;  $P = .63$ ). Spleen size was greater in patients than controls in width ( $4.3 \pm 1.0$  versus  $3.7 \pm 0.7$  cm;  $P = .008$ ) and also length ( $12.1 \pm 1.9$  versus  $10.5 \pm 1.4$  cm;  $P = .001$ ). Twenty-six of 36 patients (72.2%) had a history of appendectomy compared to 3 of 27 controls (11.1%;  $P < .001$ ). The combination of an enlarged spleen (length  $>11$  cm and/or width  $>4$  cm) gave specificity of 100% (95% confidence interval, 87%-100%) and a positive predictive value of 100% (95% confidence interval, 78%-100%) for the diagnosis of FMF in our study.

**CONCLUSIONS:** Spleen size as evaluated by sonography is larger in patients with

FMF compared to healthy controls. Most patients with FMF included in this study had undergone appendectomy. Familial Mediterranean fever should be considered as a differential diagnosis in Turkish migrants in Germany if the spleen is enlarged and a history of appendectomy is reported.

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DOI: 10.7863/ultra.33.11.1991

PMID: 25336487 [Indexed for MEDLINE]

1864. Skinmed. 2014 Jul-Aug;12(4):240-1.

The autoinflammatory assault on conventional diagnostic criteria.

Heymann WR.

PMID: 25335354 [Indexed for MEDLINE]

1865. Indian J Hematol Blood Transfus. 2014 Sep;30(Suppl 1):138-41. doi: 10.1007/s12288-013-0296-6. Epub 2013 Aug 27.

The coincidence of familial mediterranean Fever and hypereosinophilia in a patient with hereditary elliptocytosis.

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Familial Mediterranean fever (FMF) is a genetic disease with autosomal

inheritance characterized by recurrent fever, abdominal pain, and serositis attacks. It is relatively common in the races and ethnical groups around Mediterranean Sea (Sephardic Jews, Armenians, Turks and Arabians). Hereditary elliptocytosis (HE) is common genetic defect of the red blood cell membrane skeleton. Spectrin mutations are the predominant causes of HE. Hypereosinophilia is defined as a number of eosinophil granulocytes equal or greater than  $0.5 \times 10^9/L$  of circulating blood. The main causes are allergies and parasitic infections. This case report describes a Turkish female HE patient who presented with FMF and hypereosinophilia. Genetic analysis revealed heterozygous mutation in exon 10 of the MEFV gene (V726A). The patient was successfully treated with colchicine and steroid treatment at 3-month follow-up. To the best of our knowledge, this is the first report of association between FMF, HE, and hypereosinophilia.

DOI: 10.1007/s12288-013-0296-6

PMCID: PMC4192255

PMID: 25332561

1866. Clin Exp Rheumatol. 2014 Nov-Dec;32(6):994. Epub 2014 Oct 20.

The role of the F402L allele in the NLRP12-autoinflammatory disorder. Reply to: F402L variant in NLRP12 in subjects with undiagnosed periodic fevers and in healthy controls, De Pieri et al.

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Comment on

Clin Exp Rheumatol. 2013 May-Jun;31(3 Suppl 77):155-6.

Clin Exp Rheumatol. 2014 Nov-Dec;32(6):993-4.

PMID: 25327451 [Indexed for MEDLINE]



1867. Autoimmun Rev. 2015 Feb;14(2):90-7. doi: 10.1016/j.autrev.2014.10.005. Epub 2014 Oct 12.

Autoimmunity and autoinflammation as the yin and yang of idiopathic recurrent acute pericarditis.

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Autoimmunity and autoinflammation are generally considered as mutually exclusive mechanisms of diseases but may concur to specific syndromes. Idiopathic recurrent acute pericarditis (IRAP) is defined as the recurrence of pericardial symptoms at any point following the prior cessation of acute pericarditis, and the latency is generally 6 weeks. Manifestations of pericarditis such as pericardial friction rub, electrocardiographic changes, and pericardial effusion are less frequent in the subsequent episodes compared to the index attack, and in some cases the only clinical sign is represented by a suggestive chest pain. Several autoimmune diseases may manifest with pericarditis which is often related to viral infections, while postviral pericarditis may in turn display a nonspecific autoimmune background. Similarly, autoinflammatory syndromes such as familial Mediterranean fever and tumor necrosis factor receptor-associated periodic syndrome are characterized by self-limiting pericardial symptoms. Corticosteroids are generally effective, thus supporting the autoimmune nature of IRAP, but

dramatic results are obtained with interleukin-1 blocking agents in corticosteroid-dependent cases, pointing to a pathogenic role for the inflammasome. Based on these observations, we submit that IRAP represents a paradigmatic example of the putative coexistence of autoimmunity and autoinflammation: the main aim of this review is to critically discuss the hypothesis as well as the current understanding of this enigmatic clinical condition.

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DOI: 10.1016/j.autrev.2014.10.005

PMID: 25308531 [Indexed for MEDLINE]

1868. Sci China Life Sci. 2014 Dec;57(12):1156-61. doi: 10.1007/s11427-014-4758-3. Epub 2014 Oct 11.

Immunological function of familial Mediterranean fever disease protein Pyrin.

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Pyrin, encoded by MEFV gene, is conserved in humans and mice. Mutations in the MEFV gene are associated with the human autoinflammatory disease familial Mediterranean fever (FMF). Pyrin can interact with the inflammasome adaptor ASC and induce inflammatory caspase-1 activation in monocytic cells, but the physiological function of Pyrin has been unknown for many years. Here we summarize previous studies of Pyrin function under the context of FMF and immunity, and discuss a recent study demonstrating that Pyrin forms an inflammasome complex for caspase-1 activation in innate immunity. Pyrin inflammasome detects inactivating modifications of host Rho GTPases by diverse bacterial toxins and infections, including *Clostridium difficile* glucosylating cytotoxin TcdB, FIC-domain adenyltransferase effectors from *Vibrio parahaemolyticus* and *Histophilus somni*, ADP-ribosylating *Clostridium botulinum* C3 toxin as well as *Burkholderia cenocepacia* infection. The mode of Pyrin action, i.e., sensing pathogen virulence activity rather than directly recognizing a microbial molecule, represents a new paradigm in innate immunity.

DOI: 10.1007/s11427-014-4758-3

PMID: 25307949 [Indexed for MEDLINE]

1869. Nature. 2015 Jan 1;517(7532):89-93. doi: 10.1038/nature13801. Epub 2014 Oct 12.

Human intracellular ISG15 prevents interferon- $\alpha/\beta$  over-amplification and auto-inflammation.

Zhang X(1), Bogunovic D(2), Payelle-Brogard B(3), Francois-Newton V(3), Speer SD(4), Yuan C(1), Volpi S(5), Li Z(3), Sanal O(6), Mansouri D(7), Tezcan I(6), Rice GI(8), Chen C(9), Mansouri N(7), Mahdavian SA(7), Itan Y(10), Boisson B(10), Okada S(10), Zeng L(1), Wang X(1), Jiang H(11), Liu W(1), Han T(1), Liu D(12), Ma T(1), Wang B(13), Liu M(1), Liu JY(1), Wang QK(14), Yalnizoglu D(6), Radoshevich L(15), Uzé G(16), Gros P(17), Rozenberg F(18), Zhang SY(10), Jouanguy E(19), Bustamante J(20), García-Sastre A(21), Abel L(22), Lebon P(18), Notarangelo LD(23), Crow YJ(24), Boisson-Dupuis S(22), Casanova JL(25), Pellegrini S(26).

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Comment in

Nat Rev Immunol. 2014 Dec;14(12):780-1.

Intracellular ISG15 is an interferon (IFN)- $\alpha/\beta$ -inducible ubiquitin-like modifier which can covalently bind other proteins in a process called ISGylation; it is an effector of IFN- $\alpha/\beta$ -dependent antiviral immunity in mice. We previously published a study describing humans with inherited ISG15 deficiency but without unusually severe viral diseases. We showed that these patients were prone to mycobacterial disease and that human ISG15 was non-redundant as an extracellular IFN- $\gamma$ -inducing molecule. We show here that ISG15-deficient patients also display unanticipated cellular, immunological and clinical signs of enhanced IFN- $\alpha/\beta$  immunity, reminiscent of the Mendelian autoinflammatory interferonopathies Aicardi-Goutières syndrome and spondyloenchondrodysplasia. We further show that an absence of intracellular ISG15 in the patients' cells prevents the accumulation of USP18, a potent negative regulator of IFN- $\alpha/\beta$  signalling, resulting in the enhancement and amplification of IFN- $\alpha/\beta$  responses. Human ISG15, therefore, is not only redundant for antiviral immunity, but is a key negative regulator of IFN- $\alpha/\beta$  immunity. In humans, intracellular ISG15 is IFN- $\alpha/\beta$ -inducible not to serve as a substrate for ISGylation-dependent antiviral immunity, but to ensure USP18-dependent regulation of IFN- $\alpha/\beta$  and prevention of IFN- $\alpha/\beta$ -dependent autoinflammation.

DOI: 10.1038/nature13801

1870. Arthritis Rheumatol. 2015 Jan;67(1):302-14. doi: 10.1002/art.38912.

Enhanced chondrogenesis of induced pluripotent stem cells from patients with neonatal-onset multisystem inflammatory disease occurs via the caspase 1-independent cAMP/protein kinase A/CREB pathway.

Yokoyama K(1), Ikeya M, Umeda K, Oda H, Nodomi S, Nasu A, Matsumoto Y, Izawa K, Horigome K, Kusaka T, Tanaka T, Saito MK, Yasumi T, Nishikomori R, Ohara O, Nakayama N, Nakahata T, Heike T, Toguchida J.

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**OBJECTIVE:** Neonatal-onset multisystem inflammatory disease (NOMID) is a dominantly inherited autoinflammatory disease caused by NLRP3 mutations. NOMID pathophysiology is explained by the NLRP3 inflammasome, which produces interleukin-1 $\beta$  (IL-1 $\beta$ ). However, epiphyseal overgrowth in NOMID is resistant to anti-IL-1 therapy and may therefore occur independently of the NLRP3 inflammasome. This study was undertaken to investigate the effect of mutated NLRP3 on chondrocytes using induced pluripotent stem cells (iPSCs) from patients with NOMID.

**METHODS:** We established isogenic iPSCs with wild-type or mutant NLRP3 from 2 NOMID patients with NLRP3 somatic mosaicism. The iPSCs were differentiated into chondrocytes in vitro and in vivo. The phenotypes of chondrocytes with wild-type and mutant NLRP3 were compared, particularly the size of the chondrocyte tissue produced.

**RESULTS:** Mutant iPSCs produced larger chondrocyte masses than wild-type iPSCs owing to glycosaminoglycan overproduction, which correlated with increased expression of the chondrocyte master regulator SOX9. In addition, in vivo transplantation of mutant cartilaginous pellets into immunodeficient mice caused disorganized endochondral ossification. Enhanced chondrogenesis was independent of caspase 1 and IL-1, and thus the NLRP3 inflammasome. Investigation of the human SOX9 promoter in chondroprogenitor cells revealed that the CREB/ATF-binding site was critical for SOX9 overexpression caused by mutated NLRP3. This was supported by increased levels of cAMP and phosphorylated CREB in mutant

chondroprogenitor cells.

CONCLUSION: Our findings indicate that the intrinsic hyperplastic capacity of NOMID chondrocytes is dependent on the cAMP/PKA/CREB pathway, independent of the NLRP3 inflammasome.

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DOI: 10.1002/art.38912

PMID: 25302486 [Indexed for MEDLINE]

1871. Nihon Naika Gakkai Zasshi. 2014 Oct 10;103(10):2594-602.

[The Cutting-edge of Medicine: Hereditary autoinflammatory diseases: diagnosis and management].

[Article in Japanese]

Migita K, Kawakami A, Eguchi K.

PMID: 27514211 [Indexed for MEDLINE]

1872. PLoS One. 2014 Oct 8;9(10):e109095. doi: 10.1371/journal.pone.0109095. eCollection 2014.

Self DNA from lymphocytes that have undergone activation-induced cell death enhances murine B cell proliferation and antibody production.

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Systemic lupus erythematosus (SLE) is characterized by prominent autoinflammatory tissue damage associated with impaired removal of dying cells and DNA. Self DNA-containing immune complexes are able to activate both innate and adaptive immune responses and play an important role in the maintenance and exacerbation of autoimmunity in SLE. In this study, we used DNA from lymphocytes that have undergone activation-induced cell death (AICD-DNA) and analyzed its role on the activation and differentiation of B cells from normal BALB/c mice as well as lupus-prone MRL+/+ and MRL/lpr mice. We found that AICD-DNA directly increased the expression of costimulatory molecules and the survival of naïve B cells in vitro. Although AICD-DNA alone had little effect on the proliferation of naïve B cells, it enhanced LPS-activated B cell proliferation in vitro and in vivo. In addition, AICD-DNA increased plasma cell numbers and IgG production in LPS-stimulated cultures of naïve B cells, in part via enhancing IL-6 production. Importantly, B cells from lupus mice were hyperresponsive to AICD-DNA and/or LPS relative to normal control B cells in terminal plasma cell differentiation, as evidenced by increases in CD138+ cell numbers, IgM production, and mRNA levels of B lymphocyte-induced maturation protein-1 (Blimp-1) and the X-box binding protein 1 (XBP1). Furthermore, AICD-DNA enhanced CD40-activated naïve B cell proliferation. Collectively, these data indicate that self DNA can serve as a DAMP (damage-associated molecular pattern) that cooperates with signals from both innate and adaptive immunity to promote polyclonal B cell activation, a common characteristic of autoimmune diseases.

DOI: 10.1371/journal.pone.0109095

PMCID: PMC4189923

PMID: 25296026 [Indexed for MEDLINE]

1873. Ugeskr Laeger. 2014 Jul 28;176(31):1367-70.

[Autoinflammatory bone disorders in childhood].

[Article in Danish]

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Chronic non-bacterial osteomyelitis (CNO) is an autoinflammatory disease with unpredictable, painful courses of osteolytic lesions in the bones. CNO is frequently associated with psoriasis and inflammatory bowel disease. In cases with multifocal lesions the term chronic recurrent multifocal osteomyelitis (CRMO) is preferably used. SAPHO (synovitis, acne, pustulosis palmoplantaris, hyperostosis and osteitis) syndrome is regarded as CRMO in adults. New knowledge of the hereditary forms like Majeed syndrome, deficiency of IL-1-receptor antagonist and cherubism is described.

PMID: 25292328 [Indexed for MEDLINE]

1874. Int J Rheum Dis. 2016 Aug;19(8):806-13. doi: 10.1111/1756-185X.12482. Epub 2014 Oct 8.

Detection of Mediterranean fever gene mutations in Egyptian children with inflammatory bowel disease.

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AIM: The aim of the current study is to investigate the prevalence of familial Mediterranean fever gene (MEFV) mutations in a cohort of Egyptian children with inflammatory bowel disease (IBD), and to characterize familial Mediterranean fever (FMF)-IBD patients, helping better understanding of IBD pathogenesis.

METHODS: The study enrolled 17 patients with ulcerative colitis (UC), 15 with Crohn's disease(CD), 10 with indeterminate colitis (IC) and 33 healthy children as controls. All cases and controls were tested for 12 FMF gene mutations by reverse hybridization after multiplex polymerase chain reaction amplification and DNA sampling.

RESULTS: Eighty-eight percent of the IBD patients carried the mutations, with Sequence variant V627A being the commonest versus 42.4% of controls. No

associations were found between MEFV gene mutations, and phenotypic characteristics of IBD patients.

CONCLUSION: IBD patients, in populations with a high background carrier rate of MEFV variants, should be screened for MEFV gene mutations, especially those diagnosed as indeterminate colitis. Testing larger numbers of healthy Egyptian children for MEFV gene mutation is important to further determine the allele frequency in Egypt.

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DOI: 10.1111/1756-185X.12482

PMID: 25292286 [Indexed for MEDLINE]

1875. Clin Exp Immunol. 2015 Mar;179(3):392-7. doi: 10.1111/cei.12463.

Increased prevalence of MEFV exon 10 variants in Japanese patients with adult-onset Still's disease.

Nonaka F(1), Migita K, Jiuchi Y, Shimizu T, Umeda M, Iwamoto N, Fujikawa K, Izumi Y, Mizokami A, Nakashima M, Ueki Y, Yasunami M, Kawakami A, Eguchi K.

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Autoinflammatory diseases include a large spectrum of monogenic diseases, e.g. familial Mediterranean fever (FMF), as well as complex genetic trait diseases, e.g. adult-onset Still's disease (AOSD). In populations where FMF is common, an increased MEFV mutation rate is found in patients with rheumatic diseases. The aim of this study was to examine MEFV mutations in Japanese patients with AOSD. Genomic DNA was isolated from 49 AOSD patients and 105 healthy controls, and exons 1, 2, 3 and 10 of the MEFV gene genotyped by direct sequencing. MEFV mutation frequencies in AOSD patients were compared with controls. We found no significant difference in overall allele frequencies of MEFV variants between AOSD patients and controls. However, MEFV exon 10 variants (M694I and G632S) were significantly higher in AOSD patients than controls (6.1 versus 0%). In addition, there was no significant difference between MEFV variant carriers and non-carriers with clinical manifestations, but the monocyclic clinical course of

the AOSD disease phenotype was observed less frequently in patients without MEFV variants. AOSD patients had significantly higher frequencies of MEFV exon 10 mutations, suggesting that low-frequency variants of MEFV gene may be one of the susceptibility factors of AOSD.

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DOI: 10.1111/cei.12463

PMCID: PMC4337672

PMID: 25286988 [Indexed for MEDLINE]

1876. Acta Crystallogr F Struct Biol Commun. 2014 Oct;70(Pt 10):1351-6. doi: 10.1107/S2053230X14016926. Epub 2014 Sep 25.

Purification, crystallization and preliminary X-ray crystallographic analysis of human IL-18 and its extracellular complexes.

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Interleukin-18 (IL-18), a pro-inflammatory cytokine belonging to the interleukin-1 (IL-1) family, is involved in the pathogenesis of autoimmune/autoinflammatory and allergic diseases such as juvenile idiopathic arthritis and bronchial asthma. IL-18 forms a signalling complex with the IL-18 receptor  $\alpha$  (IL-18R $\alpha$ ) and  $\beta$  (IL-18R $\beta$ ) chains; however, the detailed activation mechanism remains unclear. Here, the IL-18-IL-18R $\alpha$  binary and IL-18-IL-18R $\alpha$ -IL-18R $\beta$  ternary complexes were purified and crystallized as well as IL-18 alone. An X-ray diffraction data set for IL-18 was collected to 2.33 Å resolution from a crystal belonging to space group P2<sub>1</sub>, with unit-cell parameters  $a = 68.15$ ,  $b = 79.51$ ,  $c = 73.46$  Å,  $\beta = 100.97^\circ$ . Crystals of both the IL-18 binary

and ternary complexes belonging to the orthorhombic space groups P21212 and P212121, respectively, diffracted to 3.10 Å resolution. Unit-cell parameters were determined as a = 135.49, b = 174.81, c = 183.40 Å for the binary complex and a = 72.56, b = 111.56, c = 134.57 Å for the ternary complex.

DOI: 10.1107/S2053230X14016926

PMCID: PMC4188078

PMID: 25286938 [Indexed for MEDLINE]

1877. Clin Ophthalmol. 2014 Sep 22;8:1891-911. doi: 10.2147/OPTH.S47778. eCollection 2014.

Pharmacotherapy for uveitis: current management and emerging therapy.

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Uveitis, a group of conditions characterized by intraocular inflammation, is a major cause of sight loss in the working population. Most uveitis seen in Western countries is noninfectious and appears to be autoimmune or autoinflammatory in nature, requiring treatment with immunosuppressive and/or anti-inflammatory drugs. In this educational review, we outline the ideal characteristics of drugs for uveitis and review the data to support the use of current and emerging therapies in this context. It is crucial that we continue to develop new therapies for use in uveitis that aim to suppress disease activity, prevent

accumulation of damage, and preserve visual function for patients with the minimum possible side effects.

DOI: 10.2147/OPTH.S47778

PMCID: PMC4181632

PMID: 25284976

1878. Allergy. 2014 Dec;69(12):1571-81. doi: 10.1111/all.12529.

Update on skin allergy.

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Skin diseases with an allergic background such as atopic dermatitis, allergic contact dermatitis, and urticaria are very common. Moreover, diseases arising from a dysfunction of immune cells and/or their products often manifest with skin symptoms. This review aims to summarize recently published articles in order to highlight novel research findings, clinical trial results, and current guidelines on disease management. In recent years, an immense progress has been made in understanding the link between skin barrier dysfunction and allergic sensitization initiating the atopic march. In consequence, new strategies for treatment and prevention have been developed. Novel pathogenic insights, for example, into urticaria, angioedema, mastocytosis, led to the development of new therapeutic approaches and their implementation in daily patient care. By understanding distinct pathomechanisms, for example, the role of IL-1, novel entities such as autoinflammatory diseases have been described. Considerable effort has been made to improve and harmonize patient management as documented in several guidelines and position papers.

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DOI: 10.1111/all.12529

PMID: 25283085 [Indexed for MEDLINE]

1879. J Phys Ther Sci. 2014 Sep;26(9):1459-63. doi: 10.1589/jpts.26.1459. Epub 2014 Sep 17.

Serum bone markers levels and bone mineral density in familial mediterranean Fever.

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[Purpose] The aim of this study was to measure bone mineral density, serum and urinary bone turnover parameters, and to evaluate the influence of demographic and genetic factors on these parameters in FMF patients. [Subjects and Methods] Twenty-seven attack-free patients who were diagnosed with FMF (in accordance with Tel Hashomer criteria) were recruited at outpatient rheumatology clinics. We investigated whether there were any differences between the FMF patients and a control group in terms of lumbar and femur bone mineral density (BMD), standard deviation scores (Z scores and T scores) and bone markers. [Results] In terms of the median values of lumbar BMD ( $p = 0.21$ ), lumbar T ( $p = 0.098$ ) and Z ( $p = 0.109$ ) scores, femoral neck BMD, femoral T and Z scores and total femur BMD, T ( $p = 0.788$ ) and Z scores, there were no significant differences. [Conclusion] In our study, no statistically significant differences were found between FMF patients and a control group in terms of osteoporosis. The 25-OH vitamin D was found to be significantly lower in FMF patients than in the control group.

DOI: 10.1589/jpts.26.1459

PMCID: PMC4175257

PMID: 25276036

1880. Nature. 2014 Dec 11;516(7530):246-9. doi: 10.1038/nature13788. Epub 2014 Sep 28.

Dietary modulation of the microbiome affects autoinflammatory disease.

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The incidences of chronic inflammatory disorders have increased considerably over the past three decades. Recent shifts in dietary consumption may have contributed importantly to this surge, but how dietary consumption modulates inflammatory disease is poorly defined. *Pstpip2(cmo)* mice, which express a homozygous Leu98Pro missense mutation in the Pombe Cdc15 homology family protein PSTPIP2 (proline-serine-threonine phosphatase interacting protein 2), spontaneously develop osteomyelitis that resembles chronic recurrent multifocal osteomyelitis in humans. Recent reports demonstrated a crucial role for interleukin-1 $\beta$  (IL-1 $\beta$ ) in osteomyelitis, but deletion of the inflammasome components caspase-1 and NLRP3 failed to rescue *Pstpip2(cmo)* mice from inflammatory bone disease. Thus, the upstream mechanisms controlling IL-1 $\beta$  production in *Pstpip2(cmo)* mice remain to be identified. In addition, the environmental factors driving IL-1 $\beta$ -dependent inflammatory bone erosion are unknown. Here we show that the intestinal microbiota of diseased *Pstpip2(cmo)* mice was characterized by an outgrowth of *Prevotella*. Notably, *Pstpip2(cmo)* mice that were fed a diet rich in fat and cholesterol maintained a normal body weight, but were markedly protected against inflammatory bone disease and bone erosion. Diet-induced protection against osteomyelitis was accompanied by marked reductions in intestinal *Prevotella*

levels and significantly reduced pro-IL-1 $\beta$  expression in distant neutrophils. Furthermore, pro-IL-1 $\beta$  expression was also decreased in Pstpip2(cmo) mice treated with antibiotics, and in wild-type mice that were kept under germ-free conditions. We further demonstrate that combined deletion of caspases 1 and 8 was required for protection against IL-1 $\beta$ -dependent inflammatory bone disease, whereas the deletion of either caspase alone or of elastase or neutrophil proteinase 3 failed to prevent inflammatory disease. Collectively, this work reveals diet-associated changes in the intestinal microbiome as a crucial factor regulating inflammasome- and caspase-8-mediated maturation of IL-1 $\beta$  and osteomyelitis in Pstpip2(cmo) mice.

DOI: 10.1038/nature13788

PMCID: PMC4268032

PMID: 25274309 [Indexed for MEDLINE]

1881. Clin Rheumatol. 2016 Mar;35(3):667-71. doi: 10.1007/s10067-014-2773-1. Epub 2014 Oct 3.

Evaluation of serum procalcitonin and C-reactive protein levels as biomarkers of Henoch-Schönlein purpura in pediatric patients.

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Henoch-Schönlein purpura (HSP) is a vasculitic disorder resulting from autoinflammatory-mediated tissue injury. Procalcitonin (PCT) and C-reactive protein (CRP) are two biomarkers of the immune response that recognize bacterial infection and inflammation, respectively. This study tested whether levels of PCT and CRP were associated with selected clinical features, disease severity, and organ damage in HSP. Eighty-nine pediatric patients with HSP were analyzed for clinical manifestations and organ damage. Serum CRP, PCT, and occult blood in the urine and stool (prior to steroid therapy) were measured. Disease severity was classified according to previously established clinical classifications. Sixty



patients (67.4 %) had a low clinical score (LCS) of  $<4$  (group A) while 29 patients (32.5 %) had a high clinical score (HCS) of  $\geq 4$  (group B). When patients were then classified by the presence of gastrointestinal bleeding, 66 (74.2 %) cases lacked alimentary tract hemorrhage (group C) while 23 (25.8 %) cases presented with gastrointestinal bleeding (group D). There were no significant differences in CRP (group A: median = 5.26, range = 1.00-77.60 vs. group B: median = 8.59, range = 1.00-144.00 mg/l;  $u = 1.397$ ) or PCT levels (group A: median = 0.05, range = 0.05-0.24 vs. group B: median = 0.08, range = 0.05-1.02 ng/ml;  $u = 1.709$ ) between groups A and B. When serum PCT levels were examined in relation to gastrointestinal bleeding, the levels of serum PCT were higher in group D than group C patients (group D: median = 0.09, range = 0.05-1.02 vs. group C: median = 0.05, range = 0.05-0.32 ng/ml;  $u = 2.849$ ). It is important to note that the average PCT level was below the threshold for a systemic bacterial infection (0.5 ng/ml). We did not observe a correlation between CRP levels and the absence or presence of GI bleeding in groups C or D (group C: median = 4.66, range = 1.00-144.00 vs. group D: median = 9.44, range = 1.06-124.00 mg/l;  $u = 1.783$ ), respectively. In all patients, there was a significant correlation between the concentrations of PCT and CRP ( $r = 0.721$ ,  $p = 0.002$ ). In patients with HSP, inflammatory markers are not uniformly associated with the disease and instead, show variable association depending on the clinical severity and level of organ damage. In patients with severe HSP, elevated serum PCT was significantly associated with gastrointestinal bleeding. In contrast, CRP was not a specific predictor for different clinical classifications of HSP, despite a similar pattern of concentration changes to PCT.

DOI: 10.1007/s10067-014-2773-1

PMID: 25273597 [Indexed for MEDLINE]

1882. Duodecim. 2014;130(16):1615-21.

[Still's disease--juvenile arthritis with systemic onset].

[Article in Finnish]

Kröger L, Putto-Laurila A, Vähäsalo P, Malin M, Aalto K.

Systemic onset juvenile idiopathic arthritis is a rare form of juvenile arthritis in which, contrary to autoimmune diseases in general, no association with a

certain tissue type has been detected. Together with this fact, the lack of autoantibodies and the general symptoms belonging to the diagnostic criteria of the illness such as high fever, rather speak for its classification into autoinflammatory diseases. Treatment is usually started with anti-inflammatory drugs, often requiring combination with a systemic glucocorticoid. Recognition of interleukins 1 and 6 as central mediators in the pathogenesis of the disease has brought new possibilities for its treatment.

PMID: 25269367 [Indexed for MEDLINE]

1883. Klin Med (Mosk). 2014;92(3):31-4.

[Familial Mediterranean fever (paroxysmal polyserositis, familial recurring polyserositis, periodic disease)].

[Article in Russian]

Shamov IA.

Paroxysmal polyserositis is an orphan disease most often affecting Mediterranean populations. It is caused by a mutation on chromosome 16 leading to pyrine synthesis disorder. The disease has a characteristic clinical picture, the most prominent manifestation being recurrent aseptic inflammation of serous membranes especially in peritoneum, marked temperature reaction, and apparent spontaneous recovery in the attack-free period. Inadequate or excessively intense treatment may cause complication in the form of secondary amyloidosis of internal organs. The most effective therapeutic modality is daily intake of colchicine at a dose of 1-1.5 mg.

PMID: 25269192 [Indexed for MEDLINE]

1884. Clin Exp Rheumatol. 2014 Jul-Aug;32(4 Suppl 84):S5-6. Epub 2014 Sep 29.

Self-criticism in Behçet's disease and other autoinflammatory conditions.

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PMID: 25268659 [Indexed for MEDLINE]

1885. Nat Rev Rheumatol. 2014 Nov;10(11):635. doi: 10.1038/nrrheum.2014.170. Epub 2014 Sep 30.

Autoinflammation: NLRC4 mutation causes rare autoinflammatory disease.

Bernard NJ.

Comment on

Nat Genet. 2014 Oct;46(10):1135-9.

Nat Genet. 2014 Oct;46(10):1140-6.

DOI: 10.1038/nrrheum.2014.170

PMID: 25266450 [Indexed for MEDLINE]

1886. Ann Rheum Dis. 2016 Jan;75(1):269-77. doi: 10.1136/annrheumdis-2014-205958. Epub 2014 Sep 26.

Neutrophil extracellular traps regulate IL-1 $\beta$ -mediated inflammation in familial Mediterranean fever.

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**OBJECTIVE:** Inflammatory attacks of familial Mediterranean fever (FMF) are characterised by circulation and influx of high number of polymorphonuclear neutrophils (PMN) in the affected sites and profound therapeutic effect of IL-1 $\beta$  inhibitors. We investigated the role of neutrophil extracellular traps (NET) in the pathogenesis of FMF, and their involvement in IL-1 $\beta$  production.

**METHODS:** Blood samples were obtained from six FMF patients during remissions and from three patients during attacks. NET formation and NET components were studied by fluorescence techniques, immunoblotting and MPO-DNA complex ELISA.

**RESULTS:** PMNs from patients released NETs decorated with IL-1 $\beta$  during disease attacks. On the other hand, PMNs from patients during remission were resistant to inflammatory stimuli that induce NET release in PMNs from control subjects. Lower basal autophagy levels were identified in PMNs during remission, while induction of autophagy facilitated NET release, suggesting that autophagy is involved in the regulation of NET release. During the resolution of attacks, inhibition of NET formation by negative feedback mechanism was also observed. The anti-inflammatory agents, colchicine and DNase I, inhibited IL-1 $\beta$  production in PMNs and IL-1 $\beta$  activity in NETs, respectively.

**CONCLUSIONS:** We suggest two additive events for triggering the FMF attack; the production of IL-1 $\beta$  by PMNs and its release through NETs. At the same time NETs, homeostatically, downregulate further NETosis, facilitating the resolution of attack. Compensatorily, lower basal autophagy of PMNs may protect from crises by attenuating the release of pro-inflammatory NETs.

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DOI: 10.1136/annrheumdis-2014-205958

PMID: 25261578 [Indexed for MEDLINE]

1887. Arthritis Res Ther. 2014 Sep 27;16(5):439. doi: 10.1186/s13075-014-0439-7.

Genotype-phenotype correlation in Japanese patients with familial Mediterranean fever: differences in genotype and clinical features between Japanese and Mediterranean populations.

Kishida D, Nakamura A, Yazaki M, Tsuchiya-Suzuki A, Matsuda M, Ikeda S.

**INTRODUCTION:** Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease characterized by recurrent self-limiting fever and serositis that mainly affects Mediterranean populations. Many patients with FMF have been reported in Japan due to increasing recognition of this condition and the availability of genetic analysis for the gene responsible, MEFV. The present study was performed to elucidate the clinical characteristics of Japanese FMF patients and to examine the precise genotype-phenotype correlation in a large cohort of Japanese FMF patients.

**METHODS:** We analyzed the MEFV genotypes and clinical manifestations in 116 patients clinically diagnosed as having FMF and with at least one mutation.

**RESULTS:** The most frequent mutation in Japanese patients was E148Q (40.2%), followed by M694I (21.0%), L110P (18.8%), P369S (5.4%), and R408Q (5.4%). In contrast, common mutations seen in Mediterranean patients, such as M694V, V726A, and M680I, were not detected in this population. The clinical features with M694I were associated with more severe clinical course compared to those seen with E148Q. P369S/R408Q showed variable phenotypes with regard to both clinical manifestations and severity. Patients with M694I showed a very favorable response to colchicine therapy, while those with P369S and R408Q did not.

**CONCLUSIONS:** Clinical features and efficacy of treatment in Japanese FMF patients vary widely according to the specific MEFV gene mutation, and therefore genetic analysis should be performed for diagnosis in cases of Japanese FMF.

DOI: 10.1186/s13075-014-0439-7

PMCID: PMC4201677

PMID: 25261100 [Indexed for MEDLINE]

1888. BMC Res Notes. 2014 Sep 27;7:678. doi: 10.1186/1756-0500-7-678.

Familial Mediterranean fever in which Crohn's disease was suspected: a case report.

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**BACKGROUND:** Familial Mediterranean fever is a hereditary autoinflammatory disease, mainly characterized by periodic fever and serositis. The level of awareness about familial Mediterranean fever is far from sufficient, and it is assumed that there may be many patients with this disease who are under observation without an accurate diagnosis.

**CASE PRESENTATION:** A 30-year-old Japanese man presented to us with a few years' history of recurrent episodes of fever, abdominal pain and diarrhea. He often visited a hospital when the attacks occurred; however, acute enteritis was diagnosed each time, and the symptoms resolved spontaneously within a few days. When he noticed a shortening of the interval between the attacks, he visited the hospital again. Upper endoscopy and colonoscopy performed at this hospital revealed no significant abnormal findings. He was then referred to our hospital under the suspicion of a small intestinal disease. Abdominal computed tomography revealed wall thickening and increased density of the mesenteric adipose tissue in the jejunum, which led us to suspect Crohn's disease. Oral double-balloon enteroscopy was performed; because this revealed only mild mucosal edema in the jejunum, Crohn's disease was considered to be highly improbable. Based on the patient's clinical course, we suspected familial Mediterranean fever. As the Livneh criteria for familial Mediterranean fever were satisfied, the patient was started on oral colchicine for the purpose of diagnostic treatment. A definitive diagnosis of familial Mediterranean fever was then made based on the detection of a mutation of the Mediterranean fever gene. A marked reduction in the frequency of attacks was observed in response to colchicine treatment.

**CONCLUSIONS:** Although Crohn's disease may be considered first in the differential diagnosis of young patients presenting with periodic fever, abdominal pain and diarrhea, the possibility of familial Mediterranean fever should also be borne in mind.

DOI: 10.1186/1756-0500-7-678

PMCID: PMC4182779

PMID: 25261084 [Indexed for MEDLINE]

1889. Nat Genet. 2014 Oct;46(10):1048-9. doi: 10.1038/ng.3100.

NLRC4 gets out of control.

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Comment on

Nat Genet. 2014 Oct;46(10):1135-9.

Nat Genet. 2014 Oct;46(10):1140-6.

The NLRC4 inflammasome mediates the rapid release of proinflammatory cytokines in response to various microbial stimuli, but its role in the pathology of human diseases remains unknown. Two new studies now report gain-of-function mutations in the NLRC4 gene that cosegregate with distinct autoinflammatory syndromes in affected families.

DOI: 10.1038/ng.3100

PMID: 25257084 [Indexed for MEDLINE]

1890. Clin Exp Ophthalmol. 2015 May-Jun;43(4):349-57. doi: 10.1111/ceo.12438. Epub 2014 Oct 30.

Aberrant interleukin-1 signalling does not increase susceptibility of mice to NOD2-dependent uveitis.

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**BACKGROUND:** NOD2 is the genetic cause of Blau syndrome, an autoinflammatory disease that manifests as coincident uveitis and arthritis. Since dysregulation of IL-1 signalling is considered a pathogenic mechanism in a number of related autoinflammatory conditions, we examined the extent to which unimpeded interleukin (IL)-1 signalling influences NOD2-dependent inflammation of the eye versus the joint.

**METHODS:** Mice deficient for IL-1R antagonist (IL-1Ra) were administered the NOD2 agonist muramyl dipeptide (MDP) by systemic (intraperitoneal) or local (intraocular and/or intra-articular) injections. NOD2-deficient mice received an intraocular injection of recombinant IL-1 $\beta$ . Uveitis was evaluated by intravital videomicroscopy and histopathology, and arthritis was assessed by near-infrared imaging and histopathology. Ocular levels of IL-1 $\alpha$ , IL-1 $\beta$  and IL-1Ra were quantified by enzyme-linked immunosorbent assay.

**RESULTS:** IL-1Ra deficiency did not render mice more responsive to systemic exposure of MDP. Despite the increased production of IL-1R agonists IL-1 $\alpha$  and IL-1 $\beta$  in response to intraocular injection of MDP, deficiency in IL-1Ra did not predispose mice to MDP-triggered uveitis, albeit intravascular cell rolling and adherence were exacerbated. NOD2 expression was dispensable for the potential of IL-1 to elicit uveitis. However, we find that IL-1Ra does play an important protective role in arthritis induced locally by MDP injection in the joint.

**CONCLUSIONS:** Our findings highlight the complexity of NOD2 activation and IL-1 signalling effects that can be compounded by local environmental factors of the target organ. These observations may impact how we understand the molecular mechanisms by which NOD2 influences inflammation of the eye versus joint, and consequently, treatment options for uveitis versus arthritis.

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DOI: 10.1111/ceo.12438

PMCID: PMC4375092

PMID: 25255917 [Indexed for MEDLINE]



Correcting the expression of miRNA-155 represses PP2Ac and enhances the release of IL-2 in PBMCs of juvenile SLE patients.

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MicroRNA-155 is involved in immune cell, differentiation, maturation and function. MiR-155 showed variable dysregulated expression in autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) patients. MiR-155 was previously confirmed to directly target CAMP response element binding protein (CREB), which was previously identified as a positive regulator of protein phosphatase 2A (PP2A). PP2A is a key negative regulator of interleukin-2, which is an important immune modulator and was previously shown to be decreased in SLE. In this study we aimed at investigating the regulation of PP2A by miR-155 and hence its role in juvenile SLE disease pathogenesis. MiR-155 showed significant downregulation in PBMCs from juvenile SLE and juvenile familial Mediterranean fever (FMF) and significant upregulation in PBMCs from juvenile idiopathic arthritis (JIA) patients. In SLE, miR-155 expression was negatively correlated with Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score and proteinuria and was positively correlated with white blood cell (WBC) count. The mRNA of the catalytic subunit of PP2A (PP2Ac) showed significant upregulation in PBMCs from SLE and FMF but not in JIA patients. Additionally, the relative expression of PP2Ac mRNA was positively correlated with SLEDAI score. Forced expression of miR-155 led to decreased relative expression of PP2Ac mRNA and increased IL-2 release in cultured-stimulated PBMCs. This study suggests for the first time the possible role of an miR-155-PP2Ac loop in regulating IL-2 release and identifies miR-155 as a potential therapeutic target in juvenile SLE disease through relieving IL-2 from the inhibitory role of PP2A.

DOI: 10.1177/0961203314552117

PMID: 25253569 [Indexed for MEDLINE]

1892. Nat Rev Rheumatol. 2015 Jan;11(1):11-20. doi: 10.1038/nrrheum.2014.158. Epub 2014 Sep 23.

New players driving inflammation in monogenic autoinflammatory diseases.

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Systemic autoinflammatory diseases are caused by abnormal activation of the cells that mediate innate immunity. In the past two decades, single-gene defects in different pathways, driving clinically distinct autoinflammatory syndromes, have been identified. Studies of these aberrant pathways have substantially advanced understanding of the cellular mechanisms that contribute to mounting effective and balanced innate immune responses. For example, mutations affecting the function of cytosolic immune sensors known as inflammasomes and the IL-1 signalling pathway can trigger excessive inflammation. A surge in discovery of new genes associated with autoinflammation has pointed to other mechanisms of disease linking innate immune responses to a number of basic cellular pathways, such as maintenance of protein homeostasis (proteostasis), protein misfolding and clearance, endoplasmic reticulum stress and mitochondrial stress, metabolic stress, autophagy and abnormalities in differentiation and development of myeloid cells. Although the spectrum of autoinflammatory diseases has been steadily expanding, a substantial number of patients remain undiagnosed. Next-generation sequencing technologies will be instrumental in finding disease-causing mutations in as yet uncharacterized diseases. As more patients are reported to have clinical features of autoinflammation and immunodeficiency or autoimmunity, the complex interactions between the innate and adaptive immune systems are unveiled.

DOI: 10.1038/nrrheum.2014.158  
PMID: 25247411 [Indexed for MEDLINE]

1893. Biomed Res Int. 2014;2014:616973. doi: 10.1155/2014/616973. Epub 2014 Aug 28.

New described dermatological disorders.

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Many advances in dermatology have been made in recent years. In the present review article, newly described disorders from the last six years are presented in detail. We divided these reports into different sections, including syndromes, autoinflammatory diseases, tumors, and unclassified disease. Syndromes included are "circumferential skin creases Kunze type" and "unusual type of pachyonychia congenita or a new syndrome"; autoinflammatory diseases include "chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome," "pyoderma gangrenosum, acne, and hidradenitis suppurativa (PASH) syndrome," and "pyogenic arthritis, pyoderma gangrenosum, acne, and hidradenitis suppurativa (PAPASH) syndrome"; tumors include "acquired reactive digital fibroma," "onychocytic matricoma and onychocytic carcinoma," "infundibulocystic nail bed squamous cell carcinoma," and "acral histiocytic nodules"; unclassified disorders include "saurian papulosis," "symmetrical acrokeratoderma," "confetti-like macular atrophy," and "skin spicules," "erythema papulosa semicircularis recidivans."

DOI: 10.1155/2014/616973  
PMCID: PMC4163364  
PMID: 25243162 [Indexed for MEDLINE]

1894. Rheumatology (Oxford). 2015 Apr;54(4):660-5. doi: 10.1093/rheumatology/keu359. Epub 2014 Sep 19.

Dysregulated mature IL-1 $\beta$  production in familial Mediterranean fever.

Migita K(1), Izumi Y(2), Fujikawa K(2), Agematsu K(2), Masumoto J(2), Jiuchi Y(2), Kozuru H(2), Nonaka F(2), Shimizu T(2), Nakamura T(2), Iwanaga N(2), Furukawa H(2), Yasunami M(2), Kawakami A(2), Eguchi K(2).

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Comment in

Rheumatology (Oxford). 2015 Nov;54(11):2119.

Rheumatology (Oxford). 2015 Nov;54(11):2118.

**OBJECTIVE:** The aim of this study was to analyse the role of circulating cleaved IL-1 $\beta$  in patients with FMF.

**METHODS:** We enrolled 20 patients with FMF (5 males and 15 females), 22 patients with RA (4 males and 18 females) and 22 healthy controls (6 males and 16 females). Serum levels of serum amyloid A (SAA) were measured by ELISA. We also determined whether IL-1 $\beta$  was present as the cleaved form (p17) in the sera of FMF patients by immunoblotting using anti-cleaved IL-1 $\beta$  antibody.

**RESULTS:** Although SAA concentrations were elevated in the sera, there was no significant difference in these concentrations between FMF patients and RA patients. Immunoblot analysis demonstrated that the cleaved form of IL-1 $\beta$  (p17) was present in sera from FMF patients during febrile attack periods, but not in healthy controls. Bands representing the cleaved form of IL-1 $\beta$  were not detected in serum from FMF patients at non-febrile attack periods or remission periods under colchicine treatment. The amounts of cleaved IL-1 $\beta$  (p17) were significantly higher in patients with FMF compared with those in patients with RA in the inflammatory phase.

**CONCLUSION:** The cleaved form of IL-1 $\beta$  is a valuable biomarker for monitoring disease activity and response to colchicine treatment in patients with FMF. It might be useful to discriminate FMF from other non-IL-1 $\beta$ -mediated inflammatory disorders.

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DOI: 10.1093/rheumatology/keu359

PMID: 25240611 [Indexed for MEDLINE]

1895. Rheumatology (Oxford). 2014 Dec;53(12):2312-4. doi: 10.1093/rheumatology/keu344. Epub 2014 Sep 17.

Treatment of Erdheim-Chester disease with canakinumab.

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DOI: 10.1093/rheumatology/keu344

PMID: 25234662 [Indexed for MEDLINE]

1896. Clin Exp Rheumatol. 2014 Nov-Dec;32(6 Suppl 87):S-12-3. Epub 2014 Sep 10.

Familial Mediterranean fever phenotype and MEFV variations.

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PMID: 25233909 [Indexed for MEDLINE]

1897. Pediatr Rheumatol Online J. 2014 Sep 9;12:41. doi: 10.1186/1546-0096-12-41.  
eCollection 2014.

MEFV gene mutations in Egyptian children with Henoch-Schonlein purpura.

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**BACKGROUND:** Due to an increased frequency of vasculitis in FMF patients, many investigators have studied MEFV mutations in patients with HSP. The aim of the study is to investigate the frequency and clinical significance of MEFV mutations in Egyptian children with Henoch-Schonlein purpura (HSP). Investigating MEFV mutations in controls may help in estimating the prevalence of MEFV mutation carrier rate in Egyptian children.

**METHODS:** The study enrolled 90 individuals, sixty children with Henoch-Schonlein purpura (HSP), together with 30 sex-and age-matched apparently healthy controls. The entire study group was screened for 12 common MEFV mutations using a reverse hybridization assay of biotinylated PCR products.

**RESULTS:** Patients with HSP had a significantly higher frequency of MEFV mutations (61.7%), when compared to the apparently healthy control population (36.7%). V726A was the most frequent mutation with an allelic frequency of 10.8%. Ninety-one percent of patients with MEFV mutations were heterozygous for one mutation, while 8.1% had a compound heterozygous MEFV gene mutations. The mutation V726A, followed by E148Q, were the leading mutations, present in 16.6% and in 13.3% of controls.

**CONCLUSIONS:** MEFV mutations may be related to HSP susceptibility in children. The mutations were not associated with any clinical and laboratory manifestations. Screening for MEFV mutations in larger number of HSP children may be beneficial to evaluate any possible relationship between certain types of MEFV mutations and HSP, and compare the HSP MEFV mutations to the types of MEFV mutations associated with FMF.

DOI: 10.1186/1546-0096-12-41

PMCID: PMC4165914

PMID: 25232290 [Indexed for MEDLINE]

1898. J Cereb Blood Flow Metab. 2014 Dec;34(12):1857-67. doi: 10.1038/jcbfm.2014.159. Epub 2014 Sep 17.

Molecular regulation of cell fate in cerebral ischemia: role of the inflammasome and connected pathways.

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Analogous to Toll-like receptors, NOD-like receptors represent a class of pattern recognition receptors, which are cytosolic and constitute part of different inflammasomes. These large protein complexes are activated not only by different pathogens, but also by sterile inflammation or by specific metabolic conditions. Mutations can cause hereditary autoinflammatory systemic diseases, and inflammasome activation has been linked to many multifactorial diseases, such as diabetes or cardiovascular diseases. Increasing data also support an important role in different central nervous diseases such as stroke. Thus, the current knowledge of the functional role of this intracellular 'master switch' of inflammation is discussed with a focus on its role in ischemic stroke, neurodegeneration, and also with regard to the recent data which argues for a relevant role in other organs or biologic systems which influence stroke incidence or prognosis.

DOI: 10.1038/jcbfm.2014.159

PMCID: PMC4269743

PMID: 25227604 [Indexed for MEDLINE]

1899. Clin Rheumatol. 2015 Oct;34(10):1817-20. doi: 10.1007/s10067-014-2781-1. Epub 2014 Sep 16.

Long-lasting uveitis remission and hearing loss recovery after rituximab in Vogt-Koyanagi-Harada disease.

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Vogt-Koyanagi-Harada disease (VKHD) is a multisystemic disorder characterized by granulomatous panuveitis variably combined with T cell-mediated neurologic and cutaneous manifestations. Early and aggressive treatment with systemic corticosteroids is the mainstay of treatment for VKHD. Additional use of immunosuppressants, intravenous immunoglobulins, and tumor necrosis factor-alpha inhibitors can help the most severely affected patients and work as corticosteroid-sparing agents. We report the case of a young woman with relapsing and multiresistant VKHD who demonstrated a stable remission of both uveitis and high-frequency hearing loss following rituximab intravenous administration (1 g. twice, 2 weeks apart, and 6 months later). A complete clinical response was observed 1 month since the first infusion, and no ocular relapses were recorded during the following year; in addition, audiometry showed a high-frequency hearing recovery in the right ear. Further observational studies are required to define the role of CD20 inhibition in the management of VKHD.

DOI: 10.1007/s10067-014-2781-1

PMID: 25224382 [Indexed for MEDLINE]

1900. Arthritis Rheumatol. 2014 Nov;66(11):3221-6. doi: 10.1002/art.38797.

Exertional leg pain in familial Mediterranean fever: a manifestation of an underlying enthesopathy and a marker of more severe disease.

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**OBJECTIVE:** Exertional leg pain is a characteristic musculoskeletal manifestation of familial Mediterranean fever (FMF). We aimed to define the frequency and characteristics of exertional leg pain in a large cohort of FMF patients and to evaluate for additional signs and symptoms of spondyloarthritis (SpA) in this patient population.

**METHODS:** FMF patients were allocated into study or control groups based on the presence or absence of exertional leg pain. Randomly selected patients underwent magnetic resonance imaging (MRI) of the ankle as well as plain radiography of the sacroiliac joints.

**RESULTS:** The prevalence of exertional leg pain among the 170 FMF patients included in the study was 58.2%. Patients with exertional leg pain had significantly more joint attacks (74.7% versus 40.8%;  $P < 0.0001$ ), fever attacks (35.4% versus 15.5%;  $P = 0.004$ ), and pleuritis attacks (48.5% versus 29.6%;  $P = 0.013$ ) as well as more attacks per year. Elevations of inflammation markers were significantly more frequent among the study group (for the erythrocyte sedimentation rate, 44.4% of patients versus 21.1% of patients;  $P = 0.016$ ) (for the C-reactive protein level, 48.4% of patients versus 31.8% of patients;  $P = 0.013$ ), and M694V homozygosity was more prevalent among the study group (45.5% versus 21.1%;  $P = 0.001$ ). Signs compatible with enthesopathy on MRI were observed in 73.5% of patients in the study group and in 33.3% of patients in the control group ( $P = 0.046$ ). Definite SpA was diagnosed in 41.2% of the patients in the study group compared to none of the controls ( $P = 0.07$ ) (odds ratio 1.7 [95% confidence interval 1.2-2.3]).

**CONCLUSION:** Exertional leg pain is a common manifestation of FMF and is a marker of a more severe disease phenotype. Additionally, exertional leg pain is frequently associated with sacroiliitis and an underlying ankle enthesopathy and should therefore be considered a new feature of SpA.

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DOI: 10.1002/art.38797

PMID: 25223248 [Indexed for MEDLINE]

1901. Curr Opin Chem Biol. 2014 Dec;23:23-30. doi: 10.1016/j.cbpa.2014.08.013. Epub 2014 Sep 15.

Small-molecule control of cytokine function: new opportunities for treating

immune disorders.

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Manipulating cytokine function with protein-based drugs has proven effective for treating a wide variety of autoimmune and autoinflammatory disorders. However, the limited ability of protein-based drugs to modulate intracellular targets, including many implicated by studies of the genetics and physiology of these diseases, and to coordinately neutralize redundant inflammatory cytokines, suggests an important and complementary role for small molecules in immunomodulatory drug development. The recent clinical approval of Janus kinase and phosphodiesterase inhibitors, along with emerging evidence from other compound classes, firmly establish small molecules as effective tools for modulating therapeutically relevant proteins that give rise to aberrant cytokine signaling or mediate its downstream consequences.

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DOI: 10.1016/j.cbpa.2014.08.013

PMCID: PMC5087273

PMID: 25222143 [Indexed for MEDLINE]

1902. Arthritis Rheumatol. 2015 Jan;67(1):288-95. doi: 10.1002/art.38877.

Association of a mutation in LACC1 with a monogenic form of systemic juvenile idiopathic arthritis.

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**OBJECTIVE:** The pathologic basis of systemic juvenile idiopathic arthritis (JIA) is a subject of some controversy, with evidence for both autoimmune and autoinflammatory etiologies. Several monogenic autoinflammatory disorders have been described, but thus far, systemic JIA has only been attributed to a mutation of MEFV in rare cases and has been weakly associated with the HLA class II locus. This study was undertaken to identify the cause of an autosomal-recessive form of systemic JIA.

**METHODS:** We studied 13 patients with systemic JIA from 5 consanguineous families, all from the southern region of Saudi Arabia. We used linkage analysis, homozygosity mapping, and whole-exome sequencing to identify the disease-associated gene and mutation.

**RESULTS:** Linkage analysis localized systemic JIA to a region on chromosome 13 with a maximum logarithm of odds score of 11.33, representing the strongest linkage identified to date for this disorder. Homozygosity mapping reduced the critical interval to a 1.02-Mb region defined proximally by rs9533338 and distally by rs9595049. Whole-exome sequencing identified a homoallelic missense mutation in LACC1, which encodes the enzyme laccase (multicopper oxidoreductase) domain-containing 1. The mutation was confirmed by Sanger sequencing and segregated with disease in all 5 families based on an autosomal-recessive pattern of inheritance and complete penetrance.

**CONCLUSION:** Our findings provide strong genetic evidence of an association of a mutation in LACC1 with systemic JIA in the families studied. Association of LACC1 with Crohn's disease and leprosy has been reported and justifies investigation of its role in autoinflammatory disorders.

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DOI: 10.1002/art.38877

PMID: 25220867 [Indexed for MEDLINE]

1903. Autoimmun Rev. 2014 Oct;13(10):1035-41. doi: 10.1016/j.autrev.2014.08.031. Epub 2014 Aug 23.

Long-term effectiveness and safety of interleukin-1 receptor antagonist (anakinra) in Schnitzler's syndrome: a French multicenter study.

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The aim of this study is to assess the long-term effectiveness and safety of IL1Ra in Schnitzler syndrome (SchS). Between 2010 and 2012, we performed a nationwide survey among French internal medicine departments to identify SchS patients. We retrospectively analyzed the long-term efficacy and safety of IL1Ra and the outcome of patients that did not receive this treatment. Forty-two patients were included in the study, 29 of whom received IL1Ra. The mean age at disease onset was 59.9years. Disease manifestations included urticaria (100%), fever (76%), bone/joint pain (86%), bone lesions (76%), anemia (67%), and weight loss (60%). The monoclonal gammopathy was overwhelmingly IgM kappa (83%). The mean follow-up was 9.5years (range: 1.6-35). Two patients developed Waldenström's macroglobulinemia and one developed AA amyloidosis. All of the 29 patients who received IL1Ra responded dramatically. After a median follow-up of 36months (range: 2-79), the effectiveness remained unchanged. All patients remained on anti-IL-1 therapy. Twenty-four patients (83%) went into complete remission and five (17%) into partial remission. Three patients experienced grade 3-4 neutropenia. Six patients developed severe infections. No lymphoproliferative diseases occurred while on IL1Ra. When last seen, all patients without anakinra had an active disease with variable impact on their quality of life. Their median corticosteroids dosage was 6mg/d (range: 5-25). IL1Ra is effective in SchS, with a sharp corticosteroid-sparing effect. Treatment failures should lead to reconsider the diagnosis. Long-term follow-up revealed no loss of effectiveness and a favorable tolerance profile. The long-term effects on the risk of hemopathy remain unknown.

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DOI: 10.1016/j.autrev.2014.08.031

PMID: 25220180 [Indexed for MEDLINE]

1904. Nat Genet. 2014 Oct;46(10):1135-1139. doi: 10.1038/ng.3066. Epub 2014 Sep 14.

Mutation of NLRC4 causes a syndrome of enterocolitis and autoinflammation.

Romberg N(#)(1), Al Moussawi K(#)(2), Nelson-Williams C(3)(4), Stiegler AL(5), Loring E(3), Choi M(3)(4), Overton J(3), Meffre E(2)(6), Khokha MK(1)(3), Huttner AJ(7), West B(7), Podoltsev NA(2), Boggon TJ(5), Kazmierczak BI(2)(8), Lifton RP(2)(3)(4).

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Comment in

Nat Rev Rheumatol. 2014 Nov;10(11):635.

Nat Genet. 2014 Oct;46(10):1048-9.

Upon detection of pathogen-associated molecular patterns, innate immune receptors

initiate inflammatory responses. These receptors include cytoplasmic NOD-like receptors (NLRs) whose stimulation recruits and proteolytically activates caspase-1 within the inflammasome, a multiprotein complex. Caspase-1 mediates the production of interleukin-1 family cytokines (IL1FCs), leading to fever and inflammatory cell death (pyroptosis). Mutations that constitutively activate these pathways underlie several autoinflammatory diseases with diverse clinical features. We describe a family with a previously unreported syndrome featuring neonatal-onset enterocolitis, periodic fever, and fatal or near-fatal episodes of autoinflammation. We show that the disease is caused by a de novo gain-of-function mutation in NLRC4 encoding a p.Val341Ala substitution in the HD1 domain of the protein that cosegregates with disease. Mutant NLRC4 causes constitutive IL1FC production and macrophage cell death. Infected macrophages from affected individuals are polarized toward pyroptosis and exhibit abnormal staining for inflammasome components. These findings identify and describe the cause of a life-threatening but treatable autoinflammatory disease that underscores the divergent roles of the NLRC4 inflammasome.

DOI: 10.1038/ng.3066

PMCID: PMC4177367

PMID: 25217960 [Indexed for MEDLINE]

1905. Nat Genet. 2014 Oct;46(10):1140-6. doi: 10.1038/ng.3089. Epub 2014 Sep 14.

An activating NLRC4 inflammasome mutation causes autoinflammation with recurrent macrophage activation syndrome.

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Comment in

Nat Rev Rheumatol. 2014 Nov;10(11):635.

Nat Genet. 2014 Oct;46(10):1048-9.

Inflammasomes are innate immune sensors that respond to pathogen- and damage-associated signals with caspase-1 activation, interleukin (IL)-1 $\beta$  and IL-18 secretion, and macrophage pyroptosis. The discovery that dominant gain-of-function mutations in NLRP3 cause the cryopyrin-associated periodic syndromes (CAPS) and trigger spontaneous inflammasome activation and IL-1 $\beta$  oversecretion led to successful treatment with IL-1-blocking agents. Herein we report a de novo missense mutation (c.1009A > T, encoding p.Thr337Ser) affecting the nucleotide-binding domain of the inflammasome component NLRC4 that causes early-onset recurrent fever flares and macrophage activation syndrome (MAS). Functional analyses demonstrated spontaneous inflammasome formation and production of the inflammasome-dependent cytokines IL-1 $\beta$  and IL-18, with the latter exceeding the levels seen in CAPS. The NLRC4 mutation caused constitutive caspase-1 cleavage in cells transduced with mutant NLRC4 and increased production of IL-18 in both patient-derived and mutant NLRC4-transduced macrophages. Thus, we describe a new monoallelic inflammasome defect that expands the monogenic autoinflammatory disease spectrum to include MAS and suggests new targets for

therapy.

DOI: 10.1038/ng.3089

PMCID: PMC4177369

PMID: 25217959 [Indexed for MEDLINE]

1906. Clin Rheumatol. 2016 Feb;35(2):441-6. doi: 10.1007/s10067-014-2772-2. Epub 2014 Sep 13.

Anti-IL-1 treatment in familial Mediterranean fever and related amyloidosis.

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Colchicine is the standard treatment in familial Mediterranean fever (FMF) patients. New treatment strategies are needed in FMF patients who were unresponsive to colchicine therapy or who had developed amyloidosis. The aim of this study was to present clinical-laboratory features and treatment responses of pediatric FMF patients that were treated with anti-IL-1 therapies. Files of patients who had been followed in our department with diagnosis of FMF were retrospectively evaluated. Patients that have been receiving anti-IL-1 therapies (anakinra or canakinumab) were included to the study. All patients were interpreted with respect to the demographic data, clinical and laboratory features of the disease, genetic analysis of MEFV mutations and treatment responses. Among 330 currently registered FMF patients, 13 patients were included to the study. Seven of them received anti-IL-1 therapy due to colchicine resistance and 6 due to FMF-related amyloidosis (1 of them with nephrotic

syndrome, 2 with chronic kidney disease, 3 with renal transplantation). In all treated patients, attacks completely disappeared or decreased in frequency; partial remission occurred in nephrotic syndrome patient; and their life quality improved. Anti-IL-1 therapies can be successfully used in colchicine-resistant FMF patients and patients with amyloidosis during childhood and adolescent period without major side effects.

DOI: 10.1007/s10067-014-2772-2

PMID: 25213327 [Indexed for MEDLINE]

1907. J Allergy Clin Immunol Pract. 2014 Sep-Oct;2(5):642. doi: 10.1016/j.jaip.2014.01.007. Epub 2014 Apr 18.

Possible cold autoinflammatory syndrome.

Lieberman P, Hoffman HM.

DOI: 10.1016/j.jaip.2014.01.007

PMID: 25213069 [Indexed for MEDLINE]

1908. Ann Dermatol Venereol. 2014 Aug-Sep;141(8-9):538-45; quiz 536-7, 546. doi: 10.1016/j.annder.2014.06.005. Epub 2014 Jul 9.

[Hereditary recurrent fever].

[Article in French]

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DOI: 10.1016/j.annder.2014.06.005

PMID: 25209820 [Indexed for MEDLINE]

1909. Clin Rheumatol. 2015 Apr;34(4):785-90. doi: 10.1007/s10067-014-2770-4. Epub 2014 Sep 12.

TLR2 and TLR4 gene expression levels and associated factors during acute attack and attack-free periods in familial Mediterranean fever.

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The purpose of this clinical study was to determine if the expression of the TLR2 and/or TLR4 genes is involved in triggering the auto-inflammatory attacks in patients with familial Mediterranean fever (FMF). Thirty patients with FMF and 20 healthy control subjects were recruited. Comparisons were made in TLR2 and TLR4 gene expression levels during FMF attack episodes and attack-free periods, as well as with baseline levels in healthy control subjects. There was no significant difference in TLR2 and TLR4 gene expression between the attacks and attack-free periods in the entire group of FMF patients. However, among female patients, expression level of TLR4 gene was significantly higher during the attack than in the attack-free period (TLR2 Log  $2.04 \pm 0.14$  vs.  $2.52 \pm 0.10$ , respectively,  $P = 0.02$ ). There was not a significant difference between FMF patients and healthy subjects. The patients who had higher levels of TLR2 expression during the acute attack experienced their first attacks at an earlier age ( $r = -0.571$ ;  $P = 0.001$ ). The frequency of attacks, acute-phase response, MEFV mutations, and colchicine response were not associated with TLR2 and TLR4 levels. We conclude that changes in the expression of TLR2 and TLR4 genes do not appear to be involved in triggering FMF attacks. A higher level of TLR2 expression during acute attack may be related to the early onset of the disease. Further studies using specific cell populations such as neutrophils, monocytes, and

dendritic cells may be useful to explore any changes in the sensitivity of toll-like receptors to their agonists, such as lipopolysaccharides, in the onset of attacks.

DOI: 10.1007/s10067-014-2770-4

PMID: 25208763 [Indexed for MEDLINE]

1910. *Oncol Lett.* 2014 Oct;8(4):1735-1738. Epub 2014 Aug 4.

Increased frequency of Mediterranean fever gene variants in multiple myeloma.

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High frequencies of inherited variants in the Mediterranean fever (MEFV) gene have been identified in patients with multiple myeloma (MM). The sample size of the present pilot study was small, therefore, the actual frequency of inherited variants in the MEFV gene could be investigated in patients with MM. Twenty-eight patients with MM and 65 healthy controls were included in the study. Six heterozygous and one homozygous (E148Q/E148Q) variant was identified in patients with MM. None of the patients had a family history compatible with familial Mediterranean fever. In the healthy control group, 11 heterozygous variants were identified. The difference in the overall frequency of the inherited variants in the MEFV gene between the MM patients and the controls was statistically significant ( $\chi^2=4.905$ ;  $P=0.027$ ). In conclusion, a high frequency of inherited variants in the MEFV gene was identified in patients with MM. Based on the current data, it is hypothesized that the MEFV gene is a cancer susceptibility gene. Additional evidence, such as familial aggregation, monozygotic versus dizygotic twin concordance, and tumors in genetically engineered model organisms, is required in order to support this hypothesis.

DOI: 10.3892/ol.2014.2407

PMCID: PMC4156200

PMID: 25202401

1911. Lupus. 2015 Feb;24(2):130-7. doi: 10.1177/0961203314550227. Epub 2014 Sep 8.

Pyoderma gangrenosum and systemic lupus erythematosus: a report of five cases and review of the literature.

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Pyoderma gangrenosum (PG) is an uncommon, distinctive cutaneous ulceration which is usually idiopathic, but may be associated with many systemic disorders. The etiopathogenesis of PG is still not well understood. PG is part of the spectrum of the neutrophilic dermatoses and it has been proposed as a prototype of cutaneous autoinflammatory disease. PG usually has a good outcome under immunosuppressive treatment. Although PG has been associated with several systemic diseases, it has rarely been reported in association with systemic lupus erythematosus (SLE). In this article we report five cases of SLE-related PG and review the literature. Our findings support the possible relationship between active SLE and PG, although the mechanism remains unclear. Clinical manifestations, used treatments and outcomes of SLE-related PG do not differ from the described for the general population.

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[sagepub.co.uk/journalsPermissions.nav](http://sagepub.co.uk/journalsPermissions.nav).

DOI: 10.1177/0961203314550227

PMID: 25199808 [Indexed for MEDLINE]

1912. Pediatr Ann. 2014 Sep;43(9):350-2. doi: 10.3928/00904481-20140825-04.

A 5-year-old boy with vomiting, abdominal pain, and fatigue.

Alaygut D, Kilic SC.

DOI: 10.3928/00904481-20140825-04

PMID: 25198441 [Indexed for MEDLINE]

1913. Med Sci Monit. 2014 Sep 5;20:1578-82. doi: 10.12659/MSM.892139.

Usefulness of mean platelet volume and neutrophil-to-lymphocyte ratio for evaluation of children with Familial Mediterranean fever.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is an autoinflammatory disease characterized by recurrent attacks of serositis, fever, and rash. Clinical and subclinical inflammatory processes may contribute to atherosclerosis in FMF patients, with mean platelet volume (MPV) as a potential indicator for atherosclerosis risk and neutrophil-to-lymphocyte ratio (NLR) as a marker for subclinical inflammation in these patients. In this study, we investigated whether MPV can be used as an indicator for atherosclerosis risk and if NLR is a marker for subclinical inflammation in FMF patients.

**MATERIAL AND METHODS:** The study consisted of 75 FMF patients in attack, 157 attack-free patients, and 77 healthy controls. White blood cell count neutrophil-to-lymphocyte ratio, platelet count, MPV, PDW C-reactive protein levels, and erythrocyte sedimentation rate were recorded.

**RESULTS:** There were no significant differences between attack, attack-free, and control groups in terms of mean MPV and PDW value. NLR value was higher in the attack group. NLR value was similar in attack-free and control groups.

**CONCLUSIONS:** We found that MPV and PDW values are similar in FMF patients and

healthy controls. NLR was higher in FMF patients in the attack period. Therefore, our results suggest that MPV and PDW values do not predict atherosclerosis risk in pediatric FMF patients, and NLR may be an indicator for attack period but not attack-free period.

DOI: 10.12659/MSM.892139

PMCID: PMC4165509

PMID: 25189760 [Indexed for MEDLINE]

1914. Harefuah. 2014 Jul;153(7):397-400.

[Autoimmune/autoinflammatory syndrome induced by adjuvant (ASIA)].

[Article in Hebrew]

Israeli F.

PMID: 25189030 [Indexed for MEDLINE]

1915. Autoimmun Rev. 2014 Nov;13(11):1149-59. doi: 10.1016/j.autrev.2014.08.032. Epub 2014 Aug 27.

Adult onset Still's disease (AOSD) in the era of biologic therapies: dichotomous view for cytokine and clinical expressions.

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Adult onset Still's disease (AOSD) is a rare inflammatory disorder characterized by hectic spiking fever, evanescent rash and joint involvement. Prognosis is highly variable upon disease course and specific involvements, ranging from benign and limited outcome to chronic destructive polyarthritides and/or life-threatening events in case of visceral complications or reactive hemophagocytic lymphohistiocytosis (RHL). AOSD remains a debatable entity at the frontiers of autoimmune diseases and autoinflammatory disorders. The pivotal role of macrophage cell activation leading to a typical Th1 cytokine storm is now well established in AOSD, and confirmed by the benefits using treatments targeting TNF- $\alpha$ , IL-1 $\beta$  or IL-6 in refractory patients. However, it remains difficult to determine predictive factors of outcome and to draw guidelines for patient management. Herein, reviewing literature and relying on our experience in a series of 8 refractory AOSD patients, we question nosology and postulate that different cytokine patterns could underlie contrasting clinical expressions, as well as responses to targeted therapies. We therefore propose to dichotomize AOSD according to its clinical presentation. On the one hand, 'systemic AOSD' patients, exhibiting the highest inflammation process driven by excessive IL-18, IL-1 $\beta$  and IL-6 production, would be at risk of life-threatening complications (such as multivisceral involvements and RHL), and would preferentially respond to IL-1 $\beta$  and IL-6 antagonists. On the other hand, 'rheumatic AOSD' patients, exhibiting pre-eminence of joint involvement driven by IL-8 and IFN- $\gamma$  production, would be at risk of articular destructions, and would preferentially respond to TNF- $\alpha$  blockers.

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DOI: 10.1016/j.autrev.2014.08.032

PMID: 25183244 [Indexed for MEDLINE]

1916. Autoimmun Rev. 2014 Dec;13(12):1220-9. doi: 10.1016/j.autrev.2014.08.010. Epub 2014 Aug 23.

Caveats and truths in genetic, clinical, autoimmune and autoinflammatory issues in Blau syndrome and early onset sarcoidosis.

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Blau syndrome (BS) and early onset sarcoidosis (EOS) are, respectively, the familial and sporadic forms of the pediatric granulomatous autoinflammatory disease, which belong to the group of monogenic autoinflammatory syndromes. Both

of these conditions are caused by mutations in the NOD2 gene, which encodes the cytosolic NOD2 protein, one of the pivotal molecules in the regulation of innate immunity, primarily expressed in the antigen-presenting cells. Clinical onset of BS and EOS is usually in the first years of life with noncaseating epithelioid granulomas mainly affecting joints, skin, and uveal tract, variably associated with heterogeneous systemic features. The dividing line between autoinflammatory and autoimmune mechanisms is probably not so clear-cut, and the relationship existing between BS or EOS and autoimmune phenomena remains unclear. There is no established therapy for the management of BS and EOS, and the main treatment aim is to prevent ocular manifestations entailing the risk of potential blindness and to avoid joint deformities. Nonsteroidal anti-inflammatory drugs, corticosteroids and immunosuppressive drugs, such as methotrexate or azathioprine, may be helpful; when patients are unresponsive to the combination of corticosteroids and immunosuppressant agents, the tumor necrosis factor- $\alpha$  inhibitor infliximab should be considered. Data on anti-interleukin-1 inhibition with anakinra and canakinumab is still limited and further corroboration is required. The aim of this paper is to describe BS and EOS, focusing on their genetic, clinical, and therapeutic issues, with the ultimate goal of increasing clinicians' awareness of both of these rare but serious disorders.

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DOI: 10.1016/j.autrev.2014.08.010

PMID: 25182201 [Indexed for MEDLINE]

1917. Arthritis Res Ther. 2014 Aug 30;16(4):419. doi: 10.1186/s13075-014-0419-y.

Interleukin-10 regulates the inflammasome-driven augmentation of inflammatory arthritis and joint destruction.

Greenhill CJ, Jones GW, Nowell MA, Newton Z, Harvey AK, Moideen AN, Collins FL, Bloom AC, Coll RC, Robertson AA, Cooper MA, Rosas M, Taylor PR, O'Neill LA, Humphreys IR, Williams AS, Jones SA.

**INTRODUCTION:** Activation of the inflammasome has been implicated in the pathology of various autoinflammatory and autoimmune diseases. While the NLRP3 inflammasome has been linked to arthritis progression, little is known about its synovial regulation or contribution to joint histopathology. Regulators of inflammation

activation, such as interleukin (IL)-10, may have the potential to limit the inflammasome-driven arthritic disease course and associated structural damage. Hence, we used IL-10-deficient (IL-10KO) mice to assess NLRP3 inflammasome-driven arthritic pathology.

**METHODS:** Antigen-induced arthritis (AIA) was established in IL-10KO mice and wild-type controls. Using histological and radiographic approaches together with quantitative real-time PCR of synovial mRNA studies, we explored the regulation of inflammasome components. These were combined with selective blocking agents and ex vivo investigative studies in osteoclast differentiation assays.

**RESULTS:** In AIA, IL-10KO mice display severe disease with increased histological and radiographic joint scores. Here, focal bone erosions were associated with increased tartrate-resistant acid phosphatase (TRAP)-positive cells and a localized expression of IL-1 $\beta$ . When compared to controls, IL-10KO synovium showed increased expression of Il1b, Il33 and NLRP3 inflammasome components. Synovial Nlrp3 and Casp1 expression further correlated with Acp5 (encoding TRAP), while neutralization of IL-10 receptor signaling in control mice caused increased expression of Nlrp3 and Casp1. In ex vivo osteoclast differentiation assays, addition of exogenous IL-10 or selective blockade of the NLRP3 inflammasome inhibited osteoclastogenesis.

**CONCLUSIONS:** These data provide a link between IL-10, synovial regulation of the NLRP3 inflammasome and the degree of bone erosions observed in inflammatory arthritis.

DOI: 10.1186/s13075-014-0419-y

PMCID: PMC4292830

PMID: 25175678 [Indexed for MEDLINE]

1918. Intern Med. 2014;53(17):2013-6. Epub 2014 Sep 1.

Three patients with familial Mediterranean fever: a possible underdiagnosed entity in Japan.

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Familial Mediterranean fever (FMF) is an autosomal recessive disorder

characterized by periodic fever and serosal inflammation. FMF is mostly reported in the Mediterranean region and is considered to be rare in Japan with estimated 292 cases. We treated three unrelated FMF patients in one year in a city with 144,000 residents. Two of the three patients were over 70 years old. FMF may therefore be underdiagnosed in Japan.

PMID: 25175140 [Indexed for MEDLINE]

1919. Rheumatology (Oxford). 2015 Feb;54(2):363-8. doi: 10.1093/rheumatology/keu341. Epub 2014 Aug 29.

TLR2/TLR4-dependent exaggerated cytokine production in hyperimmunoglobulinaemia D and periodic fever syndrome.

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**OBJECTIVE:** The autoinflammatory hyperimmunoglobulinaemia D and periodic fever syndrome (HIDS) is characterized by recurrent episodes of fever and inflammation. As part of the mevalonate kinase deficiency spectrum, it is caused by MVK mutations, resulting in decreased mevalonate kinase activity in the isoprenoid pathway. Although IL-1 $\beta$  is considered a major cytokine in its pathogenesis, IL-1 blockade is not successful in a proportion of patients. We aimed to further characterize the pro-inflammatory cytokine profile of HIDS.

**METHODS:** Peripheral blood mononuclear cells from HIDS patients and healthy donors

were incubated with several stimuli. Cytokine concentrations were detected by ELISA. To analyse mRNA and protein expression, we performed quantitative RT-PCR and western blot, respectively.

**RESULTS:** We observed significant differences in cytokine production when cells were incubated with ligands for Toll-like receptor 2 (TLR2), TLR4 and nucleotide-binding oligomerization domain-containing 2 (NOD2). The increased ratio between active and inactive caspase-1 protein in HIDS patients could explain why these cells are more easily triggered to secrete IL-1 $\beta$ . This is apparently not regulated at the transcriptional level, since expression levels of caspase-1 and IL-1 $\beta$  mRNA were similar in patients and controls. Both anakinra and tocilizumab treatment resulted in decreased inflammation, both ex vivo as well as in vivo.

**CONCLUSION:** The increased cytokine secretion in HIDS is specific for TLR2, TLR4 and NOD2 ligation. Although IL-1 $\beta$  is important in the HIDS pathology, our data suggest it is a multicytokine disease. A more rigorous clinical trial is required to determine whether IL-6 receptor blockade may be considered in patients not responding to anakinra treatment.

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DOI: 10.1093/rheumatology/keu341  
PMID: 25173351 [Indexed for MEDLINE]

1920. Clin Exp Immunol. 2014 Dec;178(3):405-15. doi: 10.1111/cei.12445.

Cytokines in immune-mediated inflammatory myopathies: cellular sources, multiple actions and therapeutic implications.

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The idiopathic inflammatory myopathies are a heterogeneous group of disorders characterised by diffuse muscle weakness and inflammation. A common

immunopathogenic mechanism is the cytokine-driven infiltration of immune cells into the muscle tissue. Recent studies have further dissected the inflammatory cell types and associated cytokines involved in the immune-mediated myopathies and other chronic inflammatory and autoimmune disorders. In this review we outline the current knowledge of cytokine expression profiles and cellular sources in the major forms of inflammatory myopathy and detail the known mechanistic functions of these cytokines in the context of inflammatory myositis. Furthermore, we discuss how the application of this knowledge may lead to new therapeutic strategies for the treatment of the inflammatory myopathies, in particular for cases resistant to conventional forms of therapy.

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DOI: 10.1111/cei.12445

PMCID: PMC4238868

PMID: 25171057 [Indexed for MEDLINE]

1921. Int J Med Sci. 2014 Aug 21;11(11):1140-6. doi: 10.7150/ijms.9444. eCollection 2014.

P wave dispersion and QT dispersion in adult Turkish migrants with familial mediterranean fever living in Germany.

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**BACKGROUND:** Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory disease associated with subclinical inflammation, which includes atherosclerosis arising from endothelial inflammation, which in turn increases the risk of atrial or ventricular arrhythmias. Conduction abnormalities can be detected using the electrocardiographic (ECG) indices P and QT dispersion (Pdisp and QTdisp). Currently, it is unknown whether patients with FMF are more likely to have abnormalities of these ECG indices. Moreover, existing studies were conducted in countries with higher FMF prevalence. We therefore perform the first prospective study assessing Pdisp and QTdisp in adult FMF patients in Germany, where prevalence of FMF is low.

**METHOD:** Asymptomatic FMF patients (n=30) of Turkish ancestry living in Germany and age-matched healthy controls (n=37) were prospectively assessed using 12-lead ECG.

**RESULTS:** Patients and controls were comparable in gender and body mass index, and patients had higher erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and serum amyloid A (SAA) compared to controls (ESR:  $23.7 \pm 14.3$  vs.  $16.1 \pm 13.3$  mm/1(st)h,  $p=0.03$ , CRP:  $0.73 \pm 0.9$  vs.  $0.26 \pm 0.4$  g/dl,  $p=0.01$ , SAA:  $3.14 \pm 4.8$  vs.  $0.37 \pm 0.3$  mg/dl,  $p<0.01$ ). No statistically significant difference between patients and controls respectively, for Pdisp ( $43.7 \pm 11.9$  vs.  $47.1 \pm 11.2$  ms,  $p=0.23$ ), QTdisp ( $65.9 \pm 12.3$  vs.  $67.6 \pm 12.7$  ms,  $p=0.58$ ) or corrected QTdisp (cQTdisp:  $73.9 \pm 15.0$  vs.  $76.0 \pm 13.3$  ms,  $p=0.55$ ) was found. No correlation could be found between Pdisp or QTdisp or cQTdisp and any of the biochemical markers of inflammation.

**CONCLUSION:** FMF patients living in Germany show a Pdisp and QTdisp comparable to healthy controls, with no increased risk of atrial or ventricular arrhythmias indicated.

DOI: 10.7150/ijms.9444

PMCID: PMC4147640

PMID: 25170297 [Indexed for MEDLINE]



1922. Semin Immunopathol. 2014 Sep;36(5):491-3. doi: 10.1007/s00281-014-0446-4. Epub 2014 Aug 29.

Introduction: mechanisms of tissue injury in autoimmune diseases.

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This issue of Seminars in Immunopathology is devoted to the most recent developments in our understanding of the mechanisms leading to tissue injury in autoimmune diseases. These include rheumatoid arthritis, systemic lupus erythematosus, type I diabetes, autoimmune liver diseases, inflammatory bowel diseases, autoimmune skin diseases, autoimmune uveitis, and autoinflammatory diseases. This impressive account of basic and clinical research in a wide spectrum of immunological disorders provides the reader with a comprehensive view of the common and unique features of these diverse conditions. It may also provide one with many new ideas for therapeutic intervention in the natural course of these autoimmune syndromes.

DOI: 10.1007/s00281-014-0446-4

PMID: 25168400 [Indexed for MEDLINE]

1923. Anadolu Kardiyol Derg. 2014 Nov;14(7):659-60. doi: 10.5152/akd.2014.5650. Epub 2014 Aug 22.

Related factors should be considered in evaluation of mean platelet volume in patients with familial Mediterranean fever.

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Comment in

Anadolu Kardiyol Derg. 2014 Nov;14(7):660.

Comment on

Anadolu Kardiyol Derg. 2013 Jun;13(4):357-62.

DOI: 10.5152/akd.2014.5650

PMID: 25163087 [Indexed for MEDLINE]

1924. Autoimmun Rev. 2015 Jan;14(1):1-9. doi: 10.1016/j.autrev.2014.08.008. Epub 2014 Aug 22.

Effectiveness and tuberculosis-related safety profile of interleukin-1 blocking agents in the management of Behçet's disease.

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Behçet's disease (BD) is a multi-systemic disorder of unknown etiology characterized by relapsing oral-genital ulcers, uveitis, and involvement of the articular, gastrointestinal, neurologic, and vascular systems. Although the primum movens of this condition remains unknown, a tangled plot combining autoimmune and autoinflammatory pathways has been hypothesized to explain its start and recurrence. In-depth analysis of BD pathogenetic mechanisms, involving dysfunction of multiple proinflammatory molecules, has opened new modalities of treatment: different agents targeting interleukin-1 have been studied in recent years to manage the most difficult and multi-resistant cases of BD. Growing experience with anakinra, canakinumab and gevokizumab is discussed in this review, highlighting the relative efficacy of each drug upon the protean BD clinical manifestations. Safety and tolerability of interleukin-1 antagonists in different doses have been confirmed by numerous observational studies on both large and small cohorts of patients with BD. In particular, the potential for *Mycobacterium tuberculosis* reactivation and tuberculosis development appears to be significantly lower with interleukin-1 blockers compared to tumor necrosis factor- $\alpha$  inhibitors, thus increasing the beneficial profile of this approach.

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DOI: 10.1016/j.autrev.2014.08.008

PMID: 25151975 [Indexed for MEDLINE]

1925. Rheumatol Int. 2015 Apr;35(4):629-34. doi: 10.1007/s00296-014-3116-x. Epub 2014 Aug 24.

Familial Mediterranean fever in Syrian children: phenotype-genotype correlation.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent attacks of serosal membranes. In this study, 103 unrelated Syrian children were included. Mutation screening of the MEditerranean

FeVer gene was performed for 12 mutations. Abdominal pain was observed in 91 (88.3 %) of the patients, fever in 82 (79.6 %), arthritis in 27 (26.2 %), pleuritis in 7 (6.7.5 %), rash and erysipelas-like erythema in 5 (4.8 %), myalgia in 5 (4.8 %), headache in 5 (4.8 %) and Henoch-Schonlein purpura in 1 (0.97 %). The most frequent mutation was M694V. In order to determine the association between M694V and clinical features of FMF, we compared the disease features between patients with and without this mutation. The presence of M694V was found to be associated with more severe course of FMF, earlier age of onset and more frequent arthritis in the Syrian children with FMF compared to other FMF patients who do not have this mutation.

DOI: 10.1007/s00296-014-3116-x

PMID: 25150514 [Indexed for MEDLINE]

1926. Autoimmun Rev. 2014 Sep;13(9):892-900. doi: 10.1016/j.autrev.2014.08.001. Epub 2014 Aug 20.

The hereditary autoinflammatory disorders uncovered.

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There is a thriving interest in the field of hereditary autoinflammatory disorders (HAID), a gamut of heterogeneous conditions deriving from an aberrant orchestration of innate immunity, unified by the common feature of seemingly unprovoked inflammation, which might be systemic or occur in localized niches of the organism. Recurrent fever and episodic inflammation in the joints, serosal membranes, skin, gut, and other organs are the common denominator of HAID. Mutations in the inflammasome-related genes have been associated with different

HAID, showing the intimate link existing between interleukin-1 (IL-1)-structured inflammasome and their pathogenesis. Differential diagnosis of HAID can be challenging, as there are no universally accepted diagnostic protocols, and near half of patients may remain without any genetic abnormality identified. The use of IL-1-antagonists has been associated with beneficial effects in a large number of HAID associated with excessive IL-1 signalling, such as cryopyrin-associated periodic syndromes, familial Mediterranean fever, and deficiency of IL-1 receptor antagonist. This review will discuss about the key-clues of HAID which might guide for an early recognition and drive decisions for treatment.

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DOI: 10.1016/j.autrev.2014.08.001

PMID: 25149390 [Indexed for MEDLINE]

1927. Biomed Res Int. 2014;2014:854842. doi: 10.1155/2014/854842. Epub 2014 May 15.

The effect of rilonacept versus placebo on health-related quality of life in patients with poorly controlled familial Mediterranean fever.

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**OBJECTIVE:** To examine the effect of rilonacept on the health-related quality of life (HRQoL) in patients with poorly controlled familial Mediterranean fever (FMF).

**METHODS:** As part of a randomized, double-blinded trial comparing rilonacept and placebo for the treatment of FMF, patients/parents completed the modified Child Health Questionnaire (CHQ) at baseline, and at the start and end of each of 4 treatment courses, 2 each with rilonacept and placebo.

**RESULTS:** Fourteen subjects were randomized; mean age was  $24.4 \pm 11.8$  years. At baseline the physical HRQoL score was significantly less ( $24.2 \pm 49.5$ ) but the psychosocial score was similar to the population norm ( $49.5 \pm 10.0$ ). There were significant improvements in most HRQoL concepts after rilonacept but not placebo. Significant differences between rilonacept and placebo were found in the physical ( $33.7 \pm 16.4$  versus  $23.7 \pm 14.5$ ,  $P = 0.021$ ) but not psychosocial scores ( $51.4 \pm 10.3$  versus  $49.8 \pm 12.4$ ,  $P = 0.42$ ). The physical HRQoL was significantly impacted by the treatment effect and patient global assessment.

**CONCLUSION:** Treatment with rilonacept had a beneficial effect on the physical HRQoL in patients with poorly controlled FMF and was also significantly related to the patient global assessment. This trial is registered with ClinicalTrials.gov Identifier NCT00582907.

DOI: 10.1155/2014/854842

PMCID: PMC4131422

PMID: 25147819 [Indexed for MEDLINE]

1928. Inflammation. 2015 Feb;38(1):27-31. doi: 10.1007/s10753-014-0004-1.

Efficacy of interleukin-1 targeting treatments in patients with familial mediterranean Fever.

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Herein, we reported our experience in colchicine-resistant familial Mediterranean fever (FMF) patients who are treated with anti-interleukin-1 (IL-1) drugs. A retrospective review of medical records of anti-IL-1 recipients was performed. The main clinical characteristics of these patients and the evolution after anti-IL-1 were recorded. There were 20 patients (11 male [M] and 9 female [F]). Despite regular colchicine treatment, median number of attacks per month and per year was 1 (1-4) and 12 (4-50), respectively. Twelve patients were receiving anakinra, and eight patients were treated with canakinumab. The number of monthly and yearly attacks after IL-1 treatment was significantly decreased after the biologic agent ( $p < 0.05$ ). One patient did not respond to the treatment, and one patient developed serious infection during anti-IL-1. We also observed a significant decrease in proteinuria in the amyloidosis complicated FMF patients. Anti-IL-1 targeting drugs seem safe and effective therapies in colchicine-resistant FMF.

DOI: 10.1007/s10753-014-0004-1

PMID: 25139580 [Indexed for MEDLINE]

1929. *Pediatr Rheumatol Online J*. 2014 Aug 6;12:33. doi: 10.1186/1546-0096-12-33. eCollection 2014.

Blau syndrome, the prototypic auto-inflammatory granulomatous disease.

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Blau syndrome is a monogenic disease resulting from mutations in the pattern recognition receptor NOD2, and is phenotypically characterized by the triad of granulomatous polyarthritis, dermatitis and uveitis. This paper reviews briefly the classical clinical features of the disease, as well as more recently described extra-triad symptoms. From an ongoing prospective multicenter study, we provide new data on the natural history of Blau syndrome, focusing on functional status and visual outcome. We also present an update of the range of different NOD2 mutations found in Blau syndrome as well as recent data on morphologic and immunohistochemical characteristics of the Blau granuloma. Finally, emerging insights into pathogenic mechanisms including activation of NOD2 signal transduction, and potential biomarkers of disease activity are discussed.

DOI: 10.1186/1546-0096-12-33

PMCID: PMC4136643

PMID: 25136265 [Indexed for MEDLINE]

1930. Ann Rheum Dis. 2015 Dec;74(12):2224-35. doi: 10.1136/annrheumdis-2014-205496. Epub 2014 Aug 18.

NLRP3 and ASC suppress lupus-like autoimmunity by driving the immunosuppressive effects of TGF- $\beta$  receptor signalling.

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**OBJECTIVES:** The NLRP3/ASC inflammasome drives host defence and autoinflammatory disorders by activating caspase-1 to trigger the secretion of mature interleukin (IL)-1 $\beta$ /IL-18, but its potential role in autoimmunity is speculative.

**METHODS:** We generated and phenotyped Nlrp3-deficient, Asc-deficient, Il-1r-deficient and Il-18-deficient C57BL/6-lpr/lpr mice, the latter being a mild model of spontaneous lupus-like autoimmunity.

**RESULTS:** While lack of IL-1R or IL-18 did not affect the C57BL/6-lpr/lpr phenotype, lack of NLRP3 or ASC triggered massive lymphoproliferation, lung T cell infiltrates and severe proliferative lupus nephritis within 6 months, which



were all absent in age-matched C57BL/6-lpr/lpr controls. Lack of NLRP3 or ASC increased dendritic cell and macrophage activation, the expression of numerous proinflammatory mediators, lymphocyte necrosis and the expansion of most T cell and B cell subsets. In contrast, plasma cells and autoantibody production were hardly affected. This unexpected immunosuppressive effect of NLRP3 and ASC may relate to their known role in SMAD2/3 phosphorylation during tumour growth factor (TGF)- $\beta$  receptor signalling, for example, Nlrp3-deficiency and Asc-deficiency significantly suppressed the expression of numerous TGF- $\beta$  target genes in C57BL/6-lpr/lpr mice and partially recapitulated the known autoimmune phenotype of Tgf- $\beta$ 1-deficient mice.

**CONCLUSIONS:** These data identify a novel non-canonical immunoregulatory function of NLRP3 and ASC in autoimmunity.

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DOI: 10.1136/annrheumdis-2014-205496

PMID: 25135254 [Indexed for MEDLINE]

1931. Mediators Inflamm. 2014;2014:948154. doi: 10.1155/2014/948154. Epub 2014 Jul 15.

Untangling the web of systemic autoinflammatory diseases.

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The innate immune system is involved in the pathophysiology of systemic autoinflammatory diseases (SAIDs), an enlarging group of disorders caused by dysregulated production of proinflammatory cytokines, such as interleukin-1 $\beta$  and tumor necrosis factor- $\alpha$ , in which autoreactive T-lymphocytes and autoantibodies are indeed absent. A widely deranged innate immunity leads to overactivity of proinflammatory cytokines and subsequent multisite inflammatory symptoms depicting various conditions, such as hereditary periodic fevers, granulomatous disorders, and pyogenic diseases, collectively described in this review. Further research should enhance our understanding of the genetics behind SAIDs, unearth triggers of inflammatory attacks, and result in improvement for their diagnosis and treatment.

DOI: 10.1155/2014/948154

PMCID: PMC4124206

PMID: 25132737 [Indexed for MEDLINE]

1932. Eur J Intern Med. 2014 Oct;25(8):e98-e100. doi: 10.1016/j.ejim.2014.07.010. Epub 2014 Aug 14.

A calculator for temporal artery biopsy result prediction in giant cell arteritis suspects.

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DOI: 10.1016/j.ejim.2014.07.010  
PMID: 25129703 [Indexed for MEDLINE]

1933. J Am Acad Dermatol. 2015 Mar;72(3):550-3. doi: 10.1016/j.jaad.2014.07.014. Epub 2014 Aug 12.

Palmoplantar pustules and osteoarticular pain in a 42-year-old woman.

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Key teaching points • Synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome is characterized by distinctive osteoarticular manifestations and a spectrum of neutrophilic dermatoses. • The most common dermatologic manifestations include palmoplantar pustulosis, acne conglobata, and acne fulminans. • SAPHO syndrome should be considered in patients presenting osteoarticular pain, particularly involving the anterior chest wall and/or spine, and neutrophilic skin lesions.

Published by Elsevier Inc.

DOI: 10.1016/j.jaad.2014.07.014  
PMCID: PMC4326625  
PMID: 25127881 [Indexed for MEDLINE]

1934. Quintessence Int. 2014 Oct;45(9):743-8. doi: 10.3290/j.qi.a32442.

Prevalence of periodontal disease in patients with Familial Mediterranean Fever: a cohort study from central Turkey.

Bostancı V, Toker H, Senel S, Sahin S.

**OBJECTIVE:** The aim of this study was to compare the periodontal status in patients with Familial Mediterranean Fever (FMF) and in those without this disease.

**METHOD AND MATERIALS:** 84 subjects clinically diagnosed with FMF and 75 systemically healthy controls, matched by age and gender, were recruited. All FMF patients were on a regular daily colchicine treatment and during attack-free periods. Gingival Index (GI), Plaque Index (PI), probing pocket depth (PD), and clinical attachment level (CAL) were measured in all subjects. To evaluate periodontal disease further, patients were stratified into five groups. Education information and smoking habits were recorded.

**RESULTS:** The FMF patients and healthy controls were comparable for age, gender, and smoking status ( $P>.05$ ). The FMF patients had significantly higher PI and GI values and lower PD and CAL values than those of the control group ( $P<.05$ ). However, there was no significant difference among all groups in terms of periodontal disease severity ( $P>.05$ ). In the FMF-severe periodontitis group, higher PI and GI values were seen ( $P<.05$ ). However, there was no significant difference between the FMF-severe periodontitis group and the controls with severe periodontitis regarding the PD and CAL values ( $P>.05$ ).

**CONCLUSION:** Patients with FMF using colchicine did not manifest higher attachment loss compared to age- and sex-matched systemically healthy controls.

DOI: 10.3290/j.qi.a32442

PMID: 25126643 [Indexed for MEDLINE]

1935. Clin Transplant. 2014 Oct;28(10):1177-83. doi: 10.1111/ctr.12448. Epub 2014 Sep 11.

Colchicine levels in chronic kidney diseases and kidney transplant recipients using tacrolimus.

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**BACKGROUND:** Tacrolimus is a CYP3A4 inhibitor and can alter colchicine metabolism. In this study, we aimed to evaluate plasma colchicine levels in different stages of kidney disease as well as in kidney transplant (KTx) recipients using tacrolimus.

**METHOD:** This study included six familial Mediterranean fever (FMF) patients with normal glomerular filtration rate (GFR) as controls, three patients with low GFR, six FMF patients on hemodialysis (HD), and six FMF patients who were KTx recipients using tacrolimus. After a three-d washout period, plasma colchicine levels were measured at 0 (pre-dose), one, two, four, eight, and 24 h post-dose of 1 mg oral colchicine. Area under the curve 0-24 h (AUC<sub>0-24</sub>) and maximum concentration (C<sub>max</sub>) were evaluated and compared between the groups.

**RESULTS:** Colchicine AUC<sub>0-24</sub> was six-fold higher in HD ( $p < 0.001$ ) and three-fold higher in KTx recipients ( $p < 0.001$ ) when compared to the control. The low GFR group had mildly higher AUC<sub>0-24</sub> than the control group. C<sub>max</sub> levels were also higher in HD ( $p = 0.011$ ) and KTx recipient ( $p = 0.06$ ) groups and mildly elevated in low GFR patients in comparison with controls.

**CONCLUSION:** Colchicine AUC<sub>0-24</sub> and C<sub>max</sub> were significantly increased in HD patients and KTx recipients using tacrolimus. Therefore, dose adjustments are needed to avoid toxicity in both circumstances.

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DOI: 10.1111/ctr.12448

PMID: 25125128 [Indexed for MEDLINE]

1936. PLoS One. 2014 Aug 13;9(8):e104479. doi: 10.1371/journal.pone.0104479. eCollection 2014.

Persistent release of IL-1s from skin is associated with systemic cardio-vascular disease, emaciation and systemic amyloidosis: the potential of anti-IL-1 therapy for systemic inflammatory diseases.

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The skin is an immune organ that contains innate and acquired immune systems and thus is able to respond to exogenous stimuli producing large amount of proinflammatory cytokines including IL-1 and IL-1 family members. The role of the epidermal IL-1 is not limited to initiation of local inflammatory responses, but also to induction of systemic inflammation. However, association of persistent release of IL-1 family members from severe skin inflammatory diseases such as psoriasis, epidermolysis bullosa, atopic dermatitis, blistering diseases and desmoglein-1 deficiency syndrome with diseases in systemic organs have not been so far assessed. Here, we showed the occurrence of severe systemic cardiovascular diseases and metabolic abnormalities including aberrant vascular wall remodeling with aortic stenosis, cardiomegaly, impaired limb and tail circulation, fatty tissue loss and systemic amyloid deposition in multiple organs with liver and kidney dysfunction in mouse models with severe dermatitis caused by persistent release of IL-1s from the skin. These morbid conditions were ameliorated by simultaneous administration of anti-IL-1 $\alpha$  and IL-1 $\beta$  antibodies. These findings may explain the morbid association of arteriosclerosis, heart involvement,

amyloidosis and cachexia in severe systemic skin diseases and systemic autoinflammatory diseases, and support the value of anti-IL-1 therapy for systemic inflammatory diseases.

DOI: 10.1371/journal.pone.0104479

PMCID: PMC4131904

PMID: 25119884 [Indexed for MEDLINE]

1937. Neurol Sci. 2015 May;36(5):811-2. doi: 10.1007/s10072-014-1919-x. Epub 2014 Aug 13.

Familiar Mediterranean fever and multiple sclerosis: an unreported association in the Italian population?

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DOI: 10.1007/s10072-014-1919-x

PMID: 25116260 [Indexed for MEDLINE]

1938. Pediatr Rheumatol Online J. 2014 Jul 16;12:28. doi: 10.1186/1546-0096-12-28. eCollection 2014.

Development of positive antinuclear antibodies and rheumatoid factor in systemic juvenile idiopathic arthritis points toward an autoimmune phenotype later in the disease course.

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**BACKGROUND:** Systemic juvenile idiopathic arthritis (sJIA) is commonly considered an autoinflammatory disease. However, sJIA patients may develop aggressive arthritis without systemic inflammation later in the disease, resembling an autoimmune phenotype similar to other subtypes of JIA. The objective of this study was to determine whether antinuclear antibodies (ANA) and rheumatoid factor (RF) will develop in patients with sJIA over the course of the disease.

**FINDINGS:** A single center sample of sJIA patients with follow-up of more than one year was obtained. A retrospective chart survey was used to extract demographic and clinical data as well as presence and titers of ANA and RF at diagnosis and during follow-up. 32 patients were included in the study, with a median age of 4.2 years and median follow-up of 6.0 years. 8/32 patients had ANA titers  $\geq 1:80$  at diagnosis, with 22/32 patients showing rising ANA titers with titers  $\geq 1:80$  at last follow-up ( $p = 0.001$ ). 10/32 patients had a positive RF at least once during follow-up, compared to 0/32 at diagnosis ( $p = 0.001$ ). In 5/10 patients, positive RF was documented at least twice, more than twelve weeks apart. Patients treated with TNF antagonists were not significantly more likely to develop positive ANA titers ( $p = 0.425$ ) or positive RF ( $p = 0.703$ ).

**CONCLUSIONS:** Patients with sJIA developed increased ANA titers and positive RF over the course of the disease, independent of treatment with TNF antagonists. This might point towards an autoimmune, rather than an autoinflammatory phenotype later in the course of sJIA.

DOI: 10.1186/1546-0096-12-28

PMCID: PMC4127434

PMID: 25114627 [Indexed for MEDLINE]

1939. Mediators Inflamm. 2014;2014:862969. doi: 10.1155/2014/862969. Epub 2014 Jul 8.

Drug retention rates and treatment discontinuation among anti-TNF- $\alpha$  agents in psoriatic arthritis and ankylosing spondylitis in clinical practice.

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**OBJECTIVE:** The study aim was to determine treatment persistence rates and to identify causes of discontinuation in psoriatic arthritis (PsA) and ankylosing spondylitis (AS) patients in clinical practice.

**METHODS:** Patients treated with adalimumab (ADA), etanercept (ETA), or infliximab (INF) were retrospectively included. Treatment persistence rates were analyzed by means of a stepwise logistic regression. Differences between therapy duration were assessed by means of an analysis of variance model (ANOVA), while a chi-square test was used to evaluate relationships between therapies and causes of treatment discontinuation and the administration of concomitant disease-modifying antirheumatic drugs (DMARDs) among therapies and types of disease considering completed courses of therapy versus courses that were discontinued.

**RESULTS:** 268 patients received a total of 353 anti-TNF treatment courses (97 ADA, 180 ETA, and 76 INF). Comparison among therapies showed significant difference regarding the treatment persistence rates due to the contrast between ETA and INF ( $P = 0.0062$ ). We observed that 84.7% of patients were still responding after 6 months of follow-up. Comparison among diseases showed that there were significant differences between PsA and AS ( $P = 0.0073$ ) and PsA and PsA with predominant axial involvement ( $P = 0.0467$ ) in terms of duration of the therapy, while there were no significant differences with regard to the persistence rate.

**CONCLUSIONS:** In this cohort, anti-TNF- $\alpha$  therapy was associated with high drug persistence rates. As in rheumatoid arthritis, switching to another anti-TNF- $\alpha$  agent can be an effective option when, during the treatment of AS or PsA, therapy is suspended because of inefficacy or an adverse event. Combination therapy with DMARDs was associated with a better persistence rate.

PMCID: PMC4119698

PMID: 25110401 [Indexed for MEDLINE]

1940. Biochem Soc Trans. 2014 Aug;42(4):717-25. doi: 10.1042/BST20140079.

Ribonuclease H2 in health and disease.

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Innate immune sensing of nucleic acids provides resistance against viral infection and is important in the aetiology of autoimmune diseases. AGS (Aicardi-Goutières syndrome) is a monogenic autoinflammatory disorder mimicking in utero viral infection of the brain. Phenotypically and immunologically, it also exhibits similarities to SLE (systemic lupus erythematosis). Three of the six genes identified to date encode components of the ribonuclease H2 complex. As all six encode enzymes involved in nucleic acid metabolism, it is thought that pathogenesis involves the accumulation of nucleic acids to stimulate an inappropriate innate immune response. Given that AGS is a monogenic disorder with a defined molecular basis, we use it as a model for common autoimmune disease to investigate cellular processes and molecular pathways responsible for nucleic-acid-mediated autoimmunity. These investigations have also provided fundamental insights into the biological roles of the RNase H2 endonuclease enzyme. In the present article, we describe how human RNase H2 and its role in AGS were first identified, and give an overview of subsequent structural, biochemical, cellular and developmental studies of this enzyme. These investigations have culminated in establishing this enzyme as a key genome-surveillance enzyme required for mammalian genome stability.

DOI: 10.1042/BST20140079

PMID: 25109948 [Indexed for MEDLINE]

1941. J Dermatol. 2014 Sep;41(9):827-9. doi: 10.1111/1346-8138.12588. Epub 2014 Aug 11.

Cutaneous necrotizing vasculitis as a manifestation of familial Mediterranean fever.

Komatsu S(1), Honma M, Igawa S, Tsuji H, Ishida-Yamamoto A, Migita K, Ida H, Iizuka H.

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Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory disease, which is characterized by recurrent and paroxysmal fever, peritonitis, arthritis, myalgia, and skin rashes. Although various skin lesions such as "erysipelas-like erythema", urticaria, nonspecific purpura, and subcutaneous nodules have been described, cutaneous vasculitis is rare. We report a Japanese case of sporadic FMF accompanied by cutaneous arteritis at the time of febrile attacks of FMF. Gene analysis revealed M694I mutation in a single allele of the MEFV gene, and oral colchicine successfully controlled both periodic fever and subcutaneous nodules of arteritis. Cutaneous necrotizing vasculitis repeatedly emerging with febrile attacks should be included among the skin manifestations of FMF.

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DOI: 10.1111/1346-8138.12588

PMID: 25109905 [Indexed for MEDLINE]

1942. Eur J Public Health. 2014 Aug;24 Suppl 1:92-5. doi: 10.1093/eurpub/cku108.

Immigrant health, our health.

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This final chapter reviews the main conclusions reached by the Special Issue articles in the areas of EUNAM (EU and North African Migrants: Health and Health

Systems) activities, covering well-being, health status, disease panorama and use of health services of immigrants to the EU. The reviewed chapters show that immigrants are a vulnerable population experiencing, in some aspects, discrimination and hardship similar to the socially weakest national population groups. Immigration has changed the disease spectrum, particularly in infectious diseases and recessive conditions such as sickle cell disease and familial Mediterranean fever. Importantly, health questions of immigrants cannot be separated from those of any human health issues. An imminent new immigrant question for the EU will be the massive internal migration. Although the overall disease spectrum may not be vastly different between EU countries, the internal migrants will be exposed to lifestyle-dependent ill health and diseases probably in a similar way as did migrants from outside Europe. Migrant health research requires dedicated funding, which needs to come from central EU sources because multiple nationalities are involved. This funding should be able to project the course of health from the country of origin to the country of destination and back again, which was one of guidelines in the funding that initiated EUNAM.

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DOI: 10.1093/eurpub/cku108

PMID: 25108004 [Indexed for MEDLINE]

1943. Eur J Public Health. 2014 Aug;24 Suppl 1:57-63. doi: 10.1093/eurpub/cku104.

Consanguinity and genetic diseases in North Africa and immigrants to Europe.

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Endemic diseases are caused by environmental and genetic factors. While in this

special issue several chapters deal with environmental factors, including infections, the present focus is on genetic causes of disease clustering due to inbreeding and recessive disease mechanisms. Consanguinity is implying sharing of genetic heritage because of marriage between close relatives originating from a common ancestor. With limited natural selection, recessive genes may become more frequent in an inbred compared with an outbred population. Consanguinity is common in North Africa (NA), and the estimates range from 40 to 49% of all marriages in Tunisia and 29-33% in Morocco. As a consequence, recessive disorders are common in the NA region, and we give some examples. Thalassaemia and sickle cell disease/anaemia constitute the most common inherited recessive disorders globally and they are common in NA, but with immigration they have spread to Europe and to other parts of the world. Another example is familial Mediterranean fever, which is common in the Eastern Mediterranean area. With immigration from that area to Sweden, it has become the most common hereditary autoinflammatory disease in that country, and there is no evidence that any native Swede would have been diagnosed with this disease. The examples discussed in this chapter show that the historic movement of populations and current immigration are influencing the concept of 'endemic' disease.

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DOI: 10.1093/eurpub/cku104

PMID: 25107999 [Indexed for MEDLINE]

1944. J Biol Chem. 2014 Oct 3;289(40):27757-65. doi: 10.1074/jbc.M114.571810. Epub 2014 Aug 8.

Unprenylated RhoA contributes to IL-1 $\beta$  hypersecretion in mevalonate kinase deficiency model through stimulation of Rac1 activity.

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Protein prenylation is a post-translational modification whereby non-sterol isoprenoid lipid chains are added, thereby modifying the molecular partners with which proteins interact. The autoinflammatory disease mevalonate kinase deficiency (MKD) is characterized by a severe reduction in protein prenylation. A major class of proteins that are affected are small GTPases, including Rac1 and RhoA. It is not clear how protein prenylation of small GTPases relates to GTP hydrolysis activity and downstream signaling. Here, we investigated the contribution of RhoA prenylation to the biochemical pathways that underlie MKD-associated IL-1 $\beta$  hypersecretion using human cell cultures, Rac1 and RhoA protein variants, and pharmacological inhibitors. We found that when unprenylated, the GTP-bound levels of RhoA decrease, causing a reduction in GTPase activity and increased protein kinase B (PKB) phosphorylation. Cells expressing unprenylated RhoA produce increased levels of interleukin 1 $\beta$  mRNA. Of other phenotypic cellular changes seen in MKD, increased mitochondrial potential and mitochondrial elongation, only mitochondrial elongation was observed. Finally, we show that pharmacological inactivation of RhoA boosts Rac1 activity, a small GTPase whose activity was earlier implied in MKD pathogenesis. Together, our data show that RhoA plays a pivotal role in MKD pathogenesis through Rac1/PKB signaling toward interleukin 1 $\beta$  production and elucidate the effects of protein prenylation in monocytes.

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DOI: 10.1074/jbc.M114.571810

PMCID: PMC4183811

PMID: 25107911 [Indexed for MEDLINE]

1945. Nat Rev Rheumatol. 2014 Sep;10(9):512. doi: 10.1038/nrrheum.2014.126. Epub 2014 Aug 5.

Autoinflammation: A new STING-associated monogenic autoinflammatory disease.

Onuora S.

Comment on

N Engl J Med. 2014 Aug 7;371(6):507-18.

DOI: 10.1038/nrrheum.2014.126

PMID: 25090944 [Indexed for MEDLINE]

1946. Clin Invest Med. 2014 Aug 1;37(4):E211-6.

Hypovitaminosis D in children with familial Mediterranean fever.

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**PURPOSE:** Vitamin D deficiency or insufficiency plays a role in the initiation and perpetuation of certain autoimmune diseases. The purpose of this study was to measure the vitamin D status of children with Familial Mediterranean Fever (FMF) and compare it to their healthy peers.

**METHODS:** A total of 50 FMF patients and 49 healthy children were enrolled in this prospective study. Vitamin D levels were measured via HPLC. Demographic data, FMF symptom severity scores and the levels of other disease activity markers were retrieved from our hospital database.

**RESULTS:** The mean age and gender balance of patients and controls were similar, being  $8.4 \pm 3.8$  years and 19 male patients, and  $9.1 \pm 3.0$  years and 25 male controls, respectively. The mean 25(-OH) vitamin D3 levels were  $15.94 \pm 9.66$  µg/L in FMF patients and  $41.22 \pm 21.31$  µg/L in controls. Vitamin D levels were normal in 12% of FMF patients, insufficient in 62% and deficient in 26%. No vitamin D deficiency was evident in any control subject; 30% had insufficient and 70% had normal vitamin D levels. Plasma vitamin D3 levels were similar in all patients despite varying FMF symptom severity scores.

**CONCLUSIONS:** Vitamin D deficiency is frequent in children with FMF but is not associated with disease severity score.

PMID: 25090260 [Indexed for MEDLINE]

1947. Intern Med. 2014;53(15):1659-63. Epub 2014 Aug 1.

Acute pericarditis as the first manifestation of familial Mediterranean fever: a possible relationship with idiopathic recurrent pericarditis.

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A 56-year-old man was admitted to our hospital due to periodic episodes of acute pericarditis. These episodes occurred monthly along with a high fever and elevation of the C-reactive protein (CRP) level. The patient became afebrile and his CRP level decreased following the administration of a non-steroidal anti-inflammatory drug. A mutation analysis revealed the heterozygote of the familial Mediterranean fever (FMF) gene (E84K, G304R). This finding confirmed our diagnosis, and we treated the patient with colchicine. He responded to treatment and has been visiting our hospital without disease recurrence. FMF should be included in the differential diagnosis of repeated episodes of pericarditis.

PMID: 25088882 [Indexed for MEDLINE]

1948. Rev Med Interne. 2014 Dec;35(12):838-9. doi: 10.1016/j.revmed.2014.06.005. Epub 2014 Jul 31.

[Anemia and splenomegaly in a 21-year-old woman].

[Article in French]

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DOI: 10.1016/j.revmed.2014.06.005

PMID: 25088048 [Indexed for MEDLINE]

1949. Curr Rheumatol Rep. 2014;16(9):439. doi: 10.1007/s11926-014-0439-2.

Genetic defects in cytolysis in macrophage activation syndrome.

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Macrophage activation syndrome (MAS), typically presenting beyond the first year of life, is an often lethal cousin of familial hemophagocytic lymphohistiocytosis (fHLH). Defects in natural killer (NK) cell and CD8 T cell cytotoxicity result in a pro-inflammatory cytokine storm, cytopenia, coagulopathy, and multi-organ system dysfunction. MAS can occur in association with infections (herpes viruses), cancer (leukemia), immune deficient states (post-transplantation), and in autoimmune (systemic lupus erythematosus) and autoinflammatory conditions (systemic juvenile idiopathic arthritis). The distinction between fHLH, the result of homozygous defects in cytolytic pathway genes, and MAS is becoming blurred with the identification of single or multiple mutations in the same cytolytic pathway genes in patients with later onset MAS. Here, we review the literature and present novel cytolytic pathway gene mutations identified in children with MAS. We study the inhibitory effect of one these novel mutations on NK cell function to suggest a direct link between fHLH and MAS.

DOI: 10.1007/s11926-014-0439-2

PMID: 25086802 [Indexed for MEDLINE]

1950. Korean J Gastroenterol. 2014 Jul;64(1):40-4.

A case of recurrent abdominal pain with fever and urticarial eruption.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent episodes of fever and serosal, synovial, or cutaneous inflammation, caused by a dysfunction of pyrin as a result of mutation within the MEFV gene. It occurs mainly among Mediterranean and Middle Eastern populations, including Jews, Arabs, and Turks. However, FMF cases have been reported outside the Mediterranean and Middle Eastern countries in recent years. Although FMF has been relatively rare in Korea until now, proper recognition of FMF might lead to more frequent diagnoses of FMF. We experienced an interesting case, a 31-year-old Korean man who presented with recurrent abdominal pain with fever and urticarial eruption for 10 years. DNA analysis showed complex mutations (p.Leu110Pro, p.Glu148Gln) in the MEFV gene. To date, three cases have been reported, and this case of FMF with skin conditions is the first case in Korea.

PMID: 25073670 [Indexed for MEDLINE]

1951. J Eur Acad Dermatol Venereol. 2016 Jan;30(1):141-3. doi: 10.1111/jdv.12631. Epub 2014 Jul 28.

Pyoderma gangrenosum, acne, psoriasis, arthritis and suppurative hidradenitis (PAPASH)-syndrome: a new entity within the spectrum of autoinflammatory syndromes?

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DOI: 10.1111/jdv.12631

PMID: 25070077 [Indexed for MEDLINE]

1952. Clin Exp Rheumatol. 2014 Jul-Aug;32(4 Suppl 84):S63-6. Epub 2014 Jul 17.

Serum amyloid protein A concentration in cryopyrin-associated periodic syndromes patients treated with interleukin-1 beta antagonist.

Pastore S(1), Paloni G, Caorsi R, Ronfani L, Taddio A, Lepore L; CAPS Italian Register.

Collaborators: Alessio M, Cantarini L, Cattalini M, Consolini R, Gattorno R, Gerloni V, Insalaco A, Martini G, Martini S, Obici L, Rigante D.

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**OBJECTIVES:** Cryopyrin-associated periodic syndromes (CAPS) are a group of chronic, relapsing autoinflammatory disorders which may be complicated by systemic AA amyloidosis. The aim of our study was to evaluate serum amyloid protein A (SAA) level in CAPS patients treated with Interleukin-1beta (IL-1 $\beta$ ) antagonist and to correlate its level with treatment response.

**METHODS:** All patients of CAPS Italian Register treated with IL-1 $\beta$  inhibitor were enrolled. SAA levels before starting therapy, and at last visit were evaluated. Patients were then divided in complete responders and partial responders.

**RESULTS:** Twenty-five patients were enrolled. SAA level before starting therapy was increased (median 118.5 mg/L, IQR 96.4-252.8; normal value <6.4 mg/L), while at last visit SAA was significantly reduced (median 4.3 mg/L, IQR 2.3-12.7) (p<0.001). However 12 patients still presented SAA levels beyond normal range,

10/25 patients (40%) showed a complete response to treatment. Conversely, 15 patients presented only a partial response, of which 12 for increased SAA value and 3 for increased CRP value. Patients with partial response had SAA values significantly higher than patients with complete response (median 12.6 mg/L; IQR 8.3-20.0 vs. 2.7 mg/L; IQR 1.6-4.1,  $p < 0.001$ ).

**CONCLUSIONS:** Our results confirm the long term efficacy of anti IL-1 $\beta$  treatment in CAPS and the decrease of SAA levels; however 48% of patients still presented SAA elevation despite treatment. The real risk of these patients in developing amyloidosis is not clear but the persistent increase of SAA needs a close follow-up.

PMID: 25069027 [Indexed for MEDLINE]

1953. Clin Exp Rheumatol. 2014 Jul-Aug;32(4):604-9. Epub 2014 Jul 23.

A standardized clinical and radiological follow-up of patients with chronic non-bacterial osteomyelitis treated with pamidronate.

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**OBJECTIVES:** Chronic non-bacterial osteomyelitis (CNO) is an autoinflammatory disorder of the skeletal system. Treatment with NSAIDs is generally effective in the majority of patients, however, a sizeable proportion of patients have persistent disease and subsequent treatment strategies are required. The aim of this study was to characterise the clinical and radiological disease course in CNO patients treated with the bisphosphonate pamidronate (PAM).

**METHODS:** Eight CNO patients refractory to NSAIDs, glucocorticoids and sulfasalazine were treated with 6 cycles of PAM in four-weekly intervals. The disease course was assessed by clinical examination and whole-body (WB) MRI at standardised time points during the treatment phase and in a 6 months follow-up.

**RESULTS:** Seven patients were in complete clinical remission after 6 applications of PAM. WB MRIs showed regression of inflammatory lesions in 7 patients with complete remission in only one patient and partial remission in 6 patients. One

patient developed radiological progression despite a marked improvement of clinical symptoms. In the follow-up after PAM therapy, 3 patients developed MRI confirmed relapse. Additional applications of PAM induced a sustained clinical remission and partial radiological response in two of them. Mild temporary adverse effects were noted in 5 patients.

**CONCLUSIONS:** Our study highlights that PAM is effective in controlling clinical symptoms (e.g. pain) in CNO patients. However, subclinical bone inflammation was still detectable by MRI in most of the patients and disease progression was noticed in some patients after cessation of PAM.

PMID: 25065777 [Indexed for MEDLINE]

1954. J Clin Endocrinol Metab. 2014 Oct;99(10):E2123-8. doi: 10.1210/jc.2014-2096. Epub 2014 Jul 25.

Cardiovascular and metabolic risk factors in inherited autoinflammation.

Twig G(1), Livneh A, Vivante A, Afek A, Derazne E, Leiba A, Shor DB, Meydan C, Ben-Zvi I, Tzur D, Furer A, Imazio M, Adler Y, Amital H.

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**CONTEXT:** The natural progression of metabolic abnormalities among patients with inherited autoinflammation is unclear.

**OBJECTIVE:** The objective of the study was to assess the cardiometabolic risk of participants with familial Mediterranean fever (FMF).

**DESIGN AND SETTING:** This study included nationwide cross-sectional and

longitudinal cohorts.

**PARTICIPANTS:** The prevalence of components of the metabolic syndrome at age 17 years was assessed from the medical database of the Israeli Defense Force from 1973 through 1997. Included were 745 males with FMF, 902 healthy male siblings, and a control group of 787,714 participants. A prospective follow-up study traced the incidence of components of the metabolic syndrome to age 45 years among 57 FMF and 1568 control army personnel participants.

**INTERVENTIONS:** Body mass index (BMI) and blood pressure (BP) were measured at age 17 years (cross-sectional); lifestyle, anthropometric, and biochemical data were periodically recorded from age 25 years.

**MAIN OUTCOME MEASURES:** Abnormal BMI or BP (age 17 y) and Adult Treatment Panel III criteria of the metabolic syndrome were measured.

**RESULTS:** In multivariable regression analysis adjusted for known confounders of obesity, FMF participants had an odds ratio of 0.65 for the occurrence of overweight [95% confidence interval (CI) 0.44-0.96,  $P = .03$ ] and 0.66 (95% CI 0.48-0.92,  $P = .012$ ) for hypertension-range BP; their siblings tended to obesity (odds ratio 1.48; 95% CI 1.04-2.11,  $P = .008$ ). In the follow-up arm, a multivariable analysis adjusted for age, birth year, BMI, education, socioeconomic status, ethnicity, and physical activity yielded hazard ratios of 0.32 (95% CI 0.10-0.82,  $P = .002$ ) for incident obesity, 0.49 (95% CI 0.25-0.95,  $P = .037$ ) for incident triglycerides 150 mg/dL or greater, 0.56 (95% CI 0.31-0.98,  $P = .048$ ) for low-density lipoprotein cholesterol 130 mg/dL or greater, and 2.14 (1.368-3.359,  $P = .001$ ) for high-density lipoprotein cholesterol less than 40 mg/dL for FMF participants compared with controls. Incident elevated BP was lower among FMF participants (hazard ratio 0.49; 95% CI 0.23-1.00,  $P = .05$ ), whereas dysglycemia incidence was comparable.

**CONCLUSIONS:** FMF is associated with lower rates of most components of the metabolic syndrome compared with normal subjects, unlike other inflammatory conditions.

DOI: 10.1210/jc.2014-2096

PMID: 25062460 [Indexed for MEDLINE]

1955. *Pediatr Rheumatol Online J.* 2014 Jul 17;12:30. doi: 10.1186/1546-0096-12-30. eCollection 2014.

Deregulation of the IL-1 $\beta$  axis in chronic recurrent multifocal osteomyelitis.

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**BACKGROUND:** This study aims to investigate the inflammasome response in peripheral blood mononuclear cells (PBMCs) and the expression of inflammasome components in bone biopsies from patients with chronic recurrent multifocal osteomyelitis (CRMO).

**METHODS:** The expression of inflammasome components mRNAs was evaluated in PBMCs isolated from 15 CRMO patients and 13 healthy controls by quantitative real-time PCR. The Interleukin (IL)-1 $\beta$  released in the medium of PBMC cultures after treatment with lipopolysaccharides (LPS) alone or LPS and ATP was measured by ELISA. Immunohistochemical staining for Apoptosis-associated Speck-like protein (ASC), caspase-1 (CASP-1), Nod-like receptor protein-3 (NLRP3) and IL-1 $\beta$  expression was performed in bone biopsies from CRMO patients.

**RESULTS:** mRNA levels of ASC, CASP-1 and IL-1 $\beta$  were significantly higher in freshly isolated PBMCs from CRMO patients in active disease than in healthy controls. CASP-1 and IL-1 $\beta$  transcript levels were significantly higher also in PBMCs from CRMO patients in remission compared to healthy controls. PBMCs from CRMO patients in active disease stimulated in vitro with LPS showed a significant increase in IL-1 $\beta$  release compared to healthy control cells. Immunohistochemistry staining of bone tissue revealed the expression of inflammasome components in CRMO osteoclasts.

**CONCLUSIONS:** Our data suggest that an abnormal regulation of IL-1 $\beta$  axis may be involved in CRMO pathogenesis.

DOI: 10.1186/1546-0096-12-30

PMCID: PMC4109750

PMID: 25061439 [Indexed for MEDLINE]

## Biological treatments in Behçet's disease: beyond anti-TNF therapy.

Caso F(1), Costa L(2), Rigante D(3), Lucherini OM(4), Caso P(5), Bascherini V(4), Frediani B(4), Cimaz R(6), Marrani E(6), Nieves-Martín L(7), Atteno M(2), Raffaele CG(3), Tarantino G(3), Galeazzi M(4), Punzi L(8), Cantarini L(4).

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Behçet's disease (BD) is universally recognized as a multisystemic inflammatory disease of unknown etiology with chronic course and unpredictable exacerbations: its clinical spectrum varies from pure vasculitic manifestations with thrombotic complications to protean inflammatory involvement of multiple organs and tissues. Treatment has been revolutionized by the progressed knowledge in the pathogenetic mechanisms of BD, involving dysfunction and oversecretion of multiple proinflammatory molecules, chiefly tumor necrosis factor- (TNF-)  $\alpha$ , interleukin- (IL-)  $1\beta$ , and IL-6. However, although biological treatment with anti-TNF- $\alpha$  agents has been largely demonstrated to be effective in BD, not all patients are definite responders, and this beneficial response might drop off over time.



Therefore, additional therapies for a subset of refractory patients with BD are inevitably needed. Different agents targeting various cytokines and their receptors or cell surface molecules have been studied: the IL-1 receptor has been targeted by anakinra, the IL-1 by canakinumab and gevokizumab, the IL-6 receptor by tocilizumab, the IL12/23 receptor by ustekinumab, and the B-lymphocyte antigen CD-20 by rituximab. The aim of this review is to summarize all current experiences and the most recent evidence regarding these novel approaches with biological drugs other than TNF- $\alpha$  blockers in BD, providing a valuable addition to the actually available therapeutic armamentarium.

DOI: 10.1155/2014/107421

PMCID: PMC4100257

PMID: 25061259 [Indexed for MEDLINE]

1957. BMC Musculoskelet Disord. 2014 Jul 24;15:251. doi: 10.1186/1471-2474-15-251.

Clinical and radiological dissociation of anti-TNF plus methotrexate treatment in early rheumatoid arthritis in routine care: results from the ABRAB study.

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**BACKGROUND:** Rheumatoid arthritis (RA) is a chronic autoinflammatory joint disease which leads to the destruction of joints and disability of the patients.

Anti-tumour necrosis factor (anti-TNF) drugs can halt radiological progression better than conventional DMARDs even in clinical non-responders.

**METHODS:** The efficacy of anti-TNF plus methotrexate (MTX) treatment versus MTX monotherapy on clinical and radiological outcomes were compared in early rheumatoid arthritis (RA) patients in clinical practice by retrospective analysis of an observational cohort. 49 early RA patients (group A) on first-line MTX monotherapy and 35 early RA patients (group B) on anti-TNF plus MTX treatment were selected from an observational cohort and evaluated retrospectively focusing on their first twelve months of treatment. Data on disease activity (DAS28) and functional status (HAQ-DI) were collected three monthly. One-yearly radiological progression was calculated according to the van der Heijde modified Sharp method

(vdHS). Clinical non-responder patients in both groups were selectively investigated from a radiological point of view.

**RESULTS:** Disease activity was decreased and functional status was improved significantly in both groups. One-yearly radiological progression was significantly lower in group B than in group A. The percentage of patients showing radiological non-progression or rapid radiological progression demonstrated a significant advantage for group B patients. In addition non-responder patients in group B showed similar radiological results as responders, while a similar phenomenon was not observed in patients in group A.

**CONCLUSIONS:** Clinical efficacy within our study was similar for tight-controlled MTX monotherapy as well as for combination treatment with anti-TNF and MTX. However MTX monotherapy was accompanied by more rapid radiological progression and less radiological non-progression. Anti-TNF plus MTX decreased radiological progression even in clinical non-responders supporting the advantage of anti-TNF plus MTX combination in dissociating clinical and radiological effects.

DOI: 10.1186/1471-2474-15-251

PMCID: PMC4114796

PMID: 25059769 [Indexed for MEDLINE]

1958. Clin Exp Nephrol. 2015 Jun;19(3):436-42. doi: 10.1007/s10157-014-1009-7. Epub 2014 Jul 25.

Serum galectin-3 levels were associated with proteinuria in patients with Familial Mediterranean Fever.

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**BACKGROUND:** The most common and pernicious complication of Familial Mediterranean fever (FMF) is renal amyloidosis, usually affecting the kidneys, leading to end-stage renal failure. FMF-related renal amyloidosis needed to be diagnosed early. Optimal colchicine dose is effective in preventing and reversing renal amyloidosis. Galectin-3, profibrotic mediator, has regulatory functions in inflammation, fibrosis and tumorigenesis. Galectin-3 is a strong prognostic marker for heart failure. Galectin-3 plays role in diabetic nephropathy and chronic kidney disease. The aim of the study is to investigate whether galectin-3 is related to proteinuria and amyloidosis in FMF.

**METHODS:** Seventy-five FMF patients who have no exclusion criteria and healthy controls (n = 36) were included. Serum galectin-3 was measured and morning spot urine was collected for determination of the protein/creatinine ratio (PCR).

**RESULTS:** Serum Galectin-3 levels were significantly higher in FMF patients than the control group [969.66 (3825) pg/mL vs. 238 (921) pg/mL, respectively;  $P < 0.001$ ]. We classified into two groups: Group1 (n = 48) had FMF patients with proteinuria, Group2 (n = 27) had FMF patients without proteinuria. Group1 had higher levels of galectin-3 than Group2 [1106(3812) pg/mL vs. 867.3(1433) pg/mL,  $P < 0.001$ ]. Galectin-3 levels were correlated with PCR in whole group and FMF group ( $r = 0.785$ ,  $P < 0.001$  and  $r = 0.803$ ,  $P < 0.001$ ). In ROC curve, best cutoff value = 581.50 pg/mL was used to detect proteinuria (sensitivity = 91.7 %, specificity = 71.4 %, AUC = 0.879) and optimal cutoff value = 1458.00 pg/mL was an indicator of nephrotic-range proteinuric (sensitivity = 100 %, specificity = 92.1 %, AUC = 0.983).

**CONCLUSION:** Galectin-3 is associated with proteinuria and renal amyloidosis in FMF. Galectin-3 may play role in pathogenesis of amyloidosis.

DOI: 10.1007/s10157-014-1009-7

PMID: 25059227 [Indexed for MEDLINE]

1959. Rare Dis. 2014 Jan 31;2:e27742. doi: 10.4161/rdis.27742. eCollection 2014.

SHP-1 and IL-1 $\alpha$  conspire to provoke neutrophilic dermatoses.

Lukens JR, Kanneganti TD.

Neutrophilic dermatoses are a spectrum of autoinflammatory skin disorders that are characterized by extensive infiltration of neutrophils into the epidermis and dermis. The underlining biological pathways that are responsible for this

heterogeneous group of cutaneous diseases have remained elusive. However, recent work from our laboratory and other groups has shown that missense mutations in Ptpn6, which encodes for the non-receptor protein tyrosine phosphatase Src homology region 2 (SH2) domain-containing phosphatase-1 (SHP-1), results in a skin disease with many of the major histopathological and clinical features that encompass neutrophilic dermatoses in humans. In particular, we found that loss-of-function mutation in Ptpn6 results in unremitting footpad swelling, suppurative inflammation, and neutrophilia. Dysregulated wound healing responses were discovered to contribute to chronic inflammatory skin disease in SHP-1 defective mice and genetic abrogation of interleukin-1 receptor (IL-1R) protected mice from cutaneous inflammation, suggesting that IL-1-mediated events potentiate disease. Surprisingly, inflammasome activation and IL-1 $\beta$ -mediated events were dispensable for Ptpn6(sp1n) -mediated footpad disease. Instead, RIP1-mediated regulation of IL-1 $\alpha$  was identified to be the major driver of inflammation and tissue damage.

DOI: 10.4161/rdis.27742

PMCID: PMC4091500

PMID: 25054090

1960. Arthritis Rheumatol. 2014 Nov;66(11):3241-3. doi: 10.1002/art.38777.

Canakinumab for the treatment of children with colchicine-resistant familial Mediterranean fever: a 6-month open-label, single-arm pilot study.

Brik R(1), Butbul-Avi Y, Lubin S, Ben Dayan E, Rachmilewitz-Minei T, Tseng L, Hashkes PJ.

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DOI: 10.1002/art.38777

PMID: 25049046 [Indexed for MEDLINE]

1961. Nature. 2014 Aug 7;512(7512):69-73. doi: 10.1038/nature13322. Epub 2014 Jun 29.

Negative regulation of the NLRP3 inflammasome by A20 protects against arthritis.

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Comment in

Nat Rev Rheumatol. 2014 Aug;10(8):445.

Rheumatoid arthritis is a chronic autoinflammatory disease that affects 1-2% of the world's population and is characterized by widespread joint inflammation. Interleukin-1 is an important mediator of cartilage destruction in rheumatic diseases, but our understanding of the upstream mechanisms leading to production of interleukin-1 $\beta$  in rheumatoid arthritis is limited by the absence of suitable mouse models of the disease in which inflammasomes contribute to pathology. Myeloid-cell-specific deletion of the rheumatoid arthritis susceptibility gene A20/Tnfrsf3 in mice (A20(myel-KO) mice) triggers a spontaneous erosive polyarthritis that resembles rheumatoid arthritis in patients. Rheumatoid arthritis in A20(myel-KO) mice is not rescued by deletion of tumour necrosis factor receptor 1 (ref. 2). Here we show, however, that it crucially relies on the Nlrp3 inflammasome and interleukin-1 receptor signalling. Macrophages lacking A20 have increased basal and lipopolysaccharide-induced expression levels of the inflammasome adaptor Nlrp3 and proIL-1 $\beta$ . As a result, A20-deficiency in macrophages significantly enhances Nlrp3 inflammasome-mediated caspase-1 activation, pyroptosis and interleukin-1 $\beta$  secretion by soluble and crystalline Nlrp3 stimuli. In contrast, activation of the Nlrp4 and AIM2 inflammasomes is not altered. Importantly, increased Nlrp3 inflammasome activation contributes to the pathology of rheumatoid arthritis in vivo, because deletion of Nlrp3, caspase-1 and the interleukin-1 receptor markedly protects against

rheumatoid-arthritis-associated inflammation and cartilage destruction in A20(myel-KO) mice. These results reveal A20 as a novel negative regulator of Nlrp3 inflammasome activation, and describe A20(myel-KO) mice as the first experimental model to study the role of inflammasomes in the pathology of rheumatoid arthritis.

DOI: 10.1038/nature13322

PMCID: PMC4126806

PMID: 25043000 [Indexed for MEDLINE]

1962. J Autoimmun. 2014 Nov;54:21-32. doi: 10.1016/j.jaut.2014.06.006. Epub 2014 Jul 16.

Immunization with hepatitis B vaccine accelerates SLE-like disease in a murine model.

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Hepatitis-B vaccine (HBVv) can prevent HBV-infection and associated liver diseases. However, concerns regarding its safety, particularly among patients with autoimmune diseases (i.e. SLE) were raised. Moreover, the aluminum adjuvant in HBVv was related to immune mediated adverse events. Therefore, we examined the effects of immunization with HBVv or alum on SLE-like disease in a murine model. NZBWF1 mice were immunized with HBVv (Engerix), or aluminum hydroxide (alum) or phosphate buffered saline (PBS) at 8 and 12 weeks of age. Mice were followed for weight, autoantibodies titers, blood counts, proteinuria, kidney histology, neurocognitive functions (novel object recognition, staircase, Y-maze and the forced swimming tests) and brain histology. Immunization with HBVv induced acceleration of kidney disease manifested by high anti-dsDNA antibodies ( $p < 0.01$ ), early onset of proteinuria ( $p < 0.05$ ), histological damage and deposition of HBs antigen in the kidney. Mice immunized with HBVv and/or alum had decreased cells counts mainly of the red cell lineage ( $p < 0.001$ ), memory deficits ( $p < 0.01$ ), and increased activated microglia in different areas of the brain compare with mice immunized with PBS. Anxiety-like behavior was more pronounced among mice immunized with alum. In conclusion, herein we report that immunization with the HBVv aggravated kidney disease in an animal model of SLE. Immunization with either HBVv or alum affected blood counts, neurocognitive functions and brain gliosis. Our data support the concept that different component of vaccines may be linked with immune and autoimmune mediated adverse events.

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DOI: 10.1016/j.jaut.2014.06.006

PMID: 25042822 [Indexed for MEDLINE]

1963. J Vasc Access. 2014 Sep-Oct;15(5):418-23. doi: 10.5301/jva.5000267. Epub 2014 Jul 8.

Misplaced central venous catheter in the vertebral artery: endovascular treatment of foreseen hemorrhage during catheter withdrawal.

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**PURPOSE:** We report on the endovascular management of hemorrhage with stent-graft due to a misplaced central venous catheter in the vertebral artery (VA) during percutaneous internal jugular vein catheterization in a child.

**METHODS:** A 16-year-old female was presented with the diagnosis of familial Mediterranean fever related chronic renal insufficiency. An attempt was made to place a central venous catheter via the right internal jugular vein without image guidance and the patient experienced dyspnea and pain at the catheter insertion site. Computerized tomography (CT) showed hemorrhage in the cervical region and upper mediastinum, also reformatted images showed that the catheter was passing through the proximal part of the VA and terminating in the right mediastinum. The catheter was removed during manual compression under angio-fluoroscopic monitoring and ongoing extravasation was observed. A stent-graft was placed to the bleeding site of the VA.

**RESULTS:** Angiography immediately after the stent-graft placement revealed complete disappearance of extravasation and patency of vertebral and subclavian arteries.

**CONCLUSION:** Central venous catheterization (CVC) is not a risk-free procedure and arterial injuries are in a wide spectrum from a simple puncture to rupture of the artery. Inadvertent VA cannulation is a rare and serious complication necessitating prompt diagnosis and early treatment. If an arterial injury with a large-caliber catheter occurs, endovascular treatment with stent-graft seems to be a safe and effective option in terms of achieving hemostasis and preserving arterial patency. Recent findings suggest that endovascular management of inadvertent cervical arterial injury secondary to CVC seems to be the safest strategy.

DOI: 10.5301/jva.5000267

PMID: 25041914 [Indexed for MEDLINE]

1964. FEBS J. 2014 Sep;281(17):3844-54. doi: 10.1111/febs.12912. Epub 2014 Aug 5.

Proline-serine-threonine phosphatase interacting protein 1 inhibition of T-cell receptor signaling depends on its SH3 domain.

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Proline-serine-threonine phosphatase interacting protein 1 (PSTPIP1) is an adaptor protein associated with the cytoskeleton that is mainly expressed in hematopoietic cells. Mutations in PSTPIP1 cause the rare autoinflammatory disease called pyogenic arthritis, pyoderma gangrenosum, and acne. We carried out this study to further our knowledge on PSTPIP1 function in T cells, particularly in relation to the phosphatase lymphoid phosphatase (LYP), which is involved in several autoimmune diseases. LYP-PSTPIP1 binding occurs through the C-terminal homology domain of LYP and the F-BAR domain of PSTPIP1. PSTPIP1 inhibits T-cell activation upon T-cell receptor (TCR) and CD28 engagement, regardless of CD2 costimulation. This function of PSTPIP1 depends on the presence of an intact SH3 domain rather than on the F-BAR domain, indicating that ligands of the F-BAR domain, such as the PEST phosphatases LYP and PTP-PEST, are not critical for its negative regulatory role in TCR signaling. Additionally, PSTPIP1 mutations that cause the pyogenic arthritis, pyoderma gangrenosum and acne syndrome do not affect PSTPIP1 function in T-cell activation through the TCR.

© 2014 FEBS.

DOI: 10.1111/febs.12912

PMID: 25040622 [Indexed for MEDLINE]

1965. Ann Rheum Dis. 2015 Nov;74(11):2043-9. doi: 10.1136/annrheumdis-2013-204991.  
Epub  
2014 Jul 18.

Phenotypic and genotypic characteristics of cryopyrin-associated periodic syndrome: a series of 136 patients from the Eurofever Registry.

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OBJECTIVE: To evaluate genetic, demographic and clinical features in patients

with cryopyrin-associated periodic syndrome (CAPS) from the Eurofever Registry, with a focus on genotype-phenotype correlations and predictive disease severity markers.

**METHODS:** A web-based registry retrospectively collected data on patients with CAPS. Experts in the disease independently validated all cases. Patients carrying NLRP3 variants and germline-mutation-negative patients were included.

**RESULTS:** 136 patients were analysed. The median age at disease onset was 9 months, and the median duration of follow-up was 15 years. Skin rash, musculoskeletal involvement and fever were the most prevalent features. Neurological involvement (including severe complications) was noted in 40% and 12% of the patients, respectively, with ophthalmological involvement in 71%, and neurosensory hearing loss in 42%. 133 patients carried a heterozygous, germline mutation, and 3 patients were mutation-negative (despite complete NLRP3 gene screening). Thirty-one different NLRP3 mutations were recorded; 7 accounted for 78% of the patients, whereas 24 rare variants were found in 27 cases. The latter were significantly associated with early disease onset, neurological complications (including severe complications) and severe musculoskeletal involvement. The T348M variant was associated with early disease onset, chronic course and hearing loss. Neurological involvement was less strongly associated with V198M, E311 K and A439 V alleles. Early onset was predictive of severe neurological complications and hearing loss.

**CONCLUSIONS:** Patients carrying rare NLRP3 variants are at risk of severe CAPS; onset before the age of 6 months is associated with more severe neurological involvement and hearing loss. These findings may have an impact on treatment decisions.

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DOI: 10.1136/annrheumdis-2013-204991

PMID: 25038238 [Indexed for MEDLINE]

1966. Immunol Lett. 2014 Nov;162(1 Pt A):49-52. doi: 10.1016/j.imlet.2014.07.002. Epub 2014 Jul 15.

Mutations in the B30.2 domain of pyrin and the risk of ankylosing spondylitis in the Chinese Han population: a case-control study.

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Ankylosing spondylitis (AS) and familial Mediterranean fever (FMF) are a common autoimmune disease and a classic autoinflammatory disease, respectively. Mediterranean fever (MEFV) encodes the pyrin protein and is the causal disease gene in FMF. This protein is an important regulator of innate immunity and may play a key role in the development of AS. To identify the mutations in the B30.2 domain of pyrin and to uncover the relationships between these mutations and AS risk in the Chinese Han population, we extracted genomic DNA from the peripheral blood of 200 AS patients and 200 matched controls and performed polymerase chain reactions (PCRs) and direct sequencing on those samples. Statistical analysis indicated that only Met694Val (rs61752717) in the B30.2 domain of pyrin could affect the risk of AS ( $P = 0.042$ ; odds ratio [OR] = 5.103; 95% confidence interval [CI] = 1.111-23.437 for the model of Met (M) vs. Val (V),  $P = 0.040$ ; OR = 5.211; 95% CI = 1.127-24.091 for the model of MM vs. MV+VV). Moreover, M694V is significantly associated with a higher level of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in AS patients. Our results are the first to suggest that the M694V allele of the pyrin was associated with AS risk in the Chinese Han population and that this mutation may be associated with the inflammatory response in the development of AS.

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DOI: 10.1016/j.imlet.2014.07.002

PMID: 25036284 [Indexed for MEDLINE]

1967. J Pediatr Hematol Oncol. 2015 May;37(4):296-9. doi: 10.1097/MPH.0000000000000212.

CANDLE syndrome: a recently described autoinflammatory syndrome.

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CANDLE syndrome (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature) is a recently described autoinflammatory syndrome characterized by early onset, recurrent fever, skin lesions, and multisystemic inflammatory manifestations. Most of the patients have been shown to have mutation in PSMB8 gene. Herein, we report a 2-year-old patient with young onset recurrent fever, atypical facies, widespread skin lesions, generalized lymphadenopathy, hepatosplenomegaly, joint contractures, hypertriglyceridemia, lipodystrophy, and autoimmune hemolytic anemia. Clinical features together with the skin biopsy findings were consistent with the CANDLE syndrome. The pathogenesis and treatment of this syndrome have not been fully understood. Increased awareness of this recently described syndrome may lead to recognition of new cases and better understanding of its pathogenesis which in turn may help for development of an effective treatment.

DOI: 10.1097/MPH.0000000000000212

PMID: 25036278 [Indexed for MEDLINE]

1968. N Engl J Med. 2014 Aug 7;371(6):507-518. doi: 10.1056/NEJMoa1312625. Epub 2014 Jul 16.

Activated STING in a vascular and pulmonary syndrome.

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Comment in

N Engl J Med. 2014 Aug 7;371(6):568-71.

Nat Rev Rheumatol. 2014 Sep;10(9):512.

Ann Dermatol Venereol. 2014 Dec;141(12):808-9.

**BACKGROUND:** The study of autoinflammatory diseases has uncovered mechanisms underlying cytokine dysregulation and inflammation.

**METHODS:** We analyzed the DNA of an index patient with early-onset systemic inflammation, cutaneous vasculopathy, and pulmonary inflammation. We sequenced a candidate gene, TMEM173, encoding the stimulator of interferon genes (STING), in this patient and in five unrelated children with similar clinical phenotypes.

Four children were evaluated clinically and immunologically. With the STING ligand cyclic guanosine monophosphate-adenosine monophosphate (cGAMP), we stimulated peripheral-blood mononuclear cells and fibroblasts from patients and controls, as well as commercially obtained endothelial cells, and then assayed transcription of IFNB1, the gene encoding interferon- $\beta$ , in the stimulated cells.

We analyzed IFNB1 reporter levels in HEK293T cells cotransfected with mutant or nonmutant STING constructs. Mutant STING leads to increased phosphorylation of signal transducer and activator of transcription 1 (STAT1), so we tested the effect of Janus kinase (JAK) inhibitors on STAT1 phosphorylation in lymphocytes from the affected children and controls.

**RESULTS:** We identified three mutations in exon 5 of TMEM173 in the six patients. Elevated transcription of IFNB1 and other gene targets of STING in peripheral-blood mononuclear cells from the patients indicated constitutive activation of the pathway that cannot be further up-regulated with stimulation. On stimulation with cGAMP, fibroblasts from the patients showed increased transcription of IFNB1 but not of the genes encoding interleukin-1 (IL1), interleukin-6 (IL6), or tumor necrosis factor (TNF). HEK293T cells transfected with mutant constructs show elevated IFNB1 reporter levels. STING is expressed in endothelial cells, and exposure of these cells to cGAMP resulted in endothelial activation and apoptosis. Constitutive up-regulation of phosphorylated STAT1 in patients' lymphocytes was reduced by JAK inhibitors.

**CONCLUSIONS:** STING-associated vasculopathy with onset in infancy (SAVI) is an autoinflammatory disease caused by gain-of-function mutations in TMEM173. (Funded by the Intramural Research Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases; ClinicalTrials.gov number, NCT00059748.).

DOI: 10.1056/NEJMoa1312625

PMCID: PMC4174543

PMID: 25029335 [Indexed for MEDLINE]

1969. Cytokine. 2014 Oct;69(2):248-54. doi: 10.1016/j.cyto.2014.06.012. Epub 2014 Jul 12.

Ex vivo PBMC cytokine profile in familial Mediterranean fever patients: Involvement of IL-1 $\beta$ , IL-1 $\alpha$  and Th17-associated cytokines and decrease of Th1 and Th2 cytokines.

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In order to clarify the inflammatory mechanism underlying familial Mediterranean fever (FMF), we aimed to evaluate the ex vivo cytokine profile of FMF patients during acute attacks and attack-free periods, and compare it with that of healthy controls. The study included 34 FMF patients, of whom 9 were studied during attack and remission and 24 healthy controls. Cytokine levels were evaluated by Luminex technology in serum and supernatants of PBMC (Peripheral Blood Mononuclear Cells) cultures with and without 24h stimulation of monocytes by LPS and T lymphocytes by anti-CD3/CD28 beads. Levels of IL-6 and TNF- $\alpha$  were higher in unstimulated and LPS-stimulated PBMC supernatants of FMF patients in crises compared to controls. In response to LPS stimulation, higher levels of IL-1 $\beta$  and IL-1 $\alpha$  were found in PBMC supernatants of patients during crises compared to those in remission and to controls. IFN- $\gamma$  and IL-4 levels were the lowest in unstimulated and anti-CD3/CD28 stimulated PBMCs supernatants of patients during crises compared to remission and controls. The Th17 cytokines IL-17 and IL-22 were respectively higher in anti-CD3/CD28 stimulated PBMC supernatants of FMF patients during and between crises compared to controls. Amongst cytokines tested in serum, only IL-6 and TNF $\alpha$  were enhanced in FMF patients. The ex vivo study represents an interesting approach to evaluate cytokines' involvement in FMF. Our results suggest an ongoing subclinical inflammation and define an elevated



inflammatory cytokine signature, distinctly for M694V homozygous patients. The absence of spontaneous IL-1 $\beta$  release by PBMCs reflects no constitutive activation of the inflammasome in FMF physiopathology.

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DOI: 10.1016/j.cyto.2014.06.012

PMID: 25025954 [Indexed for MEDLINE]

1970. J Dermatol Sci. 2014 Sep;75(3):208-9. doi: 10.1016/j.jdermsci.2014.06.002. Epub 2014 Jun 19.

Response to Li and Zhang: infevers, a human gene mutation database for autoinflammatory diseases including disseminated superficial actinic porokeratosis.

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Comment on

J Dermatol Sci. 2014 Jul;75(1):68-9.

DOI: 10.1016/j.jdermsci.2014.06.002

PMID: 25022922 [Indexed for MEDLINE]

1971. Clin Dermatol. 2014 Jul-Aug;32(4):488-501. doi: 10.1016/j.clindermatol.2014.02.004. Epub 2014 Feb 28.

Autoinflammatory syndromes for the dermatologist.

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While autoimmunity as cause of disease is well-established, other categories of immune-mediated diseases that are not produced by targeting of self-antigens by antibodies is in the process of being described. These so-called autoinflammatory diseases arise when an inappropriate activation of antigen-independent mechanisms occurs. Autoinflammatory diseases course with recurrent attacks of fever and multisystemic inflammation; however, the skin may also be affected by a variety of inflammatory manifestations that often alert the clinician about the presence of an autoinflammatory disease. Recognizing the cutaneous features of these syndromes will aid for prompt diagnosis and early treatment that is key for the quality of life and survival of the affected patients. In this paper, we focus on the skin manifestations of autoinflammatory diseases in children, which is the usual period of appearing of the first symptoms and signs.

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DOI: 10.1016/j.clindermatol.2014.02.004

PMID: 25017460 [Indexed for MEDLINE]

1972. Curr Opin Rheumatol. 2014 Sep;26(5):585-91. doi: 10.1097/BOR.0000000000000095.

Use of microarrays in the clinical practice of pediatric rheumatology: the future is now?

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**PURPOSE OF REVIEW:** Systems immunology is an integrative approach that leverages high throughput technologies as well as mathematical and computational tools to investigate complex immunologic diseases by looking at the state of a system on a comprehensive scale. Gene expression profiling, also known as transcriptomics, measures the expression level of mRNAs (transcripts) in a given cell population at a specific time. Over the past decade, several major gene expression discoveries have been made in pediatric rheumatology, most notably the alpha interferon signature of systemic lupus erythematosus and the interleukin-1 signature in systemic onset juvenile idiopathic arthritis. This article reviews these discoveries, their clinical implications and the recent associated literature.

**RECENT FINDINGS:** Interferon- $\alpha$  has been exploited as a therapeutic target in lupus. Interleukin-1 blockade has been utilized to treat systemic onset juvenile idiopathic arthritis and related autoinflammatory diseases.

**SUMMARY:** Current gene expression studies extend our understanding of the disease pathogenesis of lupus and systemic onset juvenile idiopathic arthritis as well as related conditions. This knowledge has translated to the bedside with implications for clinical practice and direct therapeutic targeting.

DOI: 10.1097/BOR.0000000000000095

PMID: 25014037 [Indexed for MEDLINE]

1973. Hematol Rep. 2014 Jun 19;6(2):5356. doi: 10.4081/hr.2014.5356. eCollection 2014 Apr 22.

Hemophagocytic lymphohistiocytosis and pelger-huët anomaly associated with colchicine intoxication.

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Colchicine is frequently used in the treatment of familial Mediterranean fever (FMF). First symptoms of colchicine intoxication are gastrointestinal disturbances, such as abdominal cramps, diarrhea, pancytopenia and so on. Herein, we report a female FMF patient with pancytopenia and hemophagocytic lymphohistiocytosis (HLH), following colchicine intoxication for committing suicide. To our knowledge, this is the first reported case of a patient with HLH associated with colchicine intoxication.

DOI: 10.4081/hr.2014.5356

PMCID: PMC4091288

PMID: 25013716

1974. Acta Reumatol Port. 2014 Oct-Dec;39(4):316-21.

Comparison of serum oxidant and antioxidant parameters in familial Mediterranean fever patients (FMF) with attack free period.

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**OBJECTIVE:** Familial Mediterranean fever (FMF) is an autoinflammatory, autosomal recessive, inherited disease characterized by recurrent self-limiting attacks of serosal surfaces. The imbalance of oxidants/antioxidants may play a role in such attacks. In this study, we aimed to evaluate the relationship between serum paraoxonase (PON1) activity, PON1 phenotype, and other parameters in patients with FMF and healthy controls.

**METHODS:** A total of 120 FMF patients with an attack-free period (AFP) and 65 healthy subjects were included in this study. The serum PON1 activity, stimulated paraoxonase (SPON) activity, PON1 phenotype (representing Q192R polymorphism; QQ, QR, RR), arylesterase activity, total oxidant status (TOS), total antioxidant capacity (TAC), oxidative stress index (OSI), advanced oxidative protein products (AOPP), total thiols (TTL), and ischemia-modified albumin (IMA) and cystatin-c (CYS-C) levels were measured.

**RESULTS:** For the QQ phenotype, the median TTL and AOPP levels of the control group were 264.50 (57.75) mol/L and 21.26 (21.17) mmol/L, respectively, whereas the median TTL, AOPP levels of the patients were 309.00 (47.00) mol/L and 12.98 (6.96) mmol/L, respectively. There was a statistically significant difference between the patients and controls with the QQ phenotype in terms of TTL and AOPP ( $p < 0.001$  and  $p = 0.004$ , respectively). However, there were no statistically significant differences between the QQ and QR+RR phenotypes with respect to TAC, TOS, OSI, or the other parameters.

**CONCLUSIONS:** The FMF patients with AFP had higher TTL and lower AOPP levels than the controls. However, other oxidant and antioxidant parameters were similar among the patients during AFP and the controls.

PMID: 25007287 [Indexed for MEDLINE]

1975. J Biol Chem. 2014 Aug 22;289(34):23504-19. doi: 10.1074/jbc.M114.553305. Epub 2014 Jul 8.

Identification of multifaceted binding modes for pyrin and ASC pyrin domains gives insights into pyrin inflammasome assembly.

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Inflammasomes are macromolecular complexes that mediate inflammatory and cell death responses to pathogens and cellular stress signals. Dysregulated inflammasome activation is associated with autoinflammatory syndromes and several common diseases. During inflammasome assembly, oligomerized cytosolic pattern recognition receptors recruit procaspase-1 and procaspase-8 via the adaptor protein ASC. Inflammasome assembly is mediated by pyrin domains (PYDs) and caspase recruitment domains, which are protein interaction domains of the death

fold superfamily. However, the molecular details of their interactions are poorly understood. We have studied the interaction between ASC and pyrin PYDs that mediates ASC recruitment to the pyrin inflammasome, which is implicated in the pathogenesis of familial Mediterranean fever. We demonstrate that both the ASC and pyrin PYDs have multifaceted binding modes, involving three sites on pyrin PYD and two sites on ASC PYD. Molecular docking of pyrin-ASC PYD complexes showed that pyrin PYD can simultaneously interact with up to three ASC PYDs. Furthermore, ASC PYD can self-associate and interact with pyrin, consistent with previous reports that pyrin promotes ASC clustering to form a proinflammatory complex. Finally, the effects of familial Mediterranean fever-associated mutations, R42W and A89T, on structural and functional properties of pyrin PYD were investigated. The R42W mutation had a significant effect on structure and increased stability. Although the R42W mutant exhibited reduced interaction with ASC, it also bound less to the pyrin B-box domain responsible for autoinhibition and hence may be constitutively active. Our data give new insights into the binding modes of PYDs and inflammasome architecture.

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DOI: 10.1074/jbc.M114.553305

PMCID: PMC4156052

PMID: 25006247 [Indexed for MEDLINE]

1976. Acta Reumatol Port. 2014 Oct-Dec;39(4):342-4.

Co-existence of familial Mediterranean fever and multiple sclerosis in two patients.

Ceylan G, Erten S, Ercan K.

**ABSTRACT** Two female patients, aged 23 and 25 years-old diagnosed with Familial Mediterranean fever (FMF) were presented with ataxia and headache. Multiple sclerosis plaques were detected in their spinal and cranial MRI and diagnosis of multiple sclerosis was established. Genetic analysis demonstrated M694 V mutation (one homozygous and the other heterozygous) in both of the patients. Although it is quite rare, coexistence of familial Mediterranean fever and multiple sclerosis should be kept in the mind.

PMID: 25005448 [Indexed for MEDLINE]

1977. Wien Med Wochenschr. 2014 Jul;164(13-14):274-7. doi: 10.1007/s10354-014-0290-0. Epub 2014 Jul 9.

Autoimmunity versus autoinflammation--friend or foe?

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"Autoimmunity" is a designation dependent on the conventional immunological issue of self/non-self discrimination. Identification of novel target autoantigens is still an important issue ongoing in classical tissue-specific autoimmune bullous diseases and autoimmune connective tissue diseases. In contrast, synchronized with the paradigm shift of the fundamental aspect of immunity to danger sensing/signaling, distinct collagen-like diseases have been defined by the genetic mutations causing dysregulated innate immunity/inflammation and have been designated as "autoinflammatory" diseases. Due to the clinical and etiological similarities, the concept of autoinflammatory diseases has expanded to include non-hereditary collagen-like diseases, tissue-specific chronic idiopathic inflammatory diseases and metabolic diseases. On the other hand, various genetic causes of autoimmune diseases have been identified and the border of these two pathophysiology is becoming obscure. Instead, a variable mixture of both autoimmunity and autoinflammation can cause each inflammatory phenotype with a variable level of antigen specificity

DOI: 10.1007/s10354-014-0290-0

PMID: 25004809 [Indexed for MEDLINE]

1978. Carbohydr Res. 2014 Aug 18;395:19-28. doi: 10.1016/j.carres.2014.06.003. Epub 2014 Jun 14.

Functional identification of a galactosyltransferase critical to Bacteroides

*fragilis* Capsular Polysaccharide A biosynthesis.

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Capsular Polysaccharide A (CPSA), a polymer of a four-sugar repeating unit that coats the surface of the mammalian symbiont *Bacteroides fragilis*, has therapeutic potential in animal models of Multiple Sclerosis and other autoinflammatory diseases. Genetic studies have demonstrated that CPSA biosynthesis is dependent primarily on a single gene cluster within the *B. fragilis* genome. However, the precise functions of the individual glycosyltransferases encoded by this cluster have not been identified. In this report each of these glycosyltransferases (WcfQ, WcfP, and WcfN) have been expressed and tested for their function in vitro. Using a reverse phase high performance liquid chromatography (HPLC) assay, WcfQ and WcfP were found to transfer galactose from uridine diphosphate (UDP)-linked galactose (Gal) to N-acetyl-4-amino-6-deoxy-galactosamine (AADGal) linked to a fluorescent mimic of bactoprenyl diphosphate, the native isoprenoid anchor for bacterial polysaccharide biosynthesis. The incorporation of galactose to form a bactoprenyl-linked disaccharide was confirmed by radiolabel incorporation and mass spectrometry (MS) of purified product. Using varying concentrations of UDP-Gal and enzyme, WcfQ was found to be the most effective protein at transferring galactose, and is the most likely candidate for in vivo incorporation of the sugar. WcfQ also cooperated in the presence of three preceding biosynthetic enzymes to form an isoprenoid-linked disaccharide in a single-pot reaction. This work represents a critical step in understanding the biosynthetic pathway responsible for the formation of CPSA, an unusual and potentially therapeutic biopolymer.



DOI: 10.1016/j.carres.2014.06.003  
PMCID: PMC4119839  
PMID: 24997288 [Indexed for MEDLINE]

1979. Intern Med J. 2014 Nov;44(11):1128-33. doi: 10.1111/imj.12520.

Assessment of renal involvement in patients with familial Mediterranean fever: a clinical study from Ardabil, Iran.

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**BACKGROUND AND AIM:** Familial Mediterranean fever (FMF) is an autosomal recessive disease characterised by recurrent episodes of painful inflammation in the abdomen, chest or joints. The association between FMF and non-amyloid glomerulopathies are unusual. In this study, we describe our experiences and observations about renal involvement in patients with FMF.

**METHODS:** A total of 108 patients with FMF was enrolled in the study. Twelve patients with FMF were referred to the Nephrology Service, for evaluation and assessment of the degree of renal involvement. All the 12 patients underwent percutaneous ultrasound-guided renal biopsies and genetic analysis.

**RESULTS:** On microscopic examination of the kidney specimens, six patients were found to have amyloidosis, five focal segmental glomerulosclerosis and one patient membranoproliferative glomerulonephritis. It seems that in patients with FMF and renal amyloidosis, the response to treatment with colchicine is excellent, but in patients with FMF and focal segmental glomerulosclerosis, the response to treatment with colchicine is poor. We present an evidence-based algorithm, constructed based on literature review, to aid decision making in management of renal involvement in patients with FMF.

**CONCLUSION:** The results of our study suggest that in patients with FMF and renal involvement, non-amyloid renal lesions should be considered in the differential diagnosis in addition to amyloidosis.

of Physicians.

DOI: 10.1111/imj.12520

PMID: 24989840 [Indexed for MEDLINE]

1980. Dtsch Med Wochenschr. 2014 Jul;139(28-29):1468-72. doi: 10.1055/s-0034-1370159. Epub 2014 Jul 1.

[Autoinflammatory syndromes--cutaneous manifestations].

[Article in German]

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DOI: 10.1055/s-0034-1370159

PMID: 24983195 [Indexed for MEDLINE]

1981. BMC Med Genet. 2014 Jul 1;15:74. doi: 10.1186/1471-2350-15-74.

A novel insertion mutation identified in exon 10 of the MEFV gene associated with Familial Mediterranean Fever.

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**BACKGROUND:** Familial Mediterranean Fever (FMF), characterized by recurrent fever and inflammation of serous membranes, is an autosomal recessive disease caused by mutations in the Mediterranean fever (MEFV) gene. Around 296 mutations have been reported to date.

**METHODS:** Two two-generation Turkish families with a total of four members

diagnosed with FMF clinically were screened with DNA sequencing performed on exon 2 and exon 10 of the MEFV genes. Then, complete exome sequencing analysis of MEFV gene was done for four patients in whom novel mutation was detected.

RESULTS: A novel single base Guanine (G) insertion mutation in the coding region of MEFV gene, named c.2330dupG (p.Gln778Serfs\*4 or Q778SfsX4) resulting in a mutated Pyrin/Marenostrin protein was identified.

CONCLUSIONS: This is the first report of a new mutation in exon 10 of the MEFV gene in two Turkish families. This novel pattern of insertion mutation may provide important information for further studies on FMF pathogenesis.

DOI: 10.1186/1471-2350-15-74

PMCID: PMC4094690

PMID: 24980720 [Indexed for MEDLINE]

1982. Isr Med Assoc J. 2014 May;16(5):281-4.

Treatment of familial Mediterranean fever: colchicine and beyond.

Gül A.

PMID: 24979831 [Indexed for MEDLINE]

1983. Isr Med Assoc J. 2014 May;16(5):274-6.

Familial Mediterranean fever: genetic update.

Soriano A, Pras E.

PMID: 24979829 [Indexed for MEDLINE]

1984. Isr Med Assoc J. 2014 May;16(5):271-3.

Colchicine failure in familial Mediterranean fever and potential alternatives: embarking on the anakinra trial.

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Familial Mediterranean fever (FMF) is a genetic auto-inflammatory disease characterized by spontaneous short attacks of fever, elevated acute-phase reactants, and serositis. Approximately 5%-10% of FMF patients do not respond to colchicine treatment and another 5% are intolerant to colchicine because of side effects. Recently, following the discovery of the inflammasome and recognition of the importance of interleukin-1beta (IL-1beta) as the major cytokine involved in the pathogenesis of FMF, IL-1beta blockade has been suggested and tried sporadically to treat FMF, with good results. To date, case reports and small case series involving colchicine-resistant FMF patients and showing high efficacy of IL-1beta blockade have been reported. At the Israel Center for FMF at the Sheba Medical Center the first double-blind randomized placebo-controlled trial of anakinra in FMF patients who are resistant or intolerant to colchicines is underway. In this report we discuss the mechanism of colchicine resistance in FMF patients, the data in the literature on IL1beta blockade in these patients, and the anakinra trial inclusion criteria and study protocol.

PMID: 24979828 [Indexed for MEDLINE]

1985. Isr Med Assoc J. 2014 May;16(5):269-70.

Pearls from the Third Israeli Conference on FMF, other autoinflammatory disorders and AA amyloidosis.

Livneh A, Ben-Zvi I.

PMID: 24979827 [Indexed for MEDLINE]

1986. Pediatr Phys Ther. 2014 Fall;26(3):353. doi: 10.1097/PEP.0000000000000054.

Commentary on "functional capacity, strength, and quality of life in children and youth with familial Mediterranean fever".

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Comment on

Pediatr Phys Ther. 2014 Fall;26(3):347-52.

DOI: 10.1097/PEP.0000000000000054

PMID: 24979094 [Indexed for MEDLINE]

1987. Pediatr Phys Ther. 2014 Fall;26(3):347-52. doi: 10.1097/PEP.0000000000000052.

Functional capacity, strength, and quality of life in children and youth with familial Mediterranean fever.

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Comment in

Pediatr Phys Ther. 2014 Fall;26(3):353.

**PURPOSE:** To examine functional capacity and muscle strength in children and youth with familial Mediterranean fever (FMF) as compared with controls, and to assess whether these factors influence quality of life (QOL) in FMF.

**METHODS:** A total of 100 subjects with FMF and 55 control subjects (8-18 years old) without known health issues were enrolled in the study. The 6-Minute Walk Test (6MWT) was used to evaluate functional capacity. Quadriceps strength was measured with a hand-held dynamometer. Quality of life was evaluated with the Pediatric Quality of Life Inventory 4.0 (PedsQL 4.0).

**RESULTS:** Significant differences were found between subjects with FMF and controls in the 6MWT and strength test. PedsQL scores of subjects with FMF were

significantly lower than the scores of the controls. The 6MWT and quadriceps strength were weakly correlated with the PedsQL.

CONCLUSION: Subjects with FMF displayed lower functional capacity and QOL than peers who are healthy. Decreased functional capacity was correlated with decreased QOL in those with FMF.

DOI: 10.1097/PEP.0000000000000052

PMID: 24979093 [Indexed for MEDLINE]

1988. Best Pract Res Clin Rheumatol. 2014 Apr;28(2):263-76. doi: 10.1016/j.berh.2014.05.005.

A practical approach to the diagnosis of autoinflammatory diseases in childhood.

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Autoinflammatory diseases are characterized by the presence of chronic or recurrent systemic inflammation secondary to abnormal activation of innate immunity pathways. Many of these diseases have been found to have mutations in the genes within these pathways. Due to their rarity, non-specific symptoms and the very recent genetic and phenotypic identification and recognition, a delay in diagnosis is common. Nevertheless, some specific clinical features should help the clinician to make the diagnosis. The purpose of this article is to provide a brief clinical description of these conditions and to present clinical flow-charts useful for a correct diagnosis of children with suspected autoinflammatory syndromes.

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DOI: 10.1016/j.berh.2014.05.005

PMID: 24974062 [Indexed for MEDLINE]

1989. Clin Exp Immunol. 2014 Nov;178(2):224-8. doi: 10.1111/cei.12407.

MEFV gene polymorphisms and TNFRSF1A mutation in patients with inflammatory myopathy with abundant macrophages.

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Inflammatory myopathy with abundant macrophages (IMAM) has recently been proposed as a new clinical condition. Although IMAM shares certain similarities with other inflammatory myopathies, the mechanisms responsible for this condition remain unknown. Patients with familial Mediterranean fever (FMF) and tumour necrosis factor receptor-associated periodic syndrome (TRAPS) also often develop myalgia. We therefore investigated the polymorphisms or mutations of MEFV and TNFRSF1A genes in patients with IMAM to identify their potential role in this condition. We analysed the clinical features of nine patients with IMAM and sequenced exons of the MEFV and TNFRSF1A genes. The patients with IMAM had clinical symptoms such as myalgia, muscle weakness, erythema, fever and arthralgia. Although none of the patients were diagnosed with FMF or TRAPS, seven demonstrated MEFV polymorphisms (G304R, R202R, E148Q, E148Q-L110P and P369S-R408Q), and one demonstrated a TNFRSF1A mutation (C43R). These results suggest that MEFV gene polymorphisms and TNFRSF1A mutation are susceptibility and modifier genes in IMAM.

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DOI: 10.1111/cei.12407

PMCID: PMC4233371

PMID: 24965843 [Indexed for MEDLINE]

1990. Endocr Metab Immune Disord Drug Targets. 2014;14(3):182-6.

Assessment of thyroid disorders and autoimmunity in patients with rheumatic diseases.

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We investigated whether there was a significant increase in thyroid autoimmunity, and disorders in patients with rheumatic diseases (RDs). We enrolled 201 patients with RDs (41 with ankylosing spondylitis, 15 with systemic lupus erythematosus, 80 with rheumatoid arthritis [RA], 65 with familial Mediterranean fever), and 122 healthy controls. Serum levels of thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), C-reactive protein, and thyroid autoantibodies (anti-thyroglobulin and anti-thyroid peroxidase) were measured in all participants. There were no significant differences between the ages of the patients and controls. The mean TSH values of the patients with RDs and the controls were  $3.1 \pm 2.68$  mIU/L and  $1.9 \pm 0.83$  mIU/L, respectively ( $P = 0.004$ ). The mean fT4 value of the patients with RDs was  $1.43 \pm 0.67$  ng/dL whereas that of the controls was  $1.58 \pm 0.68$  ng/dL ( $P < 0.001$ ). Subclinical hypothyroidism was detected in 24 patients with RDs. Thyroid antibodies were detected in 16 of 201 (8%) patients with RDs. Three of these patients had subclinical hypothyroidism, while the others were euthyroid. Thyroid autoantibodies were significantly higher in patients with RDs ( $P < 0.001$ ). Additionally, thyroid disorders were observed more frequently in patients with RDs than in the healthy controls. Based on our findings, we recommend that thyroid function tests should better be included in the clinical evaluation of patients with RDs.

PMID: 24965722 [Indexed for MEDLINE]

1991. Clin Exp Rheumatol. 2014 Nov-Dec;32(6):956-8. Epub 2014 Jun 24.

A novel de novo PSTPIP1 mutation in a boy with pyogenic arthritis, pyoderma gangrenosum, acne (PAPA) syndrome.

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Autoinflammatory disorders are a group of Mendelian disorders characterized by seemingly unprovoked inflammatory bouts without high-titer autoantibodies or antigen-specific T-cells and are probably due to defects in the innate immunity. We here report on a 4-year-old Arabic boy with the clinical presentation of an autoinflammatory disorder, namely Pyogenic Arthritis, Pyoderma Gangrenosum and Acne (PAPA) syndrome. The presentation includes abscess formation after immunization and recurrent mono-articular acute arthritis in various joints that responded favourably to systemic glucocorticosteroids, albeit without acne or pyoderma gangrenosum. The mutation analysis of the boy identified a novel de novo mutation in PSTPIP1, the gene responsible for PAPA syndrome. We recommend that the diagnosis of PAPA syndrome should be entertained in the differential diagnosis of patients with recurrent sterile pyogenic arthritis prior to the development of pyoderma gangrenosum or acne in order to initiate a timely management of the disorder.

PMID: 24960411 [Indexed for MEDLINE]

1992. Indian J Hum Genet. 2014 Jan;20(1):43-50. doi: 10.4103/0971-6866.132755.

Phenotype-genotype updates from familial Mediterranean fever database registry of Mansoura University Children' Hospital, Mansoura, Egypt.

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BACKGROUND: Familial Mediterranean fever (FMF) is autosomal recessive disease

that affects people from Mediterranean region, Europe and Japan. Its gene (Mediterranean fever [MEFV]) has more than 100 mostly non-sense mutations.

**OBJECTIVES:** The objective of the following study is to provide some phenotype-genotype correlates in FMF by categorizing the Egyptian FMF cases from Delta governorates after analysis of the four most common mutations of MEFV gene (M680I, M694I, M694V, V726A).

**SUBJECTS AND METHODS:** Clinically, suspected FMF cases using Tel-Hashomer criteria were enrolled in the study. Cases were referred to Mansoura University Children's Hospital that serves most of the most middle Delta governorates, in the period from 2006 to 2011. Subjects included 282 males and 144 females, mean age of onset  $9.3 \pm 2.2$  years. All cases were analyzed for these mutations using amplification refractory mutation system based on the polymerase chain reaction technique. Five FMF patients agreed to undergo renal biopsy to check for development of amyloidosis. Analysis of data was carried out using SPSS (SPSS, Inc., Chicago, IL, USA).

**RESULTS:** Mutation was found in 521 out of 852 studies alleles, the most frequent is M694V (35.4%) followed by M694I, V726A and M680I. 11 cases were homozygous; 7 M694V, 3 M680I and only one M694I case. Severe abdominal pain occurred in 31 (7.28%) but severe arthritis in 103 cases (24.2%). Strong association was found between arthritis and homozygous mutant compared with single and double heterozygous (72.7% vs. 33.3% and 20.24%,  $P < 0.001$ ). Four amyloid cases were M694V positive.

**CONCLUSION:** M694V allele is the most common among Egyptian FMF especially those with amyloidosis. We recommend routine check for amyloidosis in FMF cases to statistically validate this link.

DOI: 10.4103/0971-6866.132755

PMCID: PMC4065478

PMID: 24959013

1993. Indian J Hum Genet. 2014 Jan;20(1):1-3. doi: 10.4103/0971-6866.132741.

Familial Mediterranean fever: An unusual disease enlightening the inflammation biology.

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DOI: 10.4103/0971-6866.132741

PMCID: PMC4065472

PMID: 24959007

1994. J Biol Chem. 2014 Aug 15;289(33):22900-14. doi: 10.1074/jbc.M114.557900. Epub 2014 Jun 23.

Engagement of nucleotide-binding oligomerization domain-containing protein 1 (NOD1) by receptor-interacting protein 2 (RIP2) is insufficient for signal transduction.

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Following activation, the cytoplasmic pattern recognition receptor nucleotide-binding oligomerization domain-containing protein 1 (NOD1) interacts with its adaptor protein receptor-interacting protein 2 (RIP2) to propagate immune signaling and initiate a proinflammatory immune response. This interaction is mediated by the caspase recruitment domain (CARD) of both proteins.

Polymorphisms in immune proteins can affect receptor function and predispose individuals to specific autoinflammatory disorders. In this report, we show that mutations in helix 2 of the CARD of NOD1 disrupted receptor function but did not interfere with RIP2 interaction. In particular, N43S, a rare polymorphism, resulted in receptor dysfunction despite retaining normal cellular localization, protein folding, and an ability to interact with RIP2. Mutation of Asn-43 resulted in an increased tendency to form dimers, which we propose is the source of this dysfunction. We also demonstrate that mutation of Lys-443 and Tyr-474 in

RIP2 disrupted the interaction with NOD1. Mapping the key residues involved in the interaction between NOD1 and RIP2 to the known structures of CARD complexes revealed the likely involvement of both type I and type III interfaces in the NOD1-RIP2 complex. Overall we demonstrate that the NOD1-RIP2 signaling axis is more complex than previously assumed, that simple engagement of RIP2 is insufficient to mediate signaling, and that the interaction between NOD1 and RIP2 constitutes multiple CARD-CARD interfaces.

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DOI: 10.1074/jbc.M114.557900

PMCID: PMC4132792

PMID: 24958724 [Indexed for MEDLINE]

1995. Clin Rheumatol. 2015 Jan;34(1):17-28. doi: 10.1007/s10067-014-2721-0. Epub 2014 Jun 24.

The labyrinth of autoinflammatory disorders: a snapshot on the activity of a third-level center in Italy.

Cantarini L(1), Vitale A, Lucherini OM, De Clemente C, Caso F, Costa L, Emmi G, Silvestri E, Magnotti F, Maggio MC, Prinzi E, Lopalco G, Frediani B, Cimaz R, Galeazzi M, Rigante D.

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Autoinflammatory disorders (AIDs) are a novel class of diseases elicited by mutations in genes regulating the homeostasis of innate immune complexes, named inflammasomes, which lead to uncontrolled oversecretion of the proinflammatory cytokine interleukin-1 $\beta$ . Protean inflammatory symptoms are variably associated with periodic fever, depicting multiple specific conditions. Childhood is usually the lifetime in which most hereditary AIDs start, though still a relevant number of patients may experience a delayed disease onset and receive a definite diagnosis during adulthood. As a major referral laboratory for patients with recurrent fevers, we have tested samples from 787 patients in the period

September 2007-March 2014, with a total of 1,328 AID-related genes evaluated and a gene/patient ratio of 1.69. In this report, we describe our experience in the clinical approach to AIDs, highlight the most striking differences between child and adult-onset AIDs, and shed an eye-opening insight into their diagnostic process.

DOI: 10.1007/s10067-014-2721-0

PMID: 24953660 [Indexed for MEDLINE]

1996. Nat Immunol. 2014 Aug;15(8):738-48. doi: 10.1038/ni.2919. Epub 2014 Jun 22.

The NLRP3 inflammasome is released as a particulate danger signal that amplifies the inflammatory response.

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Assembly of the NLRP3 inflammasome activates caspase-1 and mediates the processing and release of the leaderless cytokine IL-1 $\beta$  and thereby serves a central role in the inflammatory response and in diverse human diseases. Here we found that upon activation of caspase-1, oligomeric NLRP3 inflammasome particles were released from macrophages. Recombinant oligomeric protein particles composed of the adaptor ASC or the p.D303N mutant form of NLRP3 associated with cryopyrin-associated periodic syndromes (CAPS) stimulated further activation of caspase-1 extracellularly, as well as intracellularly after phagocytosis by surrounding macrophages. We found oligomeric ASC particles in the serum of patients with active CAPS but not in that of patients with other inherited autoinflammatory diseases. Our findings support a model whereby the NLRP3 inflammasome, acting as an extracellular oligomeric complex, amplifies the inflammatory response.

DOI: 10.1038/ni.2919

PMID: 24952504 [Indexed for MEDLINE]

1997. Mod Rheumatol. 2016 Sep;26(5):798-801. doi: 10.3109/14397595.2014.924894. Epub 2014 Jun 20.

A 2-year-old Japanese girl with TNF receptor-associated periodic syndrome: A case report of the youngest diagnosed proband in Japan.

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We report a 2-year-old girl with tumor necrosis factor receptor-associated periodic syndrome (TRAPS) who is the youngest proband diagnosed in Japan. Recurrent fever had started at her 6 months of age, and she had the familial

history of recurrent fever, suggesting underlying genetic disorder, in her father and grandfather. Careful clinical observation of characteristics of fever with disease course and the familial history of recurrent fever may lead to diagnosis of TRAPS in early infancy.

DOI: 10.3109/14397595.2014.924894

PMID: 24950168 [Indexed for MEDLINE]

1998. Georgian Med News. 2014 May;(230):79-82.

Familial Mediterranean fever in Georgia.

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Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory disorder caused by mutations in the MEFV gene. Carrier rates are known to be particularly high among Sephardic Jews, Turks, Armenians and Arab populations. Our literature survey regarding FMF and MEFV mutations in Georgia revealed a lack of existing studies. We applied multiplex PCR and reverse-hybridization teststrips (FMF StripAssay) to simultaneously analyze twelve common MEFV mutations in DNA samples from dried blood on filter cards, which had been obtained from 202 unselected newborns at various hospitals in Tbilisi, Georgia. We found 30 samples to be heterozygous and one to be compound heterozygous or carrier of a complex allele (two mutations in cis). The carrier rate of MEFV mutations (15.3%) was remarkable. The most frequently observed variants were E148Q (15x), M680I G/C (5x) and M694V (4x). Five other MEFV mutations were found at lower prevalence (V726A, A744S, R761H: 2x each; P369S, F479L: 1x each). Based on these new findings, the awareness for FMF and the availability of appropriate testing should be further promoted in Georgia.

PMID: 24940862 [Indexed for MEDLINE]

1999. Arch Pediatr. 2014 Jul;21(7):765-7. doi: 10.1016/j.arcped.2014.04.024. Epub 2014 Jun 13.

[Hyperimmunoglobulinemia D and periodic fever syndrome].

[Article in French]

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We report the cases of two sisters born of parents who were first-degree cousins, who started recurrent fever with lymph node and digestive tract involvement at the age of 2 years. There was no mutation of the familial Mediterranean fever gene and a diagnosis of partial mevalonate kinase (MVK) deficiency was made. However, immunoglobulin (Ig) D and A levels were normal. Elevated mevalonic acid in the patients' urine during an episode and MVK gene analysis provided the diagnosis. Clinical remission was obtained under anti-TNF-alpha treatment with etanercept. These observations and those of several previously reported patients, particularly in French and Dutch series, illustrate the importance of considering the diagnosis in a child with early-onset auto-inflammatory syndrome even in the absence of hyper-IgD or -IgA.



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DOI: 10.1016/j.arcped.2014.04.024

PMID: 24935455 [Indexed for MEDLINE]

2000. Clin Rheumatol. 2014 Sep;33(9):1197-207. doi: 10.1007/s10067-014-2722-z. Epub 2014 Jun 17.

Key facts and hot spots on tumor necrosis factor receptor-associated periodic syndrome.

Rigante D(1), Lopalco G, Vitale A, Lucherini OM, De Clemente C, Caso F, Emmi G, Costa L, Silvestri E, Andreozzi L, Iannone F, Galeazzi M, Cantarini L.

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Tumor necrosis factor receptor-associated periodic syndrome (TRAPS), formerly known as familial Hibernian fever, is the most common autosomal dominant autoinflammatory disease, resulting from mutations in the TNFRSF1A gene, encoding the 55-kD tumor necrosis factor receptor. The pathophysiologic mechanism of TRAPS remains ambiguous and only partially explained. The onset age of the syndrome is variable and the clinical scenery is characterized by recurrent episodes of high-grade fever that typically lasts 1-3 weeks, associated with migrating myalgia, pseudocellulitis, diffuse abdominal pain, appendicitis-like findings, ocular inflammatory signs, and risk of long-term amyloidosis. Fever episodes are responsive to high-dose corticosteroids, but different classes of drugs have been reported to be ineffective. The use of etanercept is unable to control systemic inflammation, while interleukin-1 blockade has been shown as effective in the control of disease activity in many patients reported so far.

DOI: 10.1007/s10067-014-2722-z

PMID: 24935411 [Indexed for MEDLINE]

2001. J Rheumatol. 2014 Jul;41(7):1379-84. doi: 10.3899/jrheum.131227. Epub 2014 Jun 15.

Behçet syndrome manifestations and activity in the United States versus Turkey --  
a cross-sectional cohort comparison.

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**OBJECTIVE:** To compare clinical manifestations and activity of Behçet syndrome (BS) in the United States versus Turkey using validated outcome measures.

**METHODS:** Consecutive patients with BS from the US National Institutes of Health (NIH), New York University, and the University of Istanbul were evaluated.

Disease activity was measured using the Behçet's Syndrome Activity Scale (BSAS) and the Behçet's Disease Current Activity Form (BDCAF) with quality of life measured by the Behçet Disease Quality of Life (BDQOL) form. One-way ANOVA, t-tests, and multivariate regression analyses were performed.

**RESULTS:** Mean age did not differ between sites; however, more women were seen in the United States versus in Turkey ( $p < 0.001$ ), and disease duration was longer in the United States ( $p = 0.02$ ). Organ manifestations were similar for oral and genital ulcers, skin disease, arthralgia, eye disease, and thrombosis. However, more gastrointestinal ( $p < 0.001$ ) and neurologic disease ( $p = 0.003$ ) was seen in the United States. BSAS and BDCAF scores were worse in the United States compared to Turkey ( $p = 0.013$  and  $< 0.001$ , respectively). Worse mean BDQOL scores were observed at the NIH compared to Istanbul (not significant). Multivariable regression models showed worse scores in ethnically atypical patients for BSAS and BDCAF ( $p = 0.04$  and  $p = 0.001$ ), American patients for BDCAF ( $p = 0.01$ ), older age for BDCAF ( $p = 0.005$ ), and women for BDQOL ( $p = 0.01$ ).

**CONCLUSION:** Demographic and clinical manifestations of BS differ between sites with higher disease activity in the United States compared to Turkey. Referral patterns, age, sex, ethnicity, and country of origin may be important in these differences. These observations raise the question of whether pathogenic mechanisms differ in Turkish and American patients.

DOI: 10.3899/jrheum.131227

PMCID: PMC4565792

PMID: 24931953 [Indexed for MEDLINE]

2002. Gene. 2014 Aug 10;546(2):195-9. doi: 10.1016/j.gene.2014.06.019. Epub 2014 Jun 11.

Frequency of MEFV gene mutations in Hatay province, Mediterranean region of Turkey and report of a novel missense mutation (I247V).

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In the present study, 1000 patients with clinical suspicion of FMF were retrospectively reviewed to determine the spectrum of MEFV gene mutations by using DNA sequence analysis between September, 2008 and April, 2012. Sixteen different mutations and 55 different genotypes were detected in 618 of 1000 patients. Among 16 different mutations, R202Q (21.35%) was the most frequently observed mutation; followed by E148Q (8.85%), M694V (7.95%), M680I (2.40%), V726A (1.85%), M694I (0.95%), A744S (0.80%), R761H (0.55%), P283L (0.35%), K695R (0.20%), E230K (0.15%), L110P (0.10%), I247V (0.05%), G196W (0.05%) and G304R (0.05%). In the present study, a novel missense mutation (I247V) and a silent variant (G150G) were identified in the MEFV gene. On the other hand, P238L, G632A and G304R mutations are the first cases reported from Turkey. Our results indicated that MEFV mutations are highly heterogeneous in our study population as in other regions of Turkey and mutation screening techniques such as PCR-RFLP, amplification refractory mutation system or reverse hybridization do not adequately detect uncommon or novel mutations. Therefore, it was proven that sequence analysis of the MEFV gene could be useful for detection of rare or unknown mutations.

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DOI: 10.1016/j.gene.2014.06.019

PMID: 24929125 [Indexed for MEDLINE]

2003. Clin Rheumatol. 2016 May;35(5):1237-44. doi: 10.1007/s10067-014-2714-z. Epub 2014 Jun 15.

Cardiac autonomic functions in children with familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is the most common inherited autoinflammatory disease in the world. The long-term effects of subclinical inflammation in FMF are not well recognized. Some studies have suggested that FMF is associated with cardiac autonomic dysfunction in adult FMF patients. The objective of this study was to investigate the cardiac autonomic functions in pediatric FMF patients by using several autonomic tests. Thirty-five patients with FMF and 35 healthy controls were enrolled in this cross-sectional study. Demographic data, disease-specific data, and orthostatic symptoms were recorded. In all participants, 12-lead electrocardiography (ECG), 24 h ambulatory electrocardiographic monitoring, transthoracic echocardiography, treadmill exercise test, and head upright tilt-table (HUTT) test were performed. The heart rate recovery (HRR) indices of the two groups were similar. Also, chronotropic response was similar in both groups. The time-domain parameters of heart rate variability (HRV) were similar in both groups, except mean RR ( $p = 0.024$ ). Frequencies of ventricular and supraventricular ectopic stimuli were similar in both groups. There were no statistically significant differences between the groups in average QT and average corrected QT interval length, average QT interval dispersion, and average QT corrected dispersion. There was no significant difference between the two groups regarding the ratio of clinical dysautonomic reactions on HUTT. However, we observed a significantly higher rate of dysautonomic reactions on HUTT in patients with exertional leg pain than that

in patients without ( $p = 0.013$ ). When the fractal dimension of time curves were compared, FMF patients exhibited significantly lower diastolic blood pressure parameters than controls in response to HUTT. Cardiovascular autonomic dysfunction in children with FMF is not prominent. Particularly, patients with exertional leg pain are more prone to have dysautonomic features. Further studies are needed to elucidate the exact mechanisms leading to impaired cardiac autonomic functions in FMF.

DOI: 10.1007/s10067-014-2714-z

PMID: 24928342 [Indexed for MEDLINE]

2004. Clin Rheumatol. 2014;33(10):1385-8. doi: 10.1007/s10067-014-2709-9. Epub 2014 Jun 14.

The impact of familial Mediterranean fever on reproductive system.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent attacks of fever, peritonitis, pleuritis, arthritis, or erysipelas-like skin lesion. FMF is the most common periodic febrile syndrome affecting more than 150,000 people worldwide. The majority of patients develop FMF before the age of 20. FMF may cause amyloidosis, which mainly affects the kidneys but may also be accumulated in other organs such as the heart, gastrointestinal tract, and reproductive organs. FMF being a systemic disorder with a risk for amyloidosis, affecting patients in their childbearing years, and with its lifelong colchicine therapy raises concern about its effect on the reproductive system. In this article, we review the impact of FMF and its treatment to the reproductive system of male and female patients, pregnancy, and lactation.

DOI: 10.1007/s10067-014-2709-9

PMID: 24924605 [Indexed for MEDLINE]

2005. Nature. 2014 Sep 11;513(7517):237-41. doi: 10.1038/nature13449. Epub 2014 Jun 11.

Innate immune sensing of bacterial modifications of Rho GTPases by the Pyrin inflammasome.

Xu H(1), Yang J(2), Gao W(3), Li L(3), Li P(3), Zhang L(3), Gong YN(3), Peng X(3), Xi JJ(4), Chen S(3), Wang F(3), Shao F(5).

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Comment in

Cell Res. 2014 Nov;24(11):1286-7.

Nat Rev Immunol. 2014 Jul;14(7):429.

Cytosolic inflammasome complexes mediated by a pattern recognition receptor (PRR) defend against pathogen infection by activating caspase 1. Pyrin, a candidate PRR, can bind to the inflammasome adaptor ASC to form a caspase 1-activating complex. Mutations in the Pyrin-encoding gene, MEFV, cause a human autoinflammatory disease known as familial Mediterranean fever. Despite important roles in immunity and disease, the physiological function of Pyrin remains unknown. Here we show that Pyrin mediates caspase 1 inflammasome activation in response to Rho-glucosylation activity of cytotoxin TcdB, a major virulence factor of *Clostridium difficile*, which causes most cases of nosocomial diarrhoea. The glucosyltransferase-inactive TcdB mutant loses the inflammasome-stimulating activity. Other Rho-inactivating toxins, including FIC-domain

adenylyltransferases (*Vibrio parahaemolyticus* VopS and *Histophilus somni* IbpA) and *Clostridium botulinum* ADP-ribosylating C3 toxin, can also biochemically activate the Pyrin inflammasome in their enzymatic activity-dependent manner. These toxins all target the Rho subfamily and modify a switch-I residue. We further demonstrate that *Burkholderia cenocepacia* inactivates RHOA by deamidating Asn 41, also in the switch-I region, and thereby triggers Pyrin inflammasome activation, both of which require the bacterial type VI secretion system (T6SS). Loss of the Pyrin inflammasome causes elevated intra-macrophage growth of *B. cenocepacia* and diminished lung inflammation in mice. Thus, Pyrin functions to sense pathogen modification and inactivation of Rho GTPases, representing a new paradigm in mammalian innate immunity.

DOI: 10.1038/nature13449

PMID: 24919149 [Indexed for MEDLINE]

2006. Ocul Immunol Inflamm. 2014 Dec;22(6):444-8. doi: 10.3109/09273948.2014.916309. Epub 2014 Jun 9.

Retinal and choroidal thickness in children with familial Mediterranean fever.

Erdurmuş M(1), Bekdaş M, Demircioğlu F, Soydan A, Göksügür SB, Kısmet E.

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(1)Department of Ophthalmology and.

Comment in

Ocul Immunol Inflamm. 2015;23(6):467.

**PURPOSE:** The aim of the present study was to evaluate retinal and choroidal thicknesses in children with familial Mediterranean fever (FMF).

**METHODS:** Thirty patients with FMF and 28 healthy controls were included in the study. The thicknesses of the retina and choroid of each subject's right eye were measured at the fovea and horizontal nasal and temporal quadrants at 500-µm intervals to 1500 µm from the foveal center using spectral-domain optic coherence tomography.

**RESULTS:** Retinal and choroidal thicknesses at the fovea did not differ between groups ( $p = 0.32$  and  $p = 0.39$ , respectively). Horizontal nasal and temporal retinal and choroidal thickness measurements at 500-µm intervals to a distance of



1500 µm from the foveal center were also similar between the groups (all  $p > 0.05$ ).

CONCLUSIONS: The retinal and choroidal thicknesses of children with FMF do not differ from those of age- and sex-matched healthy controls.

DOI: 10.3109/09273948.2014.916309

PMID: 24911930 [Indexed for MEDLINE]

2007. Nihon Naika Gakkai Zasshi. 2014 Apr 10;103(4):972-4.

[Case report; A Japanese case of familial Mediterranean fever with pleurisy].

[Article in Japanese]

Sawada Y, Kuroda A, Aoki F, Takemura M, Kitahara S, Ueno M, Maeno T, Suga T, Kurabayashi M.

PMID: 24908995 [Indexed for MEDLINE]

2008. Rheumatology (Oxford). 2014 Nov;53(11):2002-8. doi: 10.1093/rheumatology/keu231. Epub 2014 Jun 6.

Endothelial function in patients with familial Mediterranean fever-related amyloidosis and association with cardiovascular events.

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**OBJECTIVES:** Secondary amyloidosis is the most important complication of FMF and endothelial function is more severely impaired. Elevated asymmetric dimethyl arginine (ADMA) may mediate the excess cardiovascular disease (CVD) risk of this group. We aimed to compare endothelial function characteristics, including ADMA, in patients with FMF-related amyloidosis and primary glomerulopathies and to define risk factors for a CVD event.

**METHODS:** We undertook a cross-sectional study with prospective follow-up

including consecutive patients with FMF-related amyloidosis (n = 98) or other non-diabetic glomerulopathies (n = 102). All patients had nephrotic-range proteinuria and normal glomerular filtration rate. Flow-mediated dilatation (FMD) was assessed and ADMA levels, CRP and pentraxin 3 (PTX3) were determined. Patients were followed for cardiovascular events.

**RESULTS:** Amyloidosis patients secondary to FMF showed higher levels of ADMA, CRP and PTX3 and lower FMD as compared with patients with other glomerulopathies. Cardiovascular events (n = 54) were registered during 3 years of follow-up. Increased ADMA levels and lower FMD were observed in patients with cardiovascular risk in both groups, but especially in individuals with amyloidosis.

**CONCLUSION:** Patients with FMF-related amyloidosis have increased CVD event risk, probably related to the high ADMA levels, elevated inflammatory markers and decreased FMD measures observed in these patients.

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DOI: 10.1093/rheumatology/keu231  
PMID: 24907154 [Indexed for MEDLINE]

2009. Ann Rheum Dis. 2015 Sep;74(9):1714-9. doi: 10.1136/annrheumdis-2013-204877. Epub 2014 Jun 6.

A 24-month open-label study of canakinumab in neonatal-onset multisystem inflammatory disease.

Sibley CH(1), Chioato A(2), Felix S(2), Colin L(2), Chakraborty A(2), Plass N(1), Rodriguez-Smith J(1), Brewer C(3), King K(3), Zalewski C(3), Kim HJ(3), Bishop R(4), Abrams K(2), Stone D(1), Chapelle D(1), Kost B(1), Snyder C(1), Butman JA(5), Wesley R(6), Goldbach-Mansky R(1).

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**OBJECTIVE:** To study efficacy and safety of escalating doses of canakinumab, a fully human anti-IL-1 $\beta$  monoclonal antibody in the severe cryopyrin-associated periodic syndrome, neonatal-onset multisystem inflammatory disease (NOMID).

**METHODS:** 6 patients were enrolled in this 24-month, open-label phase I/II study. All underwent anakinra withdrawal. The initial subcutaneous canakinumab dose was 150 mg (or 2 mg/kg in patients  $\leq 40$  kg) or 300 mg (or 4 mg/kg) with escalation up to 600 mg (or 8 mg/kg) every 4 weeks. Full remission was remission of patient-reported clinical components and measures of systemic inflammation and CNS inflammation. Hearing, vision and safety were assessed. Primary endpoint was full remission at month 6.

**RESULTS:** All patients flared after anakinra withdrawal, and symptoms and serum inflammatory markers improved with canakinumab. All patients required dose escalation to the maximum dose. At month 6, none had full remission, although 4/6 achieved inflammatory remission, based on disease activity diary scores and normal C-reactive proteins. None had CNS remission; 5/6 due to persistent CNS leucocytosis. At the last study visit, 5/6 patients achieved inflammatory remission and 4/6 had continued CNS leucocytosis. Visual acuity and field were stable in all patients, progressive hearing loss occurred in 1/10 ears. Adverse events (AEs) were rare. One serious AE (abscess due to a methicillin-resistant *Staphylococcus aureus* infection) occurred.

**CONCLUSIONS:** Canakinumab at the studied doses improves symptoms and serum inflammatory features of NOMID, although low-grade CNS leukocytosis in four patients and headaches in one additional patient persisted. Whether further dose intensifications are beneficial in these cases remains to be assessed.

CLINICALTRIALSGOV IDENTIFIER: NCT00770601.

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DOI: 10.1136/annrheumdis-2013-204877

PMCID: PMC4258169

2010. Clin Exp Immunol. 2014 Oct;178(1):48-56. doi: 10.1111/cei.12394.

Expression of cytokines, chemokines and other effector molecules in two prototypic autoinflammatory skin diseases, pyoderma gangrenosum and Sweet's syndrome.

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Erratum in

Clin Exp Immunol. 2015 Jul;181(1):188.

Pyoderma gangrenosum (PG) and Sweet's syndrome (SS) are two inflammatory skin diseases presenting with painful ulcers and erythematous plaques, respectively; both disorders have a debilitating clinical behaviour and PG is potentially life-threatening. Recently, PG and SS have been included among the autoinflammatory diseases, which are characterized by recurrent episodes of sterile inflammation, without circulating autoantibodies and autoreactive T cells. However, an autoinflammatory pattern clearly supporting this inclusion has never been demonstrated. We studied 16 patients with PG, six with SS and six controls, evaluating, using a sandwich-based protein antibody array method, the expression profile of inflammatory effector molecules in PG, SS and normal skin. The expressions of interleukin (IL)-1 beta and its receptor I were significantly higher in PG ( $P = 0.0001$  for both) and SS ( $P = 0.004$ - $0.040$ ) than in controls. In PG, chemokines such as IL-8 ( $P = 0.0001$ ), chemokine (C-X-C motif) ligand (CXCL) 1/2/3 ( $P = 0.002$ ), CXCL 16 ( $P = 0.003$ ) and regulated upon activation normal T cell expressed and secreted (RANTES) ( $P = 0.005$ ) were over-expressed. In SS, IL-8 ( $P = 0.018$ ), CXCL 1/2/3 ( $P = 0.006$ ) and CXCL 16 ( $P = 0.036$ ) but not RANTES were over-expressed, suggesting that chemokine-mediated signals are lower than in PG. Fas/Fas ligand and CD40/CD40 ligand systems were over-expressed in PG ( $P = 0.0001$  for Fas,  $P = 0.009$  for Fas ligand,  $P = 0.012$  for CD40,  $P = 0.0001$  for CD40

ligand), contributing to tissue damage and inflammation, while their role seems to be less significant in SS. Over-expression of cytokines/chemokines and molecules amplifying the inflammatory network supports the view that PG and SS are autoinflammatory diseases. The differences in expression profile of inflammatory effectors between these two disorders may explain the stronger local aggressiveness in PG than SS.

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DOI: 10.1111/cei.12394

PMCID: PMC4360193

PMID: 24903614 [Indexed for MEDLINE]

2011. Wien Med Wochenschr. 2014 Jul;164(13-14):263-73. doi: 10.1007/s10354-014-0285-x. Epub 2014 Jun 5.

Pyoderma gangrenosum: pathogenetic oriented treatment approaches.

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Pyoderma gangrenosum (PG) shows features of autoimmune and autoinflammatory disorders. Genetic defects which affect the inflammasome, and in particular the NLRP3 zone, can cause an abnormal secretion of interleukin 1 (IL-1). IL-1 may be involved in clinical manifestation of certain (genetic) forms of PG. IL-1 receptor antagonists reduce the activity of IL-1 $\alpha$  and IL-1 $\beta$ . Mutations in the PSTPIP1 gene have been identified in patients with pyogenic arthritis, pyoderma gangrenosum and acne syndrome. In patients with a pyoderma gangrenosum, acne, and suppurative hidradenitis syndrome these mutations cannot be found and the effect of IL-1 inhibition is questionable. Another upcoming opportunity is targeted therapy by tumor necrosis factor- $\alpha$  inhibitors in steroid-resistant patients. This review has been focused on (1) the modern pathogenetic concepts, (2) the currently accepted criteria for differentiating the disease, (3) the target therapy and (4) valuable advice to the clinicians regarding a number of

medicaments capable of aggravating or inducing the PG.

DOI: 10.1007/s10354-014-0285-x

PMID: 24898196 [Indexed for MEDLINE]

2012. Int J Dermatol. 2014 Jul;53(7):866-8. doi: 10.1111/ijd.12525. Epub 2014 Jun 5.

IL36RN mutation causing generalized pustular psoriasis in a Palestinian patient.

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Deficiency of interleukin-36 (IL-36) receptor antagonist (DITRA; OMIM 614204) is a rare autoinflammatory disorder characterized by periodic fever associated with a generalized erythematous and pustular skin rash. A 6-year-old Arab-Palestinian boy presented with a history of periodic fever and unremitting, erythematous, scaly skin rash accompanied by widespread pustules that had been present since the age of one month. The patient's skin lesions were compatible with generalized pustular psoriasis. Sequence analysis revealed a homozygous nonsense mutation, c.28C>T (p.Arg10X) in the IL36RN gene. The patient improved with oral methotrexate in combination with oral and topical corticosteroids. The molecular basis for DITRA has only recently been identified, and the mutation spectrum for this disorder in many populations is still obscure. This paper reports the presence of the c.28C>T mutation in an Arab-Palestinian patient and thus represents the first description of this mutation in a non-Japanese subject.

© 2014 The International Society of Dermatology.

DOI: 10.1111/ijd.12525

PMID: 24898045 [Indexed for MEDLINE]

2013. Ann Rheum Dis. 2014 Aug;73(8):e53. doi: 10.1136/annrheumdis-2014-205819. Epub 2014 Jun 3.

Response to: 'The country of residence affects the phenotype of familial Mediterranean fever? Is it real or a selection bias?' by Korkmaz.

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Comment on

Ann Rheum Dis. 2014 Apr;73(4):662-7.

Ann Rheum Dis. 2014 Aug;73(8):e52.

DOI: 10.1136/annrheumdis-2014-205819

PMID: 24894191 [Indexed for MEDLINE]

2014. Arthritis Rheumatol. 2014 Sep;66(9):2621-7. doi: 10.1002/art.38727.

Brief Report: Involvement of TNFRSF11A molecular defects in autoinflammatory disorders.

Jéru I(1), Cochet E, Duquesnoy P, Hentgen V, Copin B, Mitjavila-Garcia MT, Sheykhholeslami S, Le Borgne G, Dastot-Le Moal F, Malan V, Karabina S, Mahevas M, Chantot-Bastaraud S, Lecron JC, Faivre L, Amselem S.

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**OBJECTIVE:** Autoinflammatory disorders are caused by a primary dysfunction of the innate immune system. Among these disorders are hereditary recurrent fevers, which are characterized by recurrent episodes of fever and inflammatory manifestations affecting multiple tissues. Hereditary recurrent fevers often lack objective diagnostic criteria, thereby hampering the identification of disease-causing genes. This study was undertaken to identify a gene responsible for hereditary recurrent fevers.



**METHODS:** Copy number variations and point mutations were sought by array-comparative genomic hybridization and polymerase chain reaction sequencing, respectively. Serum cytokine levels were measured using Luminex technology. The effect of TNFRSF11A molecular defects on NF- $\kappa$ B signaling in cells expressing wild-type and mutated forms of the receptor was evaluated by luciferase assay.

**RESULTS:** A patient with multiple congenital anomalies and hereditary recurrent fever was found to carry a de novo heterozygous complex chromosomal rearrangement encompassing a duplication of TNFRSF11A, a gene known to regulate fever in rodents. We also identified a heterozygous frameshift mutation (p.Met416Cysfs\*110) in TNFRSF11A in a mother and daughter with isolated hereditary recurrent fever. This mutation was associated with increased secretion of several inflammatory cytokines (tumor necrosis factor  $\alpha$  [TNF $\alpha$ ], interleukin-18 [IL-18], IL-1 receptor antagonist, interferon- $\gamma$ ) and altered the biologic effects of the receptor on NF- $\kappa$ B signaling. The disease in the patients described herein exhibits striking clinical similarities to TNF receptor-associated periodic syndrome, another hereditary recurrent fever involving a gene of the same family (TNFRSF1A).

**CONCLUSION:** The involvement of TNFRSF11A in hereditary recurrent fever highlights the key role of this receptor in innate immunity. The present results also suggest that TNFRSF11A screening could serve as a new diagnostic test for autoinflammatory disorders.

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DOI: 10.1002/art.38727

PMID: 24891336 [Indexed for MEDLINE]

2015. Arthritis Res Ther. 2014 May 28;16(3):R117. doi: 10.1186/ar4570.

Decreased interleukin 27 expression is associated with active uveitis in Behçet's disease.

Wang C, Tian Y, Ye Z, Kijlstra A, Zhou Y, Yang P.

**INSTRUCTION:** Interleukin 27 (IL-27) is an important regulator of the proinflammatory T-cell response. In this study, we investigated its role in the pathogenesis of Behçet's disease (BD).

**METHODS:** IL-27 mRNA in peripheral blood mononuclear cells (PBMCs) was examined by

performing RT-PCRs. Cytokine levels in sera or supernatants of PBMCs, naïve CD4(+) T cells, dendritic cells (DCs) and DC/T cells were determined by enzyme-linked immunosorbent assay. We used RNA interference in naïve CD4(+) T cells to study the role of interferon regulatory factor 8 (IRF8) in the inhibitory effect of IL-27 on Th17 cell differentiation. Flow cytometry was used to evaluate the frequency of IL-17- and interferon  $\gamma$ -producing T cells.

**RESULTS:** The expression of IL-27p28 mRNA by PBMCs and IL-27 in the sera and supernatants of cultured PBMCs were markedly decreased in patients with active BD. A higher frequency of IL-17-producing CD4(+) T (Th17) cells and increased IL-17 production under Th17 polarizing conditions were observed in patients with active BD. IL-27 significantly inhibited Th17 cell differentiation.

Downregulation of IRF8 by RNA interference abrogated the suppressive effect of IL-27 on Th17 differentiation. IL-27 inhibited the production of IL-1 $\beta$ , IL-6 and IL-23, but promoted IL-10 production, by DCs. IL-27-treated DCs inhibited both the Th1 and Th17 cell responses.

**CONCLUSIONS:** The results of the present study suggest that a decreased IL-27 expression is associated with disease activity in BD patients. Low IL-27 expression may result in a higher Th1 and Th17 cell response and thereby promote the autoinflammatory reaction observed in BD. Manipulation of IL-27 may offer a new treatment modality for this disease.

DOI: 10.1186/ar4570

PMCID: PMC4095700

PMID: 24887071 [Indexed for MEDLINE]

2016. Eur J Rheumatol. 2014 Jun;1(2):58-61. Epub 2014 Jun 1.

Heart rate variability in familial Mediterranean fever patients.

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**OBJECTIVE:** Familial Mediterranean fever (FMF) is an autosomal recessive autoimmune disease, presenting with the attacks of fever and inflammation of serous membranes. One of the leading causes of death in autoimmune rheumatologic diseases is cardiovascular events. The purpose of this study is to evaluate the effects of FMF on the autonomic nerve and cardiovascular systems by measuring the indices of heart rate variability (HRV).

**MATERIAL AND METHODS:** Thirty FMF patients and the same number of healthy volunteers were enrolled to the study. Standard deviation of all R-R intervals (SDNN), the square root of the sum of the square of the differences between successive R-R intervals (RMSSD), standard deviation of 5-minute mean values of R-R interval (SDANN), low frequency (LF), and high frequency (HF) were measured.

**RESULTS:** Time domain indices (SDNN, SDANN, and RMSSD) were:  $124.67 \pm 40.79$ ,  $129.87 \pm 36.43$  ( $p=0.605$ );  $11.43 \pm 38.41$ ,  $11.23 \pm 38.98$  ( $p=0.984$ ); and  $33.43 \pm 17.39$ ,  $38.17 \pm 12.8$  ( $p=0.235$ ) for FMF patients and controls, respectively, and similar in both groups. Frequency domain indices (HF, LF, and LF/HF) were:  $290.41 \pm 290.25$ ,  $322.20 \pm 222.54$  ( $p=0.639$ );  $596.16 \pm 334.07$ ,  $805.80 \pm 471.00$  ( $p=0.051$ ); and  $3.57 \pm 2.57$ ,  $3.05 \pm 1.40$  ( $p=0.338$ ) for FMF patients and controls, respectively, and similar in both groups.

**CONCLUSION:** The HRV parameters were similar in both groups. However, studies including larger populations and using different methods are required to clarify if autonomic dysfunction exists in patients with FMF.

DOI: 10.5152/eurjrheumatol.2014.013

PMCID: PMC5042279

PMID: 27708876

2017. Metallomics. 2014 Aug;6(8):1513-20. doi: 10.1039/c4mt00067f.

Colchicine induced intraneuronal free zinc accumulation and dentate granule cell degeneration.

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Colchicine has been discovered to inhibit many inflammatory processes such as gout, familial Mediterranean fever, pericarditis and Behcet disease. Other than these beneficial anti-inflammatory effects, colchicine blocks microtubule-assisted axonal transport, which results in the selective loss of dentate granule cells of the hippocampus. The mechanism of the colchicine-induced dentate granule cell death and depletion of mossy fiber terminals still remains unclear. In the present study, we hypothesized that colchicine-induced dentate granule cell death may be caused by accumulation of labile intracellular zinc. 10  $\mu\text{g kg}^{-1}$  of colchicine was injected into the adult rat hippocampus and then brain sections were evaluated at 1 day or 1 week later. Neuronal cell death was evaluated by H&E staining or Fluoro-Jade B. Zinc accumulation and vesicular zinc were detected by N-(6-methoxy-8-quinolyl)-para-toluene sulfonamide (TSQ) staining. To test whether an extracellular zinc chelator can prevent this process, CaEDTA was injected into the hippocampus over a 5 min period with colchicine. To test whether other microtubule toxins also produce similar effects as colchicine, vincristine was injected into the hippocampus. The present study found that colchicine injection induced intracellular zinc accumulation in the dentate granule cells and depleted vesicular zinc from mossy fiber terminals. Injection of a zinc chelator, CaEDTA, did not block the zinc accumulation and neuronal death. Vincristine also produced intracellular zinc accumulation and neuronal death. These results suggest that colchicine-induced dentate granule cell death is caused by blocking axonal zinc flow and accumulation of intracellular labile zinc.

DOI: 10.1039/c4mt00067f

PMID: 24874779 [Indexed for MEDLINE]

2018. Can J Ophthalmol. 2014 Jun;49(3):304-6. doi: 10.1016/j.jcjo.2014.01.007.

First report of keratitis in familial cold autoinflammatory syndrome.

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**OBJECTIVE:** To report corneal manifestations of familial cold autoinflammatory syndrome (FCAS) for the first time.

**DESIGN:** small case series

**PARTICIPANTS:** Medical records of three members of a single family were reviewed after obtaining institutional review board (IRB) approval and informed consent.

**METHODS:** All three members presented with a long history of maculopapular rash after cold exposure starting in childhood associated with nausea, low-grade fever, fatigue and arthralgia that lasted less than 24 hours. Their ocular manifestations consisted of ocular pain, photophobia and keratitis with subsequent stromal haziness.

**RESULTS:** Patients underwent systemic therapy with canakinumab (Ilaris). They responded very well to repeated injections of Ilaris without side effects.

**CONCLUSIONS:** FCAS causes lifelong debilitating effects that restrict patients' daily activities. Ilaris is an FDA-approved treatment for this condition and that typically results in dramatic improvement in clinical and laboratory measures of inflammation, and is well tolerated. Our report is the first small case series of FCAS with keratitis that responded to Ilaris beautifully.

Published by Elsevier Inc.

DOI: 10.1016/j.jcjo.2014.01.007

PMID: 24862780 [Indexed for MEDLINE]

2019. Singapore Med J. 2014 May;55(5):242-3.

Paediatric rheumatology: a subspecialty in its infancy that is making leaps and bounds.

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Paediatric rheumatology is an exciting field exploding with new knowledge of autoimmune and autoinflammatory conditions and how to treat them. It is, however,

a relatively new subspecialisation in Asia. There is thus a great need to educate the public and medical community about paediatric rheumatic diseases so that children with such conditions are given the highest possibility of achieving normal function in their daily lives.

PMCID: PMC4291978

PMID: 24862745 [Indexed for MEDLINE]

2020. Mol Diagn Ther. 2014 Oct;18(5):549-57. doi: 10.1007/s40291-014-0105-4.

MEFV mutations in Egyptian children with systemic-onset juvenile idiopathic arthritis.

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**BACKGROUND AND OBJECTIVES:** Systemic-onset juvenile idiopathic arthritis (SoJIA) is a chronic auto-inflammatory disease of childhood, with a complex genetic trait, which is characterized by arthritis associated with systemic manifestations. Familial Mediterranean fever (FMF) is another auto-inflammatory disorder that is monogenic. There are speculations as to whether Mediterranean fever (MEFV) mutations are among the genetic determinants of SoJIA. Our aim was to explore the frequency and clinical significance of MEFV mutations in Egyptian SoJIA patients. A group of healthy children were assigned to the control group in an attempt to estimate the carrier rate of MEFV mutations in Egypt.

**METHODS:** Eighty-four children were recruited in this study; 54 children, age (mean  $\pm$  standard deviation;  $8.31 \pm 2.85$  years), diagnosed as having SoJIA with no typical symptoms of FMF; 30 healthy age- and gender-matched children served as the control group. All recruited children were screened for 12 common MEFV mutations using a reverse hybridization assay of biotinylated PCR products.

**RESULTS:** SoJIA patients had a significantly higher frequency of MEFV mutations (66.7 %) than in the healthy control population (16.7 %). V726A was the leading mutation in SoJIA patients, with an allelic frequency of 15.74 %, followed by E148Q, with an allelic frequency of 7.4 %. Children who were carriers of MEFV mutations had an 18 times higher risk of developing SoJIA than wild-type carriers

[odds ratio 18.0 (95 % CI 5-69),  $P < 0.01$ ]. E148Q was the leading mutation, present in 13.3 % of healthy controls.

CONCLUSION: These findings suggest that MEFV mutations may be responsible for auto-inflammatory diseases other than FMF, and patients with SoJIA, especially those with a positive family history of FMF or SoJIA, should be screened for MEFV mutations in countries where FMF is frequent.

DOI: 10.1007/s40291-014-0105-4

PMID: 24862656 [Indexed for MEDLINE]

2021. Ann Allergy Asthma Immunol. 2014 Jun;112(6):489-95. doi: 10.1016/j.anai.2014.04.007.

Primary immunodeficiency disorders: general classification, new molecular insights, and practical approach to diagnosis and treatment.

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DOI: 10.1016/j.anai.2014.04.007

PMID: 24860921 [Indexed for MEDLINE]

2022. Int J Rheum Dis. 2017 Dec;20(12):2086-2092. doi: 10.1111/1756-185X.12401. Epub 2014 May 24.

Assessment of autonomic functions in children with familial Mediterranean fever by using heart rate variability measurements.

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**AIM:** The aim of this study is to analyze possible autonomic nerve system alterations and assess the efficacy of heart rate variability (HRV) analysis in anticipation of cardiovascular risks in pediatric patients with familial Mediterranean fever (FMF).

**METHOD:** In this study, cardiac autonomic functions were investigated in children with FMF by analyzing HRV and its other probable cardiac effects by echocardiography. We studied 70 pediatric patients with FMF and 50 healthy controls.

**RESULTS:** The time-domain parameters of HRV were compared between the FMF and control groups. SDNN (standard deviation of all NN intervals) was significantly decreased in patients with FMF as compared to control subjects. The other time-domain parameters of HRV and the frequency-domain parameters of HRV were similar in both groups. Frequency-dependent HRV parameters were similar in both groups, as were conventional echocardiographic parameters.

**CONCLUSION:** HRV is a convenient and reliable technique for evaluation of autonomic functions. There are only a few studies on the assessment of autonomic functions by means of HRV in adult FMF patients but not in pediatric patients. Further studies are required to assess whether there is autonomic dysfunction in children with FMF.

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DOI: 10.1111/1756-185X.12401

PMID: 24860912 [Indexed for MEDLINE]

2023. Semin Immunopathol. 2014 Sep;36(5):581-94. doi: 10.1007/s00281-014-0433-9. Epub 2014 May 24.



Autoimmune and autoinflammatory mechanisms in uveitis.

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The eye, as currently viewed, is neither immunologically ignorant nor sequestered from the systemic environment. The eye utilises distinct immunoregulatory mechanisms to preserve tissue and cellular function in the face of immune-mediated insult; clinically, inflammation following such an insult is termed uveitis. The intra-ocular inflammation in uveitis may be clinically obvious as a result of infection (e.g. toxoplasma, herpes), but in the main infection, if any, remains covert. We now recognise that healthy tissues including the retina have regulatory mechanisms imparted by control of myeloid cells through receptors (e.g. CD200R) and soluble inhibitory factors (e.g. alpha-MSH), regulation of the blood retinal barrier, and active immune surveillance. Once homeostasis has been disrupted and inflammation ensues, the mechanisms to regulate inflammation, including T cell apoptosis, generation of Treg cells, and myeloid cell suppression in situ, are less successful. Why inflammation becomes persistent remains unknown, but extrapolating from animal models, possibilities include differential trafficking of T cells from the retina, residency of CD8(+) T cells, and alterations of myeloid cell phenotype and function. Translating lessons learned from animal models to humans has been helped by system biology approaches and informatics, which suggest that diseased animals and people share similar changes in T cell phenotypes and monocyte function to date. Together the data infer a possible cryptic infectious drive in uveitis that unlocks and drives persistent autoimmune responses, or promotes further innate immune responses. Thus there may be many mechanisms in common with those observed in autoinflammatory disorders.

DOI: 10.1007/s00281-014-0433-9

PMCID: PMC4186974

PMID: 24858699 [Indexed for MEDLINE]

2024. Cell. 2014 May 22;157(5):1013-22. doi: 10.1016/j.cell.2014.04.007.

Mechanisms and functions of inflammasomes.

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Recent studies have offered a glimpse into the sophisticated mechanisms by which inflammasomes respond to danger and promote secretion of interleukin (IL)-1 $\beta$  and IL-18. Activation of caspases 1 and 11 in canonical and noncanonical inflammasomes, respectively, also protects against infection by triggering pyroptosis, a proinflammatory and lytic mode of cell death. The therapeutic potential of inhibiting these proinflammatory caspases in infectious and autoimmune diseases is raised by the successful deployment of anti-IL-1 therapies to control autoinflammatory diseases associated with aberrant inflammasome signaling. This Review summarizes recent insights into inflammasome biology and discusses the questions that remain in the field.

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DOI: 10.1016/j.cell.2014.04.007

PMID: 24855941 [Indexed for MEDLINE]

2025. FEBS Lett. 2014 Nov 17;588(22):4158-66. doi: 10.1016/j.febslet.2014.05.007. Epub 2014 May 17.

Epithelial CaSR deficiency alters intestinal integrity and promotes proinflammatory immune responses.

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The intestinal epithelium is equipped with sensing receptor mechanisms that interact with luminal microorganisms and nutrients to regulate barrier function and gut immune responses, thereby maintaining intestinal homeostasis. Herein, we clarify the role of the extracellular calcium-sensing receptor (CaSR) using intestinal epithelium-specific *Casr*(-/-) mice. Epithelial CaSR deficiency diminished intestinal barrier function, altered microbiota composition, and skewed immune responses towards proinflammatory. Consequently, *Casr*(-/-) mice were significantly more prone to chemically induced intestinal inflammation resulting in colitis. Accordingly, CaSR represents a potential therapeutic target for autoinflammatory disorders, including inflammatory bowel diseases.

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DOI: 10.1016/j.febslet.2014.05.007

PMCID: PMC4234694

PMID: 24842610 [Indexed for MEDLINE]

2026. Genet Mol Res. 2014 Apr 29;13(2):3292-300. doi: 10.4238/2014.April.29.7.

Genetic polymorphisms of paraoxonase1 192 and glutathione peroxidase1 197 enzymes in familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is an autosomal recessive disorder and is the most frequent of the periodic febrile inflammatory syndromes. The pathogenesis of the disease is not completely understood, even though the FMF gene has been identified. Oxidative stress and inflammation may play a role in the pathogenesis of FMF. We investigated gene polymorphisms of the antioxidative enzymes, glutathione peroxidase (GPX) and paraoxonase (PON) in FMF patients, and possible associations with FMF pathogenesis. Sixty FMF patients during an attack-free period and 51 healthy children as the control group were included in our study. PON1 Q/R192 and GPX1 Pro197Leu gene polymorphisms were assayed. Blood urea nitrogen, creatinine and serum lipid profile were also measured. PON1 Q/R192 genotype distribution was 52% QQ, 46% QR and 2% RR in the FMF group and 45% QQ, 45% QR and 10% RR in the control group ( $P>0.05$ ). GPX1 Pro197Leu genotype distribution was 28% PP, 57% PL, 15% LL in the FMF group and 18% PP, 53% PL, 29% LL in the control group ( $P>0.05$ ). Blood urea nitrogen, serum creatinine, lipid levels, and the distribution of PON1 Q/R192 and GPX1 Pro197Leu genotypes were similar in the two groups. We conclude that the PON1 Q/R192 and GPX1 Pro197Leu gene polymorphisms are not important risk factors in the development of FMF. However, larger studies are warranted to validate these conclusions.

DOI: 10.4238/2014.April.29.7

PMID: 24841661 [Indexed for MEDLINE]

2027. Arthritis Rheumatol. 2014 Sep;66(9):2645. doi: 10.1002/art.38698.

The systemic-onset variant of juvenile idiopathic arthritis needs to be recorded as an autoinflammatory syndrome: comment on the review by Nigrovic.

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Comment in

Arthritis Rheumatol. 2014 Sep;66(9):2645-6.

Comment on

Arthritis Rheumatol. 2014 Jun;66(6):1405-13.

DOI: 10.1002/art.38698

PMID: 24839178 [Indexed for MEDLINE]

2028. Semin Immunopathol. 2014 Sep;36(5):595-609. doi: 10.1007/s00281-014-0434-8. Epub 2014 May 17.

Beyond canonical inflammasomes: emerging pathways in IL-1-mediated autoinflammatory disease.

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In recent years, non-communicable chronic diseases that are potentiated by sterile inflammation have replaced infectious diseases as the major threat to human health. Sterile inflammation that results from aberrant tissue damage plays pivotal roles in the pathogenesis of numerous acute and chronic inflammatory diseases including atherosclerosis, type 2 diabetes, cancer, obesity, and multiple neurodegenerative diseases. The cellular events and molecular signaling pathways that govern sterile inflammation currently remain poorly defined; however, emerging data suggest central roles for IL-1 in driving autoimmune and inflammatory disease pathogenesis. Improved characterization of the immunological pathways that contribute to sterile inflammation are desperately needed to develop effective therapeutics to treat these devastating diseases. In this review, we discuss recent advances in our understanding of how IL-1 is regulated in response to tissue damage. In particular, we highlight recent studies that

describe novel roles for conventional cell death molecules in the regulation of IL-1 $\beta$  production.

DOI: 10.1007/s00281-014-0434-8

PMCID: PMC4189983

PMID: 24838628 [Indexed for MEDLINE]

2029. Tohoku J Exp Med. 2014 Jun;233(2):73-7.

Overlap syndrome between Familial Mediterranean fever and tumor necrosis factor receptor-associated periodic syndrome in a lupus patient.

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Autoinflammatory diseases represent an expanding spectrum of genetic and non-genetic inflammatory diseases characterized by recurrent episodes of fever and systemic inflammation, affecting joints, skin and serosal surfaces. Familial Mediterranean fever (FMF) is the most common autosomal recessive hereditary autoinflammatory disease. Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is an autosomal dominant hereditary autoinflammatory disease. They share some clinical manifestations such as a periodic fever and skin rash. We present here the association of FMF with TRAPS in a systemic lupus erythematosus (SLE) patient. A 54-year-old SLE patient with recurrent attacks of fever, arthritis, and skin rashes was referred to our hospital. She had been diagnosed with lupus nephritis at 19 years old. Her lupus nephritis was controlled by steroid treatments; however, since childhood she has suffered from recurrent episodes of periodic fever, abdominal pain, arthritis, and erythematous skin rashes. An initial diagnosis of FMF was suspected based on the genetic analysis, showing the compound heterozygous L110P/E148Q mutations in the MEFV gene that is responsible for FMF. Her symptoms responded to colchicine, but the febrile attacks were not completely resolved. Therefore, genetic testing for TRAPS was performed. The results revealed a heterozygous T61I mutation in the TNFRSF1A gene that encodes tumor necrosis factor- $\alpha$  receptor and is responsible for TRAPS. The patient was diagnosed with overlapping FMF and TRAPS, in addition to SLE. This is the first report of SLE associated with both FMF and TRAPS.

PMID: 24835548 [Indexed for MEDLINE]

2030. Contemp Clin Trials. 2014 Jul;38(2):204-12. doi: 10.1016/j.cct.2014.05.001. Epub 2014 May 12.

Enhancing crossover trial design for rare diseases: limiting ineffective exposure and increasing study power by enabling patient choice to escape early.

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**BACKGROUND:** Addressing the two most important considerations in designing clinical trials, i.e. maximizing study power and minimizing patient exposure to ineffective treatment, is particularly challenging for trials of rare diseases. The familial Mediterranean fever (FMF) rilonacept trial (Hashkes et al., Ann Intern Med 2012;157:533-41) demonstrates a novel crossover design by enabling patient choice to early escape for rare disease.

**PURPOSE:** To investigate the effect on study power, exposure to the ineffective treatment arm and dropout rate by implementing early escape to crossover design, and to propose a Bayesian modeling approach.

**METHOD:** Based on the FMF trial data, simulation studies compared study power and dropout rate among three types of designs for crossover trial: traditional without early escape, early escape per-patient-choice, and early escape per-protocol.

**RESULTS:** The early escape per patient choice or per protocol design achieved  $0.89 \pm 0.12$  and  $0.78 \pm 0.20$  of the study efficiency when compared to the traditional crossover design assuming no dropout. Early escape per patient choice compared to early escape per protocol improved power by  $1.29 \pm 0.26$ , and reduced the dropout rate by 8-29%, but with greater patient exposure to the less effective treatment arm.

**CONCLUSIONS:** The results of the FMF trial and simulation studies suggest that

allowing early escape in crossover trial enhanced the design by minimizing patient's exposure to the ineffective treatment arm while maintaining a reasonable study power, which is particularly important for rare disease trials. Choice between the two types of early escape presents tradeoff between study power and exposure to ineffective treatment.

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DOI: 10.1016/j.cct.2014.05.001

PMID: 24833067 [Indexed for MEDLINE]

2031. Int J Cancer. 2015 Jan 1;136(1):127-37. doi: 10.1002/ijc.28973. Epub 2014 May 28.

Development of thyroglobulin antibodies after GVAX immunotherapy is associated with prolonged survival.

De Remigis A(1), de Gruijl TD, Uram JN, Tzou SC, Iwama S, Talor MV, Armstrong TD, Santeagoets SJ, Slovin SF, Zheng L, Laheru DA, Jaffee EM, Gerritsen WR, van den Eertwegh AJ, Le DT, Caturegli P.

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Cancer immunotherapy induces a variety of autoinflammatory responses, including those against the thyroid gland, which can be exploited to predict clinical outcomes. Considering the paucity of information about thyroid autoimmunity in patients receiving cancer vaccines, we designed our study to assess the development of thyroglobulin antibodies (TgAbs) in patients treated with GVAX (vaccine made of a tumor cell type transfected with GM-CSF) and/or ipilimumab and correlated seroconversion with survival. Using both in house and commercial ELISA assays, we measured TgAbs in patients with pancreatic (No. = 53), prostate (No. = 35) or colon (No. = 8) cancer, before and after treatment with GVAX only (No. = 34), GVAX plus ipilimumab (No. = 42) or ipilimumab (No. = 20), and correlated their levels with patient's survival, disease status and T-cell surface markers. Antibodies to thyroperoxidase, myeloperoxidase, proteinase 3, insulin and actin were also measured. TgAbs specifically developed after GVAX, independent of the underlying cancer (81% in prostate, 75% colon cancer and 76% pancreatic cancer) and co-administration of ipilimumab (75% in GVAX only and 78%



in GVAX plus ipilimumab). This TgAbs seroconversion could be detected mainly by the in house assay, suggesting that the thyroglobulin epitopes recognized by the antibodies induced by GVAX are different from the epitopes seen in the classic form of Hashimoto thyroiditis. Notably, TgAbs seroconversion was associated with significantly prolonged survival ( $p = 0.01$  for pancreas and  $p = 0.005$  for prostate cancer). In conclusion, GVAX immunotherapy induces the appearance of TgAbs that recognize a unique antigenic repertoire and associate with prolonged survival.

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DOI: 10.1002/ijc.28973

PMCID: PMC4199892

PMID: 24832153 [Indexed for MEDLINE]

2032. Rheumatology (Oxford). 2014 Nov;53(11):1927-39. doi: 10.1093/rheumatology/keu170. Epub 2014 May 15.

Monogenic autoinflammatory diseases.

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During the past 15 years, a growing number of monogenic inflammatory diseases have been described and their respective responsible genes identified. The proteins encoded by these genes are involved in the regulatory pathways of

inflammation and are mostly expressed in cells of the innate immune system. Diagnosis remains clinical, with genetic confirmation where feasible. Although a group of patients exhibit episodic systemic inflammation (periodic fevers), these disorders are mediated by continuous overproduction and release of pro-inflammatory mediators, such as IL-1 and IL-6, and TNF and are best considered as autoinflammatory diseases rather than periodic fevers. Treatment with biologic agents that block these cytokines, particularly IL-1, has proved to be dramatically effective in some patients. Still, in many cases of autoinflammation no genetic abnormalities are detected and treatment remains suboptimal, raising the question of novel pathogenic mutations in unexplored genes and pathways.

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DOI: 10.1093/rheumatology/keu170  
PMID: 24831056 [Indexed for MEDLINE]

2033. Ann Rheum Dis. 2014 Aug;73(8):e52. doi: 10.1136/annrheumdis-2014-205795. Epub 2014 May 14.

The country of residence affects the phenotype of familial Mediterranean fever:  
is it real or a selection bias?

Korkmaz C.

Comment in  
Ann Rheum Dis. 2014 Aug;73(8):e53.

Comment on  
Ann Rheum Dis. 2014 Apr;73(4):662-7.

DOI: 10.1136/annrheumdis-2014-205795  
PMID: 24827534 [Indexed for MEDLINE]

2034. Rheumatology (Oxford). 2014 Oct;53(10):1783-7. doi: 10.1093/rheumatology/keu180.

Epub 2014 May 11.

Early progression of atherosclerosis in children with chronic infantile neurological cutaneous and articular syndrome.

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**OBJECTIVE:** Chronic inflammation plays a key role in the development of atherosclerosis. Early progression of atherosclerosis has been reported in patients with RA. Cryopyrin-associated periodic syndromes (CAPS) are autosomal dominant autoinflammatory disorders caused by heterozygous NLRP3 gene mutations. Chronic infantile neurological cutaneous and articular (CINCA) syndrome is the most severe form of CAPS and patients display early onset of rash, fever, uveitis and joint manifestations. However, there has been no previous report on atherosclerosis in patients with CAPS. The objective of this study is to assess the development of atherosclerosis in patients with CINCA syndrome.

**METHODS:** Intima-media thickness (IMT) of the carotid arteries, stiffness parameter  $\beta$ , ankle brachial index (ABI) and pressure wave velocity (PWV) were evaluated by ultrasonography in 3 patients with CINCA syndrome [mean age 9.0 years (S.D. 5.3)] and 19 age-matched healthy controls [9.3 years (S.D. 4.3)].

**RESULTS:** The levels of carotid IMT, stiffness parameter  $\beta$  and PWV in CINCA syndrome patients were significantly higher than those in healthy controls [0.51 mm (S.D. 0.05) vs 0.44 (0.04),  $P = 0.0021$ ; 6.1 (S.D. 1.7) vs 3.9 (1.0),  $P = 0.0018$ ; 1203 cm/s (S.D. 328) vs 855 (114),  $P = 0.017$ , respectively].

**CONCLUSION:** Patients with CINCA syndrome showed signs of atherosclerosis from their early childhood. The results of this study emphasize the importance of chronic inflammation in the development of atherosclerosis. Further analysis on atherosclerosis in young patients with CINCA syndrome may provide more insights into the pathogenesis of cardiovascular disease.

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DOI: 10.1093/rheumatology/keu180

PMID: 24821850 [Indexed for MEDLINE]

2035. Klin Padiatr. 2014 May;226(3):133-42. doi: 10.1055/s-0034-1366987. Epub 2014 May 12.

Autoinflammatory diseases (AID).

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Most of the autoinflammatory diseases (AID) are orphan diseases with recurrent episodes of systemic inflammation. Fever and exanthema are leading features. Given the ongoing elucidation of pathogenic causes and hence therapeutic approaches, we provided a review of the current literature of AID.

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DOI: 10.1055/s-0034-1366987

PMID: 24819385 [Indexed for MEDLINE]

2036. Clin Pediatr (Phila). 2014 Oct;53(11):1106-8. doi: 10.1177/0009922814533593. Epub 2014 May 7.

A young girl with familial Mediterranean fever and abdominal pain.

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DOI: 10.1177/0009922814533593

PMID: 24807979 [Indexed for MEDLINE]

2037. J Oral Pathol Med. 2014 Oct;43(9):691-5. doi: 10.1111/jop.12182. Epub 2014 May 7.

Serum Th1, Th2 and Th17 cytokine profiles and alpha-enolase levels in recurrent aphthous stomatitis.

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**BACKGROUND:** All aspects of aetiopathogenesis of recurrent aphthous stomatitis (RAS) have not been elucidated. RAS and Behçet's disease (BD) have clinical and immunological characteristics in common. Although T17 cytokines and alpha-enolase have been shown to play effective roles in BD and many other autoinflammatory diseases recently, their roles in RAS have not been studied extensively. In the present study, we investigated levels of several Th1, Th2 and Th17 pathways related cytokines and alpha-enolase to elucidate pathogenesis of RAS and to obtain data about possible treatment alternatives for the condition.

**METHODS:** Serum interleukin-1, interleukin-13, interleukin-17, interleukin-18, interferon gamma and alpha-enolase levels in 24 patients with RAS, 30 patients with BD and 20 healthy controls were measured.

**RESULTS:** Serum interleukin-1, interleukin-13, interleukin-17, interleukin-18, interferon gamma and alpha-enolase levels were higher in patients with RAS and patients with BD than in healthy controls ( $P < 0.005$ ).

**CONCLUSION:** Like Th1 and Th2 cells, Th17 cells were found to be effective in pathogenesis of RAS. In addition, alpha-enolase, the levels of which were high, may play an important role in etio-pathogenesis of RAS. Further studies to be designed in the light of these findings are required to shed light on pathogenesis and treatment of the condition.

DOI: 10.1111/jop.12182

PMID: 24801453 [Indexed for MEDLINE]

2038. Case Rep Pediatr. 2014;2014:296479. doi: 10.1155/2014/296479. Epub 2014 Mar 27.

Familial mediterranean Fever: diagnosing as early as 3 months of age.

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Familial Mediterranean Fever is an autosomal recessive disease. Major symptoms of disease are recurrent fever accompanied by serositis attacks. The disease is usually diagnosed before 20 years of age. Symptoms related to FMF are noted when children become more verbal, usually after 2 years of age. In this case report, the youngest patient with the diagnosis of FMF is presented. She was consulted to pediatric rheumatology for the high acute phase response and fever. It was learned that her mother had recurrent swelling of her ankle joints. Mutation analysis was performed and two homozygous mutations (M694V and R202Q) were identified. She was diagnosed as FMF at 3 months of age and colchicine was started. She responded to colchicine. Her uncontrolled acute phase response declined gradually. This case was reported to point out the importance of early remembrance of autoinflammatory diseases even at very early ages especially at endemic countries.

DOI: 10.1155/2014/296479

PMCID: PMC3985156

PMID: 24800095

2039. Medicine (Baltimore). 2014 May;93(3):158-64. doi: 10.1097/MD.0000000000000029.

Familial Mediterranean fever: genotype-phenotype correlations in Japanese patients.

Migita K, Agematsu K, Yazaki M, Nonaka F, Nakamura A, Toma T, Kishida D, Uehara R, Nakamura Y, Jiuchi Y, Masumoto J, Furukawa H, Ida H, Terai C, Nakashima Y, Kawakami A, Nakamura T, Eguchi K, Yasunami M, Yachie A.

Familial Mediterranean fever (FMF) is an autoinflammatory disease caused by MEditerranean FeVer gene (MEFV) mutations. In Japan, patients with FMF have been previously reported, including a mild or incomplete form. Several factors are presumed to contribute to the variable penetrance and to the phenotypic variability of FMF. We conducted the current study to investigate the correlation of variable clinical presentations and MEFV genotypic distributions in Japanese FMF patients. We analyzed demographic, clinical, and genetic data for 311 FMF patients enrolled in the study. Clinically, we classified FMF into 2 phenotypes: 1) the "typical" form of FMF, and 2) the "atypical" form of FMF according to the Tel Hashomer criteria. Patients with the typical FMF phenotype had a higher frequency of febrile episodes, a shorter duration of febrile attacks, more frequent thoracic pain, abdominal pain, a family history of FMF, and MEFV exon 10 mutations. Conversely, patients with the atypical FMF phenotype had a lower frequency of fever episodes and more frequent arthritis in atypical distribution, myalgia, and MEFV exon 3 mutations. Multivariate analysis showed that the variable associated with typical FMF presentation was the presence of MEFV exon 10 mutations. Typical FMF phenotype frequencies were decreased in patients carrying 2 or a single low-penetrance mutations compared with those carrying 2 or a single high-penetrance mutations (M694I), with an opposite trend for the atypical FMF phenotype. In addition, patients having more than 2 MEFV mutations had a younger disease onset and a higher prevalence of thoracic pain than those carrying a single or no mutations. Thus, MEFV exon 10 mutations are associated with the more typical FMF phenotype. In contrast, more than half of the Japanese FMF patients without MEFV exon 10 mutations presented with an atypical FMF phenotype, indicating that Japanese FMF patients tend to be divided into 2 phenotypes by a variation of MEFV mutations.

DOI: 10.1097/MD.0000000000000029

PMCID: PMC4632911

PMID: 24797171 [Indexed for MEDLINE]

Hemophagocytic syndromes--an update.

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Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome and not an independent disease. HLH represents the extreme end of a severe uncontrolled hyperinflammatory reaction that can occur in many underlying conditions. Genetic forms of HLHs are due to defects in transport, processing and function of cytotoxic granules in natural killer cells and cytotoxic T lymphocytes, and are not restricted to manifestation in childhood. Acquired forms of HLH are encountered in infections, autoinflammatory and autoimmune diseases, malignancies, acquired immune deficiency. Functional tests allow for differentiation between genetic and acquired HLH. Treatment aims at suppressing hypercytokinemia and eliminating activated and infected cells. It includes immunomodulatory and immunosuppressive agents, cytostatics, T-cell and cytokine antibodies. In genetic HLH cure can only be achieved with hematopoietic stem cell transplantation. Reduced-intensity conditioning regimens have considerably improved survival.

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DOI: 10.1016/j.blre.2014.03.002

PMID: 24792320 [Indexed for MEDLINE]

2041. Am J Hum Genet. 2014 May 1;94(5):790-7. doi: 10.1016/j.ajhg.2014.04.005.

AP1S3 mutations are associated with pustular psoriasis and impaired Toll-like receptor 3 trafficking.

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Kirby B(7), Kolios A(8), Seyger MM(9), Prins C(10), Smahi A(11), Trembath RC(12), Fraternali F(2), Smith CH(1), Barker JN(1), Capon F(13).

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Adaptor protein complex 1 (AP-1) is an evolutionary conserved heterotetramer that promotes vesicular trafficking between the trans-Golgi network and the endosomes. The knockout of most murine AP-1 complex subunits is embryonically lethal, so the identification of human disease-associated alleles has the unique potential to deliver insights into gene function. Here, we report two founder mutations (c.11T>G [p.Phe4Cys] and c.97C>T [p.Arg33Trp]) in AP1S3, the gene encoding AP-1 complex subunit  $\sigma$ 1C, in 15 unrelated individuals with a severe autoinflammatory skin disorder known as pustular psoriasis. Because the variants are predicted to destabilize the 3D structure of the AP-1 complex, we generated AP1S3-knockdown

cell lines to investigate the consequences of AP-1 deficiency in skin keratinocytes. We found that AP1S3 silencing disrupted the endosomal translocation of the innate pattern-recognition receptor TLR-3 (Toll-like receptor 3) and resulted in a marked inhibition of downstream signaling. These findings identify pustular psoriasis as an autoinflammatory phenotype caused by defects in vesicular trafficking and demonstrate a requirement of AP-1 for Toll-like receptor homeostasis.

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DOI: 10.1016/j.ajhg.2014.04.005

PMCID: PMC4067562

PMID: 24791904 [Indexed for MEDLINE]

2042. *Xenobiotica*. 2014 Oct;44(10):933-40. doi: 10.3109/00498254.2014.915071. Epub 2014 Apr 28.

Association analysis of three ABCB1 (MDR1) gene variants (C1236T, G2677A/T and C3435T) and their genotype/haplotype combinations with the familial Mediterranean fever.

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1. Familial Mediterranean fever (FMF) is considered an autosomal recessive disorder, associated with a single gene named Mediterranean fever (MEFV). The aim of this study was to perform genotyping and haplotyping analysis of the multidrug resistance (ATP-binding cassette, subfamily B, member 1 - ABCB1) gene in FMF patients. 2. Three ABCB1 gene polymorphisms (C1236T, G2677T/A and C3435T) were analyzed in 309 FMF patients and 250 healthy control subjects. All subjects were genotyped by PCR-restriction fragment length polymorphism analysis, and statistical analysis was performed using the Arlequin 3.1.1 and SPSS 16.0 software packages. 3. The CT genotype frequency of the C3435T polymorphism ( $p = 0.003$ ), the CT-GT-CT (C1236T-G2677T/A-C3435T) triple genotype ( $p = 0.001$ ) and the

C-G (C1236T-G2677T/A) haplotype ( $p = 0.030$ ) were more common in the FMF patients. The CT-GG-CC triple genotype and T-G-C, C-T-T and T-G-T haplotypes (C1236T-G2677T/A-C3435T) were higher in the control subjects ( $p = 0.011$ ,  $0.001$ ,  $0.009$  and  $0.000$ , respectively). The CT-GG binary genotype and C-T and T-G haplotypes for C1236T-G2677T/A polymorphisms may have a high degree of protective effect against FMF ( $p = 0.0005$ ,  $0.002$  and  $0.000$ , respectively). 4. Our study showed that genotypes and haplotypes of ABCB1 gene polymorphisms may affect patients' FMF susceptibility.

DOI: 10.3109/00498254.2014.915071

PMID: 24773260 [Indexed for MEDLINE]

2043. Exp Anim. 2014;63(2):235-46.

Rag2-deficient IL-1 Receptor Antagonist-deficient Mice Are a Novel Colitis Model in Which Innate Lymphoid Cell-derived IL-17 Is Involved in the Pathogenesis.

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Il1rn(-/-) mice spontaneously develop arthritis and aortitis by an autoimmune mechanism and also develop dermatitis by an autoinflammatory mechanism. Here, we show that Rag2(-/-)Il1rn(-/-) mice develop spontaneous colitis with high mortality, making a contrast to the suppression of arthritis in these mice. Enhanced IL-17A expression in group 3 innate lymphoid cells (ILC3s) was observed in the colon of Rag2(-/-)Il1rn(-/-) mice. IL-17A-deficiency prolonged the survival of Rag2(-/-)Il1rn(-/-) mice, suggesting a pathogenic role of this cytokine in the development of intestinal inflammation. Although IL-17A-producing T cells were increased in Il1rn(-/-) mice, these mice did not develop colitis, because CD4(+)Foxp3(+) regulatory T cell population was also expanded. Thus, excess IL-1 signaling and IL-1-induced IL-17A from ILC3s cause colitis in Rag2(-/-)Il1rn(-/-) mice in which Treg cells are absent. These observations suggest that the balance between IL-17A-producing cells and Treg cells is important to keep the immune homeostasis of the colon.

PMCID: PMC4160983

PMID: 24770649 [Indexed for MEDLINE]

2044. Clin Dermatol. 2014 May-Jun;32(3):376-88. doi:  
10.1016/j.clindermatol.2013.11.004. Epub 2013 Dec 3.

Neutrophilic dermatoses as systemic diseases.

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Neutrophilic dermatoses (ND) are inflammatory skin conditions characterized by a sterile infiltrate of normal polymorphonuclear leukocytes. The main clinical forms of ND include Sweet syndrome, pyoderma gangrenosum, erythema elevatum diutinum, subcorneal pustular dermatosis, and their atypical or transitional forms. ND are often idiopathic, but they may be associated with myeloid hematologic malignancies (Sweet syndrome), inflammatory bowel disease or rheumatoid arthritis (pyoderma gangrenosum), and monoclonal gammopathies (erythema elevatum diutinum, subcorneal pustular dermatosis). The possible infiltration of internal organs with neutrophils during the setting of ND underlies the concept of a neutrophilic systemic disease. ND may be seen as a polygenic autoinflammatory syndrome due to their frequent association with other autoinflammatory disorders (monogenic or polygenic) and the recent published efficacy of interleukin-1 blocking therapies in their management.

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DOI: 10.1016/j.clindermatol.2013.11.004

PMID: 24767185 [Indexed for MEDLINE]

2045. F1000Prime Rep. 2014 Apr 1;6:21. doi: 10.12703/P6-21. eCollection 2014.

Treatment advances in systemic juvenile idiopathic arthritis.

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Systemic juvenile idiopathic arthritis (JIA) is an autoinflammatory condition that is distinct from other forms of childhood arthritis. Recently, biologic agents that specifically inhibit the cytokines interleukin (IL)-1 and IL-6 have demonstrated remarkable clinical effectiveness and confirmed the importance of these cytokines in the disease process. Future studies are likely to optimize the care of children with systemic arthritis and further elucidate the disease pathogenesis.

DOI: 10.12703/P6-21

PMCID: PMC3974570

PMID: 24765526

2046. Rheumatology (Oxford). 2014 Oct;53(10):1767-72. doi: 10.1093/rheumatology/keu138. Epub 2014 Apr 24.

Can colchicine response be predicted in familial Mediterranean fever patients?

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**OBJECTIVES:** The aims of this study were to explore whether the demographic and clinical features of paediatric familial Mediterranean fever (FMF) patients with different colchicine response vary or not and to determine whether colchicine response can be predicted in FMF patients.

**METHODS:** Files of patients who have been on colchicine therapy for at least 6 months were retrospectively evaluated. Patients were divided into two groups: group I included patients with no attacks after colchicine and group II comprised patients with ongoing attacks. Thereafter group II was further divided into two groups according to the reduction rate of attack frequency: group IIA (>50%) and group IIB ( $\leq$ 50%).

**RESULTS:** The study group comprised 221 FMF patients (116 females, 105 males). There were 131 patients in group I and 90 patients in group II (54 in group IIA and 36 in group IIB). Leg pain and M694V homozygosity were more frequent in group II ( $P < 0.05$ ). Final colchicine doses, disease severity scores and number of patients with elevated acute phase reactant levels (attack-free period) were significantly higher and colchicine compliance was lower in group II when compared with group I ( $P < 0.05$ ). Erysipelas-like erythema (ELE), leg pain and protracted arthritis/protracted febrile myalgia/vasculitis were more frequently detected in group IIB ( $P < 0.05$ ).

**CONCLUSION:** Colchicine response is excellent in the majority of FMF patients, however, colchicine unresponsiveness cannot be predicted easily at onset. More rarely encountered clinical findings such as ELE, leg pain and protracted complaints and M694V homozygosity may be a clue for less colchicine response.

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DOI: 10.1093/rheumatology/keu138

PMID: 24764265 [Indexed for MEDLINE]

2047. Proc Natl Acad Sci U S A. 2014 May 6;111(18):6696-701. doi: 10.1073/pnas.1405634111. Epub 2014 Apr 21.

Endoscopic photoconversion reveals unexpectedly broad leukocyte trafficking to and from the gut.

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Given mounting evidence of the importance of gut-microbiota/immune-cell interactions in immune homeostasis and responsiveness, surprisingly little is known about leukocyte movements to, and especially from, the gut. We address this topic in a minimally perturbant manner using Kaede transgenic mice, which universally express a photoconvertible fluorescent reporter. Transcutaneous exposure of the cervical lymph nodes to violet light permitted punctual tagging of immune cells specifically therein, and subsequent monitoring of their immigration to the intestine; endoscopic flashing of the descending colon allowed specific labeling of intestinal leukocytes and tracking of their emigration. Our data reveal an unexpectedly broad movement of leukocyte subsets to and from the gut at steady state, encompassing all lymphoid and myeloid populations examined. Nonetheless, different subsets showed different trafficking proclivities (e.g., regulatory T cells were more restrained than conventional T cells in their exodus from the cervical lymph nodes). The novel endoscopic approach enabled us to evidence gut-derived Th17 cells in the spleens of K/BxN mice at the onset of their genetically determined arthritis, thereby furnishing a critical mechanistic link between the intestinal microbiota, namely segmented filamentous bacteria, and an extraintestinal autoinflammatory disease.

DOI: 10.1073/pnas.1405634111

PMCID: PMC4020091

PMID: 24753589 [Indexed for MEDLINE]

2048. Peptides. 2014 Jul;57:17-9. doi: 10.1016/j.peptides.2014.03.010. Epub 2014 Apr 18.

Serum antimicrobial peptides in patients with familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is characterized by recurrent inflammation of serosal and synovial membranes. Despite the fact that it is a genetic disease, environmental factors, including infections, are shown to be triggering factors associated with the precipitation of attacks in FMF. Antimicrobial peptides (AMPs) are components of innate immunity which exert antimicrobial activity against many microorganisms. Human AMPs; cathelicidin (LL37) and defensins have immunomodulatory properties and are involved in the pathogenesis of many inflammatory disorders. Hence, we investigated serum AMPs in 23 newly diagnosed FMF patients. Blood samples were obtained at baseline, 6 months after initiation of colchicine and during an attack. Twenty-four healthy individuals constituted the control group. The concentrations of LL37, alpha-1, beta-1 and beta-2 defensins were determined by ELISA. Serum AMPs did not change during attacks and did not correlate with acute phase reactants. However, serum LL37 and defensins were found to be remarkably higher in FMF patients compared to healthy individuals both at baseline and 6 months after initiation of colchicine therapy which suggest that AMPs might have a role in the pathogenesis of FMF.

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DOI: 10.1016/j.peptides.2014.03.010

PMID: 24747281 [Indexed for MEDLINE]

2049. Int J Pediatr Otorhinolaryngol. 2014 Jun;78(6):964-8. doi: 10.1016/j.ijporl.2014.03.026. Epub 2014 Apr 1.

Vitamin D levels and effects of vitamin D replacement in children with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome.

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**BACKGROUND:** The periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome is an autoinflammatory disease characterized by regularly recurrent fever episodes due to seemingly unprovoked inflammation.

**OBJECTIVE:** To assess serum 25-hydroxyvitamin D [25(OH)D] concentrations in children with PFAPA syndrome and evaluate longitudinally the effect of wintertime vitamin D supplementation on the disease course.

**STUDY DESIGN:** We have evaluated 25 Italian patients (19 males, 6 females, aged 2.4-5.3 years), fulfilling the Euro-Fever PFAPA criteria. For each patient, we recorded demographic and anthropometric data, clinical manifestations, serum calcium, phosphate, and 25(OH)D. After 400 IU vitamin D supplementation during wintertime, clinical and auxological characteristics, calcium, phosphate, and 25(OH)D levels were re-evaluated. Data were compared with a sex- and age-matched control group.

**RESULTS:** PFAPA patients showed reduced 25(OH)D levels than controls ( $p<0.0001$ ). Regarding the effect of seasons on vitamin D, winter 25(OH)D levels were significantly reduced than summer ones ( $p<0.005$ ). Moreover, these levels were significantly lower than in healthy controls ( $p<0.005$ ), and correlated with both fever episodes ( $p<0.005$ ) and C-reactive protein values ( $p<0.005$ ). After vitamin D supplementation, PFAPA patients showed a significantly decreased number of febrile episodes and modification of their characteristics (mean duration of fever episodes,  $p<0.05$ ; number of febrile episodes per year  $p<0.005$ ).

**CONCLUSIONS:** Deficient and insufficient vitamin D serum levels were found in most children with PFAPA syndrome, and hypovitaminosis D might be a significant risk factor for PFAPA flares. However, vitamin D supplementation seems to significantly reduce the typical PFAPA episodes and their duration, supporting the role of vitamin D as an immune-regulatory factor in this syndrome.

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DOI: 10.1016/j.ijporl.2014.03.026

PMID: 24746456 [Indexed for MEDLINE]

2050. Clin Rheumatol. 2014 Jul;33(7):969-74. doi: 10.1007/s10067-014-2598-y. Epub 2014 Apr 17.

Diagnostic validity of colchicine in patients with Familial Mediterranean fever.

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Although response to colchicine has been proposed as one of the diagnostic criteria in patients with Familial Mediterranean fever (FMF), the validity of this response has not been validated. The aim of this study was to assess the efficacy of the response to colchicine and to evaluate the extent of the effect of placebo. A double-blind randomized placebo-controlled trial with a cross-over design was conducted. The frequency of FMF attacks, the disease score, physical examination, and acute phase reactants were assessed at 0, 3, and 6 months. Blood samples were collected for complete blood count (CBC), erythrocyte sedimentation rate (ESR), levels of serum C-reactive protein (CRP) and serum amyloid A (SAA), and MEFV mutation analysis in 79 patients with a preliminary diagnosis of FMF. Patients were randomly allocated to receive either drug A or drug B in a double-blind fashion. The designated drug was switched at 3 months. Patients taking colchicine had less frequent FMF attacks (median 0) and lower FMF disease score (median 0) when compared to those on placebo (median 1 and 3, respectively) ( $p = 0.002$  and  $p = 0.007$ , respectively). In genetically confirmed FMF patients, median attack number and median disease score was 0 under colchicine treatment, whereas these parameters were significantly higher in the placebo group (median 2 and 8, respectively) ( $p = 0.007$  and  $p = 0.02$ , respectively) suggesting that colchicine is more effective than placebo in reducing attacks and disease score. Positive and negative predictive values were 70.2 and 37.5 %, respectively. During the placebo period, patients had less FMF attacks when compared to that of the pre-study period (median 2 vs 6, respectively) ( $p < 0.001$ ). The high false positive rate raises concerns for considering the colchicine response test as diagnostic for FMF. The role of placebo on the attacks of periodic fever syndromes needs to be further investigated.

DOI: 10.1007/s10067-014-2598-y

2051. Klin Onkol. 2014;27(2):111-26.

[Anakinra treatment in Schnitzler syndrome - results of the first retrospective multicenter study in six patients from the Czech Republic].

[Article in Czech]

Szturz P, Sedivá A, Zurek M, Adam Z, Stork J, Cermáková Z, Steyerová P, Vokáčová A, Hrbek J, Sýkora M, Spička I, Mechl Z, Mayer J.

**BACKGROUND:** Schnitzler syndrome is a very rare, acquired, autoinflammatory disease of mostly adult onset with characteristic combination of chronic recurrent urticaria and monoclonal immunoglobulin M or G gammopathy predisposing the patients to malignant lymphoproliferation. In this work, we analyzed the results of bio-logical therapy with anakinra on a national level aiming to supply data for effective pharmaco-economic estimates, lay the grounds of nationwide patient registry, raise awareness among professional public and optimize provided health care.

**PATIENTS AND METHODS:** The retrospective study (10/2006-9/2013) included six males with definite Schnitzler syndrome verified by the new Strasbourg criteria. All patients were pretreated with antihistamines, nonsteroidal antiinflammatory drugs and glucocorticoids. Four patients underwent two or more treatment lines including intravenous bisphosphonates, 2-chlorodeoxyadenosine (cladribine), interferon $\alpha$ , PUVA photochemotherapy, cyclosporine A, thalidomide, bortezomib, chlorambucil, cyclophosphamide, colchicine and methotrexate. Anakinra monotherapy was initiated in standard dosing (100 mg subcutaneously daily).

**RESULTS:** Complete and partial remissions were achieved in five (83%) and one patients (17%), respectively. Complete remission was characterized by urticaria and pain regression (within hours), normalization of inflammatory markers (with--in days) and bone metabolism improvement assessed by the markers of osteoblastic osteoformation and osteoclastic osteoresorption in one case (within weeks). With normalized inflammatory markers (including interleukin6 and interleukin18), arthralgia and sporadic exacerbations of urticaria and fevers persist in the patient in partial remission with proven Q703K polymorphism in NLRP3 gene. The median treatment followup was 30.5 months ( $37.2 \pm 31.2$  (n = 6)). The dosing interval was prolonged in one case of complete remission to 48 hours.

No serious adverse reactions occurred during anakinra application.

**CONCLUSION:** In Schnitzler syndrome, anakinra represents an effective, verified and safe medication with potentially longterm administration not compromising its original efficacy and subjective tolerance. Anakinra, blocking autonomous inflammatory reaction of the organism via interleukin1 pathway, is a generally accepted first line treatment that should be made available in standard dosing for all Schnitzler patients.

PMID: 24739048 [Indexed for MEDLINE]

2052. Nucl Med Commun. 2014 Aug;35(8):797-807. doi: 10.1097/MNM.000000000000126.

Chronic recurrent multifocal osteomyelitis: typical patterns of bone involvement in whole-body bone scintigraphy.

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Chronic recurrent multifocal osteomyelitis (CRMO) is an autoinflammatory bone disease of unknown etiology. It affects children and adolescents predominantly and occurs mostly in the female population. It is characterized by the insidious onset of pain and swelling, with a fluctuating clinical course of relapses and remissions. Typically, several bones are affected, either synchronously or metachronously, and bilateral involvement is common. CRMO most commonly affects the metaphysis of long bones, especially the tibia, femur, and clavicle. The spine, pelvis, ribs, sternum, and mandible may also be affected. Although lesions are mostly multiple, patients may present with a single symptomatic focus. Radiographic findings may be negative early in the course of the disease. Bone scintigraphy is useful in determining the presence of abnormality and the extent of disease. The imaging and clinical features of CRMO overlap with those of infectious osteomyelitis, bone malignancy, and inflammatory arthritis. Nonetheless, CRMO can be confidently diagnosed with the recognition of typical imaging patterns in the appropriate clinical setting. This article reviews imaging findings with special emphasis on bone scintigraphy and specific disease

sites.

DOI: 10.1097/MNM.0000000000000126

PMID: 24736329 [Indexed for MEDLINE]

2053. Ann Biol Clin (Paris). 2014 Mar-Apr;72(2):236-40. doi: 10.1684/abc.2014.0938.

[Idiopathic capillary hyperpermeability syndrome revealing of Waldenström disease].

[Article in French]

Benjelloun S(1), Tlamçani I(2), Yahyaoui G(2), Moudden MK(3), Benseddik N(1), El Boukhrissi F(1), Amrani MH(2), El Baaj M(3), Balouch L(1), Bamou Y(1).

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Waldenstrom disease is a rare hematologic disorder characterized by lymphoplasmacytic proliferation associated with the production of monoclonal IgM. Visceral injuries are described but some are rare (lung), others never reported (cardiac). We report for information and discussion a case representing these particular situations, considering that these attacks were revealing. It is a 63 year old man who was admitted to the emergency room in an array of tamponade, with edema at the front and four members. Clinical and radiological examinations were objectified bilateral pleural effusion, ascite and pericarditis. The biological exploration showed pancytopenia, serum proteins 120 g/L and a monoclonal peak migrant beta2 globulin electrophoresis which is made by monoclonal immunoglobulin M (IgM kappa). The bone marrow confirmed the diagnosis of the Waldenström disease. This is a mode of revelation never described before. Considering this case, it would be wise to think of a Waldenström disease before any polyserositis.

DOI: 10.1684/abc.2014.0938

PMID: 24736145 [Indexed for MEDLINE]

2054. J Dig Dis. 2014 Feb;15(2):102-4.

Late onset of Crohn's disease in familial Mediterranean fever: the necessity of anti-TNF treatment.

Kosmidou M, Mpolotsis V, Christou L, Tsianos EV.

PMID: 24734305 [Indexed for MEDLINE]

2055. Clin Rheumatol. 2015 May;34(5):981-4. doi: 10.1007/s10067-014-2601-7. Epub 2014 Apr 15.

Anakinra treatment in patients with gout and type 2 diabetes.

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We report three Caucasian patients affected by gout and type 2 diabetes, who were treated with the recombinant nonglycosylated human interleukin-1 receptor antagonist anakinra (100 mg/day subcutaneously) after an unsatisfactory or incomplete response to urate-lowering therapy, colchicine, nonsteroidal anti-inflammatory drugs, and prednisone. The remarkable clinical improvement in joint symptoms within 24 h and in glycemic control during a 6-month period gives anakinra a potential therapeutic role in the management of gout and type 2 diabetes. When anakinra was discontinued, a gout attack occurred within 3-25 days in all three patients. The contribution of anakinra in the treatment of such syndromes is encouraging, but requires further studies to establish its long-term efficacy.

DOI: 10.1007/s10067-014-2601-7

PMID: 24733251 [Indexed for MEDLINE]

2056. Clin Rheumatol. 2015 Jun;34(6):1141-3. doi: 10.1007/s10067-014-2589-z. Epub 2014 Apr 15.

Paradoxical mucocutaneous flare in a case of Behçet's disease treated with tocilizumab.

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We report on a patient with a long-standing history of recurrent oral aphthosis and pseudofolliculitis, diagnosed with Behçet's disease (BD), previously treated with high-dose prednisone, colchicine, cyclosporine, cyclophosphamide and methotrexate, all of which were partially effective. Treatment with the chimeric mouse-human anti-tumour necrosis factor (TNF)- $\alpha$  monoclonal antibody infliximab brought about the resolution of mucocutaneous lesions for a period of 6 years. After an oral and articular BD relapse, the anti-interleukin-6 agent tocilizumab was started in association with high-dose prednisone. Unexpectedly, the patient experienced a paradoxical mucocutaneous flare following tocilizumab administration, which worsened after the second infusion. Tocilizumab was then discontinued, and total recovery was achieved after the patient was started on the fully human anti-TNF- $\alpha$  monoclonal antibody golimumab in association with colchicine and methylprednisolone.

DOI: 10.1007/s10067-014-2589-z

PMID: 24733249 [Indexed for MEDLINE]

2057. BMJ Case Rep. 2014 Apr 12;2014. pii: bcr2013201627. doi: 10.1136/bcr-2013-201627.

Recurrent fevers in children: TRAPS for young players.

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We present the case of an 11-month-old girl who presented with recurrent febrile episodes and was found to have tumour necrosis factor receptor-associated periodic syndrome due to a novel mutation in the TNFRSF1A gene. The concept of autoinflammatory diseases is discussed and the management of this condition reviewed.

DOI: 10.1136/bcr-2013-201627

PMCID: PMC3987302

PMID: 24729107 [Indexed for MEDLINE]

2058. Ann Intern Med. 2014 Feb 18;160(4):291-2. doi: 10.7326/L14-5004-6.

Correction: rilonacept for colchicine-resistant or -intolerant familial mediterranean Fever.

[No authors listed]

DOI: 10.7326/L14-5004-6

PMID: 24727851

2059. Clin Infect Dis. 2014 May;58(9):1273, 1338. doi: 10.1093/cid/cit952.

PHOTO QUIZ. Recurrent buttock cellulitis in a female adolescent.

Kanj SS, Sharara AI.

DOI: 10.1093/cid/cit952

PMID: 24723579 [Indexed for MEDLINE]

2060. Autoimmunity. 2014 Sep;47(6):389-94. doi: 10.3109/08916934.2014.906582. Epub 2014 Apr 10.

TH17 cells are increased in the peripheral blood of patients with SAPHO syndrome.



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To assess whether the immune derangement previously observed in SAPHO syndrome could be linked to variations in blood TH1, TH2 or TH17 lymphocytes frequency. Seven SAPHO patients with a protracted course of the disease were studied ex-vivo for intracellular cytokines production by means of flow-cytometry and compared with matched groups of Psoriatic Arthritis patients and healthy controls. The Kruskal-Wallis test on the median of the three categories showed that there is a significant association between the TH17 levels and the category (p value = 0.02474). The mean and variance for the proportion of IL-17 producing CD4+ cells were compared between groups showing significant differences between SAPHO versus PsA subgroup (p = 0.05) and SAPHO versus healthy controls (p = 0.008). Interestingly, activation of TH17 axis, but not of TH1 and TH2, has been found, and can be observed both in patients with different activity of the disease or treated with different drugs. The TH17 increase in peripheral blood of our SAPHO subjects resembles the one recently found in patients with different AIDs. Novel therapeutic options in these patients may therefore include IL-17 blockade.

DOI: 10.3109/08916934.2014.906582

PMID: 24720503 [Indexed for MEDLINE]

2061. Clin Rheumatol. 2014 Dec;33(12):1765-71. doi: 10.1007/s10067-014-2602-6. Epub 2014 Apr 10.

Clinical evaluation of R202Q alteration of MEFV genes in Turkish children.

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To date, over 200 alterations have been reported in Mediterranean fever (MEFV) genes, but it is not clear whether all these alterations are disease-causing mutations. This study aims to evaluate the clinical features of the children with R202Q alteration. The medical records of children with R202Q alteration were reviewed retrospectively. A total of 225 children, with 113 males, were included. Fifty-five patients were heterozygous, 30 patients were homozygous for R202Q, and 140 patients were compound heterozygous. Classical familial Mediterranean fever (FMF) phenotype was present in 113 patients: 2 heterozygous and 7 homozygous R202Q, 46 double homozygous R202Q and M694V, and 58 compound heterozygous. The main clinical characteristics of the patients were abdominal pain in 71.5 %, fever in 37.7 %, arthralgia/myalgia in 30.2 %, arthritis in 10.2 %, chest pain in 14.6 % and erysipelas-like erythema in 13.3 %. The frequency of abdominal pain was significantly lower in patients with homozygous R202Q alteration ( $p = 0.021$ ), whereas patients with heterozygous R202Q mutations, though not statistically significant, had a higher frequency of arthralgia/myalgia (40.0 %,  $p = 0.05$ ). R202Q alteration of the MEFV gene leads to symptoms consistent with FMF in some cases. This alteration may be associated with a mild phenotype and shows phenotypic differences other than the common MEFV mutations.

DOI: 10.1007/s10067-014-2602-6

PMID: 24718488 [Indexed for MEDLINE]

2062. PLoS One. 2014 Apr 9;9(4):e94475. doi: 10.1371/journal.pone.0094475. eCollection 2014.

Immune dysregulation as a cause of autoinflammation in fragile X premutation carriers: link between FMRI CGG repeat number and decreased cytokine responses.

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**BACKGROUND:** Increased rates of autoinflammatory and autoimmune disorders have been observed in female premutation carriers of CGG repeat expansion alleles of between 55-200 repeats in the fragile X mental retardation 1 (FMR1) gene. To determine whether an abnormal immune profile was present at a cellular level that may predispose female carriers to autoinflammatory conditions, we investigated dynamic cytokine production following stimulation of blood cells. In addition, splenocyte responses were examined in an FMR1 CGG knock-in mouse model of the fragile X premutation.

**METHODS:** Human monocyte and peripheral blood leukocytes (PBLs) were isolated from the blood of 36 female FMR1 premutation carriers and 15 age-matched controls. Cells were cultured with media alone, LPS or PHA. In the animal model, splenocytes were isolated from 32 CGG knock-in mice and 32 wild type littermates. Splenocytes were cultured with media alone or LPS or PMA/Ionomycin. Concentrations of cytokines (GM-CSF, IL-1 $\beta$ , IL-6, IL-10, IL-13, IL-17, IFN $\gamma$ , TNF $\alpha$ , and MCP-1) were determined from the supernatants of cellular cultures via Luminex multiplex assay. Additionally, phenotypic cellular markers were assessed on cells isolated from human subjects via flow cytometry.

**RESULTS:** We found decreases in cytokine production in human premutation carriers as well as in the FMR1 knock-in mice when compared with controls. Levels of cytokines were found to be associated with CGG repeat length in both human and mouse. Furthermore, T cells from human premutation carriers showed decreases in cell surface markers of activation when compared with controls.

**CONCLUSIONS:** In this study, FMR1 CGG repeat expansions are associated with decreased immune responses and immune dysregulation in both humans and mice. Deficits in immune responses in female premutation carriers may lead to increased susceptibility to autoimmunity and further research is warranted to determine the link between FMR1 CGG repeat lengths and onset of autoinflammatory conditions.

DOI: 10.1371/journal.pone.0094475

PMCID: PMC3981824

PMID: 24718368 [Indexed for MEDLINE]

2063. Case Rep Pediatr. 2014;2014:936890. doi: 10.1155/2014/936890. Epub 2014 Mar 3.

Neonatal hepatitis as first manifestation of hyperimmunoglobulinemia d syndrome.

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Hyper IgD syndrome (HIDS) is a rare metabolic autoinflammatory syndrome characterised by recurrent febrile episodes, accompanied by various inflammatory symptoms. We present a case of severe HIDS in a young girl, whose symptoms started in the neonatal period with hepatomegaly, hepatitis, thrombocytopenia, and conjugated hyperbilirubinemia. From the age of five months, the child had recurrent febrile episodes, stomatitis, adenitis, and persistent hepatomegaly. The diagnosis of HIDS was established when she was three years and eight months old. This case report suggests that HIDS should be included in the differential diagnosis of neonatal hepatitis and conjugated hyperbilirubinemia.

DOI: 10.1155/2014/936890

PMCID: PMC3971522

PMID: 24716072

2064. Arthritis Res Ther. 2014 Apr 8;16(2):R89. doi: 10.1186/ar4533.

Ultrasonographic assessment reveals detailed distribution of synovial inflammation in Blau syndrome.

Ikeda K, Kambe N, Takei S, Nakano T, Inoue Y, Tomiita M, Oyake N, Satoh T, Yamatou T, Kubota T, Okafuji I, Kanazawa N, Nishikomori R, Shimojo N, Matsue H, Nakajima H.

**INTRODUCTION:** Arthritis is the most frequent manifestation of Blau syndrome, an autoinflammatory disorder caused by the genetic mutation of NOD2. However, detailed information on arthritis in Blau syndrome on which the therapeutic strategy should be based on is lacking. This multi-center study aimed to accurately characterize the articular manifestation of Blau syndrome and also to

demonstrate the utility of musculoskeletal ultrasound in Blau syndrome.

**METHODS:** Patients who had been diagnosed with Blau syndrome by genetic analysis of NOD2 were recruited. A total of 102 synovial sites in 40 joints were assessed semiquantitatively by ultrasound for gray-scale synovitis and synovial power Doppler (PD) signal.

**RESULTS:** In total, 10 patients whose age ranged from 10 months to 37 years enrolled in this study. Although only 4 joints (0.8%) were tender on physical examination, 81 joints (16.9%) were clinically swollen. Moreover, 240 (50.0%), and 124 (25.8%) joints showed gray-scale (GS) synovitis and synovial PD signal on ultrasound, respectively. Importantly, GS synovitis was present in 168 out of 399 non-swollen joints, in which 61 also exhibited synovial PD signal. Among 40 joint regions, the ankle, the wrist, and the proximal interphalangeal joints were the most frequently and severely affected joints. Comparisons between different synovial tissues demonstrated a significantly higher proportion of the joints with tenosynovitis as compared with that with intra-articular synovitis (41.5% versus 27.9%,  $P < 0.0001$ ). In respect of age and treatment, synovial PD signals were minimal in the youngest patient and in the oldest two patients, and were relatively mild in patients receiving treatment with methotrexate plus TNF antagonists. In two patients who underwent the second ultrasound examination, total PD scores markedly decreased after initiating the treatment with a tumor necrosis factor (TNF) antagonist.

**CONCLUSIONS:** The detailed information on synovial inflammation obtained by ultrasound confirms the dissociation between pain and inflammation and the frequently involved joint regions and synovial tissue in the arthritis of Blau syndrome. Our data also demonstrate that ultrasonography can be a potent tool in monitoring the activity of synovial inflammation and in investigating the pathophysiology of arthritis in this rare but archetypical autoinflammatory condition.

DOI: 10.1186/ar4533

PMCID: PMC4060485

PMID: 24713464 [Indexed for MEDLINE]

2065. Int J Neurosci. 2015 Feb;125(2):116-22. doi: 10.3109/00207454.2014.913170. Epub 2014 May 27.

The relationship between familial Mediterranean fever gene (MEFV) mutations and clinical and radiologic parameters in multiple sclerosis patients.

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**OBJECTIVE:** Central nervous system (CNS) involvement in patients with familial Mediterranean fever (FMF) is considerably rare. Patients with FMF may exhibit clinical and radiologic symptoms similar to multiple sclerosis (MS). However, the impact of the Familial Mediterranean Fever Gene (MEFV) mutations on the clinical course of MS is not fully understood as yet.

**METHODS:** In our study, we investigated the presence of probable MEFV mutations in patients diagnosed with definite MS and the association of these mutations with the clinical course, radiologic characteristics and disability status of the individuals. A total of 105 patients diagnosed with definite MS according to the McDonald criteria and a control group of 112 non-symptomatic individuals were included in the study.

**RESULTS:** Thirty-seven patients (35.2%) had MEFV gene mutations; three were compound heterozygotes (M694V/E148Q; M694V/V726A; P369S/E148Q) and one was homozygous for P369S. No statistically significant differences were found among patients with MS and healthy individuals with respect to existing mutations. In addition, we did not observe a statistically significant relationship between MEFV mutations and the gender of the patients, oligoclonal band (OCB) positivity, Expanded Disability Status Scale (EDSS), disease onset age, clinical presentation, affected neurologic systems, existence of spinal lesions, response to immunomodulatory treatment, time to reach EDSS scores of 3 and 6, the number of attacks and the average number of lesions on a brain MRI.

**CONCLUSION:** Our results indicate that MEFV gene mutations do not affect the neurologic prognosis in patients with MS. However, additional research studies involving more patients with MS and clinical forms are warranted to confirm our results.

DOI: 10.3109/00207454.2014.913170

PMID: 24712487 [Indexed for MEDLINE]

Efficacy of anakinra in refractory Behçet's disease sacroiliitis.

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Comment in

Clin Exp Rheumatol. 2014 Jul-Aug;32(4 Suppl 84):S172.

Comment on

Clin Exp Rheumatol. 2013 May-Jun;31(3 Suppl 77):152-3.

PMID: 24709061 [Indexed for MEDLINE]

2067. Clin Exp Rheumatol. 2014 Jul-Aug;32(4 Suppl 84):S45-8. Epub 2014 Apr 7.

Periodic fevers in adult Greeks: clinical and molecular presentation.

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**OBJECTIVES:** Hereditary periodic fever syndromes (HPFS) are rare diseases characterised by recurrent, self-limited episodes of fever and localised inflammation, which arise from monogenic defects. In the present study we describe the clinical features, laboratory parameters and genetic profile of adult patients.

**METHODS:** Samples examined between May 2010 and December 2012 at the laboratory of genetic molecular diagnosis of the department of Pathophysiology of School of Medicine, National University of Athens.

**RESULTS:** Of the MEFV gene variants the most frequent genotype was the E148Q heterozygosity, with patients presenting with the typical clinical picture, two

patients were positive for the pR92Q/c.362G>A mutation in heterozygosity. The testing for the Hyper IgD Syndrome was positive for the pV377I/c.1129 G>A heterozygosity in a patient with the corresponding typical picture and the testing for the CAPS syndromes was positive for a new mutation, pR170H/c.509G>A in heterozygosity, in a case with less typical clinical features.

CONCLUSIONS: Availability of genetic testing in everyday clinical practice can provide valuable information regarding the clinical diversity, geographic distribution and genetic characteristics of these rare disease in all age groups.

PMID: 24708999 [Indexed for MEDLINE]

2068. J Mol Med (Berl). 2014 Jun;92(6):583-94. doi: 10.1007/s00109-014-1150-5. Epub 2014 Apr 6.

Tumor necrosis factor receptor-associated periodic syndrome as a model linking autophagy and inflammation in protein aggregation diseases.

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Autophagy prevents cellular damage by eliminating insoluble aggregates of mutant misfolded proteins, which accumulate under different pathological conditions. Downregulation of autophagy enhances the inflammatory response and thus represents a possible common pathogenic event underlying a number of autoinflammatory syndromes, such as tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS). The pathogenesis of other monogenic or complex disorders that display symptoms of excessive inflammation also involve the autophagy pathway. Studies have shown that TRAPS-associated TNFRSF1A mutations induce cytoplasmic retention of the TNFR1 receptor, defective TNF-induced apoptosis, and production of reactive oxygen species (ROS). Furthermore, autophagy impairment may account for the pathogenic effects of TNFRSF1A mutations, thus inducing inflammation in TRAPS. In this review, we summarize the molecular interactions and functional links between autophagy with regard to nuclear factor-kappa B activation, ROS production, and apoptosis.



Furthermore, we propose a complex interplay of these pathways as a model to explain the relationship between mutant protein misfolding and inflammation in genetically determined and aggregation-prone diseases. Accordingly, autophagy function should be investigated in all diseases showing an inflammatory component, and for which the molecular pathogenesis is still unclear.

DOI: 10.1007/s00109-014-1150-5

PMID: 24706103 [Indexed for MEDLINE]

2069. Int J Rheum Dis. 2017 Dec;20(12):2118-2121. doi: 10.1111/1756-185X.12374. Epub 2014 Apr 7.

Non-response to colchicine in familial Mediterranean fever should be identified accurately.

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AIM: Colchicine prophylaxis is the single most important factor in ameliorating familial Mediterranean fever (FMF) for the prevention of both attacks and secondary amyloidosis. The aim of the present study was to evaluate the exact proportion of those patients who do not respond to colchicine and to characterize their demographic, sociodemographic and clinical aspects.

METHODS: One hundred and eight patients with FMF were included in our study. The demographic (age, gender), socioeconomic (education level, employment status, economic income level) and clinical features (age at onset of FMF, age at FMF diagnosis, family history of FMF, mean duration of colchicine use and mean daily colchicine dose) of the patients were evaluated. The patients unresponsive to colchicine therapy, according to their statements, were recorded. Also with another question, patients' routine colchicine-consuming habits were elucidated in a self-answering format. 'Non-responders' were defined as patients who experienced FMF attacks at a frequency greater than once every 3 months despite treatment with 2 mg colchicine daily. Data were analyzed with the chi-square test

and Fisher's exact test.

**RESULTS:** There were 50 female and 58 male patients with a mean age of  $42.4 \pm 11.3$  years. The mean age at FMF onset and at FMF diagnosis were  $14.3 \pm 10.5$  and  $19.1 \pm 12.9$  years, respectively. Sixteen percent of the patients defined themselves as 'suffering from attacks in spite of regular colchicine'. Irregular colchicine usage was determined in 11% of the patients who were considered as 'unresponsive to colchicine therapy' according to their statements. In spite of regular colchicine regimen, attacks were present in 5% of the patients in our study. Although there was no difference in demographic and clinical aspects, patients with irregular colchicine usage were found to be from lower socioeconomic backgrounds, had less education and more unemployment ( $P < 0.001$ ).

**CONCLUSION:** Regular colchicine usage anamnesis may be misleading in the first evaluation and this risk seems to be higher in patients from lower socioeconomic background. Routine colchicine-consuming habits should be detailed in patients with FMF before claiming its failure.

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DOI: 10.1111/1756-185X.12374

PMID: 24702830 [Indexed for MEDLINE]

2070. Int J Rheum Dis. 2017 Dec;20(12):2113-2117. doi: 10.1111/1756-185X.12356. Epub 2014 Apr 7.

Familial Mediterranean fever gene mutations as a risk factor for early coronary artery disease.

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**OBJECTIVE:** Cardiovascular diseases (CVD) are very common in the general population. Atherosclerosis is the main pathogenesis. Familial Mediterranean fever (FMF) is an autosomal recessive disease. The gene causing FMF, designated MEFV, encodes a protein called pyrin or marenostrin that is expressed mainly in myeloid bone marrow precursors, neutrophils and monocytes. We herein aimed to determine the prevalence of MEFV mutations (all exon 2, 10 mutations) in patients with early coronary heart disease (early CHD) and coronary heart disease (CHD) with multiple risk factors and among the healthy subjects as controls.

**METHODS:** A total of 197 patients and 119 healthy subjects were recruited and enrolled into three groups in terms of inclusion criteria. Ninety-one patients diagnosed with early CHD enrolled into group one (men < 45 years of age, women < 40 years of age), 106 patients with CHD (men > 50 years of age) to group two and 119 healthy controls enrolled into group three. None of patients was diagnosed with FMF. The diagnosis of CHD was established on electrocardiographic changes, echocardiography and coronary angiography.

**RESULTS:** Thirty-eight patients (41.8%) with early CHD, 17 patients (16%) with CHD and 24 healthy controls (20.2%) carried at least one mutated MEFV allele. Young patients with CHD have different risk factor profiles, clinical presentations and prognoses than older patients. Young patients with CHD usually have multiple risk factors.

**CONCLUSION:** This study suggests that MEFV mutations in early CHD patients had significantly increased in contrast to CHD patients and healthy controls.

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DOI: 10.1111/1756-185X.12356

PMID: 24702757 [Indexed for MEDLINE]

2071. J Clin Lab Anal. 2015 Jan;29(1):80-3. doi: 10.1002/jcla.21732. Epub 2014 Mar 28.

Neutrophil-lymphocyte ratio in patients with familial Mediterranean fever.

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**BACKGROUND:** Blood neutrophil-to-lymphocyte (N/L) ratio is an indicator of the overall inflammatory status of the body, and an alteration in N/L ratio may be found in patients with familial Mediterranean fever (FMF). The aim of this study was to investigate the interrelationship between N/L ratio and FMF.

**METHODS:** One hundred and fifteen patients and controls were enrolled in the study. The cases in the study were categorized as FMF with attack, FMF with attack-free period, and controls. The neutrophil and lymphocyte counts were recorded, and the N/L ratio was calculated from these parameters. All patients were diagnosed according to Tel Hashomer criteria.

**RESULTS:** A total of 79 FMF patients were included in the study and all subjects were receiving colchicine treatment at the time. The serum N/L ratios of active patients were significantly higher than those of attack-free FMF patients and controls ( $P < 0.001$ ). The optimum N/L ratio cut-off point for active FMF was 2.63 with sensitivity, specificity, positive predictive value, and negative predictive value of 0.62 (0.41-0.80), 0.85 (0.72-0.93), 0.67 (0.44-0.85), and 0.82 (0.69-0.91), respectively. The overall accuracy of the N/L ratio in determination of FMF patients during attack was 71%.

**CONCLUSION:** Our results demonstrate that N/L ratio is higher in patients with active FMF compared with FMF patients in remission and controls, and a cut-off value of 2.63 can be used to identify patients with active FMF.

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DOI: 10.1002/jcla.21732

PMID: 24687426 [Indexed for MEDLINE]

2072. Mol Ther. 2014 May;22(5):1018-28. doi: 10.1038/mt.2014.41. Epub 2014 Mar 6.

Suppression of murine colitis and its associated cancer by carcinoembryonic antigen-specific regulatory T cells.

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Comment in

Mol Ther. 2014 May;22(5):899-900.

The adoptive transfer of regulatory T cells (Tregs) offers a promising strategy to combat pathologies that are characterized by aberrant immune activation, including graft rejection and autoinflammatory diseases. Expression of a chimeric antigen receptor (CAR) gene in Tregs redirects them to the site of autoimmune activity, thereby increasing their suppressive efficiency while avoiding systemic immunosuppression. Since carcinoembryonic antigen (CEA) has been shown to be overexpressed in both human colitis and colorectal cancer, we treated CEA-transgenic mice that were induced to develop colitis with CEA-specific CAR Tregs. Two disease models were employed: T-cell-transfer colitis as well as the azoxymethane-dextran sodium sulfate model for colitis-associated colorectal cancer. Systemically administered CEA-specific (but not control) CAR Tregs accumulated in the colons of diseased mice. In both model systems, CEA-specific CAR Tregs suppressed the severity of colitis compared to control Tregs. Moreover, in the azoxymethane-dextran sodium sulfate model, CEA-specific CAR Tregs significantly decreased the subsequent colorectal tumor burden. Our data demonstrate that CEA-specific CAR Tregs exhibit a promising potential in ameliorating ulcerative colitis and in hindering colorectal cancer development. Collectively, this study provides a proof of concept for the therapeutic potential of CAR Tregs in colitis patients as well as in other autoimmune inflammatory disorders.

DOI: 10.1038/mt.2014.41

PMCID: PMC4015241

PMID: 24686242 [Indexed for MEDLINE]

2073. Br J Dermatol. 2014 Sep;171(3):646-9. doi: 10.1111/bjd.13012. Epub 2014 Aug 7.

Partial clinical response to anakinra in severe palmoplantar pustular psoriasis.

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**BACKGROUND:** Palmoplantar pustular psoriasis is a clinical psoriasis variant characterised by a high impact on quality of life and poor response to biologics approved for plaque type psoriasis. The recombinant interleukin-1 (IL-1) receptor antagonist anakinra has been recently used for the treatment of isolated refractory cases of generalised pustular psoriasis with contrasted results.

**OBJECTIVES:** To report the clinical response in two patients treated with anakinra as salvage therapy in two patients with severe palmoplantar pustular psoriasis refractory to currently available antipsoriatic systemic therapies.

**METHODS:** Anakinra was given subcutaneously at the daily dose of 100 mg, and clinical response was evaluated using the palmoplantar psoriasis area and severity index (PPPASI).

**RESULTS:** Only partial and transient responses were observed in both patients, who had to stop anakinra due to lack of efficacy and to side effects.

**CONCLUSION:** Anakinra appears to provide only partial clinical improvement in refractory palmoplantar pustular psoriasis. Prospective clinical studies on larger populations are warranted to investigate more accurately both efficacy and safety of IL-1-inhibiting strategies in pustular psoriasis.

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DOI: 10.1111/bjd.13012

PMID: 24684162 [Indexed for MEDLINE]

2074. Vnitr Lek. 2014 Jan;60(1):17-9.

[Autoinflammation - pathological impact of dysregulation of inflammatory reaction].

[Article in Czech]

Lokaj J.

Comment on

Vnitr Lek. 2014 Jan;60(1):30-7.

Vnitr Lek. 2014 Jan;60(1):25-9.

Vnitr Lek. 2014 Jan;60(1):80-5.

PMID: 24683668 [Indexed for MEDLINE]

2075. Cytokine. 2014 May;67(1):1-6. doi: 10.1016/j.cyto.2014.01.007. Epub 2014 Feb 22.

The role of IL-4 gene 70 bp VNTR and ACE gene I/D variants in Familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is characterized by recurrent attacks of fever

and inflammation in the peritoneum, synovium, or pleura, accompanied by pain. It is an autosomal recessive disease caused by mutations in the MEFV (MEditerranean FeVer) gene. Patients with similar genotypes exhibit phenotypic diversity. As a result, the variations in different genes could be responsible for the clinical findings of this disease. In previous studies genes encoding Angiotensin-Converting Enzyme (ACE) and IL-4 (Interleukin-4) were found to be associated with rheumatologic and autoimmune diseases. In the present study we hypothesized whether ACE I/D or IL-4 70 bp variable tandem repeats (VNTR) genes are associated with FMF and its clinical findings in Turkish patients. Genomic DNA obtained from 670 persons (339 patients with FMF and 331 healthy controls) was used in the study. Genotypes for an ACE gene I/D polymorphism and IL-4 gene 70 bp VNTR were determined by polymerase chain reaction with specific primers. To our knowledge, this is the first study examining ACE gene I/D polymorphism and IL-4 gene 70 bp VNTR polymorphism in FMF patients. As a result, there was a statistically significant difference between the groups with respect to genotype distribution ( $p < 0.001$ ). According to our results, ACE gene DD genotype was associated with an increased risk in FMF [ $p < 0.001$ ; OR (95%): 7.715 (4.503-13.22)]. When we examined ACE genotype frequencies according to the clinical characteristics, we found a statistically significant association between DD+ID genotype and fever ( $p = 0.04$ ). In addition IL-4 gene P1P1 genotype was associated with FMF ( $p < 0.001$ ). We propose that D allele or DD genotype of ACE gene and P1 allele or P1P1 genotype of IL-4 gene may be important molecular markers for susceptibility of FMF.

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DOI: 10.1016/j.cyto.2014.01.007

PMID: 24680475 [Indexed for MEDLINE]

2076. Mod Rheumatol. 2014 Nov;24(6):997-1000. doi: 10.3109/14397595.2014.895122. Epub 2014 Mar 26.

Periodic fever, aphthous stomatitis, pharyngitis and cervical adenopathy syndrome is associated with activation of GM-CSF and burst-like expression of IL-8 in peripheral blood.

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**INTRODUCTION:** Periodic fever, aphthous stomatitis, pharyngitis and cervical adenopathy (PFAPA) is an autoinflammatory syndrome characterized by periodic fever with aphthous stomatitis, cervical lymphadenopathy, myalgia, and abdominal pain. Peripheral blood concentrations of selected cytokines of PFAPA patients during and between febrile episodes were analyzed in a search for PFAPA-specific molecular signature.

**METHODS:** 23 children with PFAPA (age  $6.07 \pm 2.94$  years, range 5-9 years) and three control children with severe oropharyngeal infections (age  $6.2 \pm 7.95$  years, range 1-17 years) participated in the study. Peripheral blood concentrations of IL-1 $\beta$ , IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IFN- $\gamma$ , GM-CSF, TNF- $\alpha$  were measured using Luminex technology.

**RESULTS:** PFAPA febrile episodes were characterized by detection of GM-CSF -  $134.07 \pm 315.5$  pg/mL; significant ( $P < 0.001$ ), compared to baseline and controls, elevation of concentrations of IL-8 ( $3193.7 \pm 2508$  pg/mL vs.  $100.36 \pm 119.$  pg/mL vs.  $2.04 \pm 4.08$  pg/mL, respectively), IL-6 ( $1355.38 \pm 2026.53$  pg/mL vs.  $28.8 \pm 44.2$  pg/mL and  $27.13 \pm 26.42$  pg/mL, respectively). IL-1 $\beta$  was detected only in febrile and afebrile PFAPA patients ( $922.8 \pm 1639$  pg/mL vs.  $10.98 \pm 19.4$  pg/ml,  $P < 0.002$ , respectively), but not in controls. Peripheral blood concentration of TNF $\alpha$  did not differ significantly between study groups. IL-2, IL-4, IL-5, and IL-10 were negligible in all study subjects.

**DISCUSSION:** PFAPA febrile episodes are characterized by activation of GM-CSF and IL-8 with Th1 skewing. We propose a molecular mechanism governing this phenomenon.

DOI: 10.3109/14397595.2014.895122

PMID: 24670131 [Indexed for MEDLINE]

2077. Eur Rev Med Pharmacol Sci. 2014;18(5):657-60.

The prevalence of Familial Mediterranean Fever common gene mutations in patients with simple febrile seizures.

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**BACKGROUND:** Febrile seizures (FS) represent the most common form of childhood seizures that occurs in 2-5 % of the children younger than 6 years. There have been many recent reports on the molecular genetic and pathogenesis of FC. It has been recognized that there is significant genetic component for susceptibility of FC with different reported mutation. FEB1, FEB2, FEB4, SCNA1, SCNA2, GABRG2 and IL-1 $\beta$  are related to with febrile convulsions (FCs). Interleukin 1 $\beta$  (IL-1 $\beta$ ) is a cytokine that contributes to febrile inflammatory responses. There are conflicting results on increasing this cytokine in serum during FC.

**AIM:** The determine the association between mutations of MEFV gene product pyrine and febrile seizures.

**PATIENTS AND METHODS:** The study was carried out on 104 children that were diagnosed as FS and 96 healthy children. MEFV gene mutations were detected and analyzed with PyroMark Q24. PCR was performed using the PyroMark PCR Kit and pyrosequencing reaction was conducted on instrument instructions.

**RESULTS:** M694V is the most common mutation in our patient group and we found a significant association between MEFV gene mutations and FSs. Of 104 patients, 68 were heterozygotes for any mutation and 10 patients were compound. 17.7% of control group were heterozygotes for any studied mutation. Statistical analyses showed that there was strongly significant statistical difference between results obtained from FS and control group ( $X = 46.20$ ,  $p < 0.0001$ ).

**CONCLUSIONS:** MEFV gene mutations, especially M694V mutation, are positively associated with FSs.

PMID: 24668705 [Indexed for MEDLINE]

2078. Eur J Immunol. 2014 Jul;44(7):2096-110. doi: 10.1002/eji.201344328. Epub 2014 Jun 10.

A pro-inflammatory signalome is constitutively activated by C33Y mutant TNF receptor 1 in TNF receptor-associated periodic syndrome (TRAPS).

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Mutations in TNFRSF1A encoding TNF receptor 1 (TNFR1) cause the autosomal dominant TNF receptor-associated periodic syndrome (TRAPS): a systemic autoinflammatory disorder. Misfolding, intracellular aggregation, and ligand-independent signaling by mutant TNFR1 are central to disease pathophysiology. Our aim was to understand the extent of signaling pathway perturbation in TRAPS. A prototypic mutant TNFR1 (C33Y), and wild-type TNFR1 (WT), were expressed at near physiological levels in an SK-Hep-1 cell model. TNFR1-associated signaling pathway intermediates were examined in this model, and in PBMCs from C33Y TRAPS patients and healthy controls. In C33Y-TNFR1-expressing SK-Hep-1 cells and TRAPS patients' PBMCs, a subtle, constitutive upregulation of a wide spectrum of signaling intermediates and their phosphorylated forms was observed; these were associated with a proinflammatory/antiapoptotic phenotype. In TRAPS patients' PBMCs, this upregulation of proinflammatory signaling pathways was observed irrespective of concurrent treatment with glucocorticoids, anakinra or etanercept, and the absence of overt clinical symptoms at the time that the blood samples were taken. This study reveals the pleiotropic effect of a TRAPS-associated mutant form of TNFR1 on inflammatory signaling pathways (a proinflammatory signalome), which is consistent with the variable and limited efficacy of cytokine-blocking therapies in TRAPS. It highlights new potential target pathways for therapeutic intervention.

© 2014 The Authors. European Journal of Immunology published by WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

DOI: 10.1002/eji.201344328

PMCID: PMC4285816

PMID: 24668260 [Indexed for MEDLINE]

2079. Curr Opin Rheumatol. 2014 May;26(3):252-8. doi: 10.1097/BOR.0000000000000059.

Treatment of hereditary autoinflammatory diseases.

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Erratum in

Curr Opin Rheumatol. 2014 Jul;26(4):458.

**PURPOSE OF REVIEW:** The purpose of this review is to summarize recent advances in the treatment of the hereditary autoinflammatory diseases, focusing on Familial Mediterranean fever (FMF), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndromes (CAPS) and mevalonate kinase deficiency (MKD). We discuss recently published studies and their implications for current patient care and future clinical research.

**RECENT FINDINGS:** Interleukin (IL)-1 blockade is effective in most autoinflammatory conditions. Younger patients require a higher dose per kg of body weight. In FMF, colchicine remains the treatment of choice. Single daily dosing appears adequate. When colchicine fails, IL-1 blockade is effective. In CAPS, the beneficial effect of IL-1 blockade is sustained, and side-effects are limited. There is no evidence that one IL-1 blocker is superior to the other. In TRAPS and MKD, IL-1 blockade appears effective. Some patients have sufficient suppression of inflammatory symptoms with NSAIDs or corticosteroids.

**SUMMARY:** Apart from CAPS and FMF, therapy of autoinflammatory diseases is based on small and retrospective studies. IL-1 blockade appears effective, but larger prospective trials are needed, especially in MKD, TRAPS and colchicine-resistant FMF patients.

**VIDEO ABSTRACT:**

DOI: 10.1097/BOR.0000000000000059

PMID: 24667287 [Indexed for MEDLINE]

2080. Int J Rheum Dis. 2018 Oct;21(10):1873-1877. doi: 10.1111/1756-185X.12354. Epub 2014 Mar 25.

Two elderly cases of familial mediterranean fever with rheumatoid arthritis.

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Familial Mediterranean fever (FMF) is a genetic autoinflammatory disorder that usually develops before 20 years of age and is characterized by periodic fever with serositis and arthritis. Both FMF and rheumatoid arthritis (RA) involve arthritis; however, their coexistence is rare. We describe two RA patients with an MEFV mutation in exon 2, who were diagnosed with FMF at an age of over 50 years. We also discuss the possibility that MEFV mutations could modulate RA disease activity.

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DOI: 10.1111/1756-185X.12354

PMID: 24661635

2081. Clin Rheumatol. 2014 Aug;33(8):1165-7.

Serum amyloid-A in Behçet's disease.

Vitale A(1), Rigante D, Lopalco G, Brizi MG, Caso F, Franceschini R, Denaro R, Galeazzi M, Punzi L, Iannone F, Lapadula G, Simpatico A, Marrani E, Costa L, Cimaz R, Cantarini L.

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Comment in

Clin Rheumatol. 2016 Feb;35(2):551-2.

Serum amyloid-A (SAA) is an acute phase protein, synthesized by the liver and previously investigated as a marker of disease activity in many rheumatologic disorders. Its significance in Behçet's disease (BD), a chronic inflammatory disorder at the crossroad between autoimmune and autoinflammatory syndromes, is still unraveled. Our aim was to assess the role of SAA levels as a potential marker of disease activity in patients with BD. According to our findings, the occurrence of oral aphthosis, neurological impairment, and ocular disease is significantly associated with SAA serum levels higher than 30, 50, and 150 mg/L, respectively. We also suggest that increased SAA levels might identify a thrombotic risk in BD with previous or concurrent vascular involvement.

DOI: 10.1007/s10067-014-2555-9

PMID: 24659331 [Indexed for MEDLINE]

2082. J Clin Immunol. 2014 May;34(4):478-90.

Primary immunodeficiency disorders in Iran: update and new insights from the third report of the national registry.

Aghamohammadi A, Mohammadinejad P, Abolhassani H, Mirminachi B, Movahedi M, Gharagozlou M, Parvaneh N, Zeiaee V, Mirsaeed-Ghazi B, Chavoushzadeh Z, Mahdavian A, Mansouri M, Yousefzadegan S, Sharifi B, Zandieh F, Hedayat E, Nadjafi A, Sherkat R, Shakerian B, Sadeghi-Shabestari M, Hosseini RF, Jabbari-Azad F, Ahanchian H, Behmanesh F, Zandkarimi M, Shirkani A, Cheraghi T, Fayezi A, Mohammadzadeh I, Amin R, Aleyasin S, Moghtaderi M, Ghaffari J, Arshi S, Javahertrash N, Nabavi M, Bermanian MH, Shafiei A, Kalantari N, Ahmadiafshar A, Khazaei HA, Atarod L, Rezaei N.

**BACKGROUND:** Primary immunodeficiency disorders (PID) are a group of heterogeneous disorders mainly characterized by severe and recurrent infections and increased susceptibility to malignancies, lymphoproliferative and autoimmune conditions. National registries of PID disorders provide epidemiological data and increase the awareness of medical personnel as well as health care providers.

**METHODS:** This study presents the demographic data and clinical manifestations of Iranian PID patients who were diagnosed from March 2006 till the March of 2013 and were registered in Iranian PID Registry (IPIDR) after its second report of 2006.

**RESULTS:** A total number of 731 new PID patients (455 male and 276 female) from 14

medical centers were enrolled in the current study. Predominantly antibody deficiencies were the most common subcategory of PID (32.3 %) and were followed by combined immunodeficiencies (22.3 %), congenital defects of phagocyte number, function, or both (17.4 %), well-defined syndromes with immunodeficiency (17.2 %), autoinflammatory disorders (5.2 %), diseases of immune dysregulation (2.6 %), defects in innate immunity (1.6 %), and complement deficiencies (1.4 %). Severe combined immunodeficiency was the most common disorder (21.1 %). Other prevalent disorders were common variable immunodeficiency (14.9 %), hyper IgE syndrome (7.7 %), and selective IgA deficiency (7.5 %).

**CONCLUSIONS:** Registration of Iranian PID patients increased the awareness of medical community of Iran and developed diagnostic and therapeutic techniques across more parts of the country. Further efforts must be taken by increasing the coverage of IPIDR via electronically registration and gradual referral system in order to provide better estimation of PID in Iran and reduce the number of undiagnosed cases.

DOI: 10.1007/s10875-014-0001-z

PMID: 24659230 [Indexed for MEDLINE]

2083. Autoimmun Rev. 2014 Jul;13(7):708-22. doi: 10.1016/j.autrev.2014.01.058. Epub 2014 Mar 19.

Adult-onset Still's disease.

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First described in 1971, adult-onset Still's disease (AOSD) is a rare multisystemic disorder considered as a complex (multigenic) autoinflammatory syndrome. A genetic background would confer susceptibility to the development of autoinflammatory reactions to environmental triggers. Macrophage and neutrophil activation is a hallmark of AOSD which can lead to a reactive hemophagocytic lymphohistiocytosis. As in the latter disease, the cytotoxic function of natural killer cells is decreased in patients with active AOSD. IL-18 and IL-1 $\beta$ , two proinflammatory cytokines processed through the inflammasome machinery, are key factors in the pathogenesis of AOSD; they cause IL-6 and Th1 cytokine secretion as well as NK cell dysregulation leading to macrophage activation. The clinico-biological picture of AOSD usually includes high spiking fever with joint symptoms, evanescent skin rash, sore throat, striking neutrophilic leukocytosis, hyperferritinemia with collapsed glycosylated ferritin (<20%), and abnormal liver function tests. According to the clinical presentation of the disease at diagnosis, two AOSD phenotypes may be distinguished: i) a highly symptomatic, systemic and feverish one, which would evolve into a systemic (mono- or polycyclic) pattern; ii) a more indolent one with arthritis in the foreground and poor systemic symptomatology, which would evolve into a chronic articular pattern. Steroid- and methotrexate-refractory AOSD cases benefit now from recent insights into autoinflammatory disorders: anakinra seems to be an efficient, well tolerated, steroid-sparing treatment in systemic patterns; tocilizumab seems efficient in AOSD with active arthritis and systemic symptoms while TNF $\alpha$ -blockers could be interesting in chronic polyarticular refractory AOSD.

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DOI: 10.1016/j.autrev.2014.01.058

PMID: 24657513 [Indexed for MEDLINE]

2084. Gene. 2014 Jun 1;542(2):217-20. doi: 10.1016/j.gene.2014.03.031. Epub 2014 Mar 18.

Hyper-IgD and periodic fever syndrome: a new MVK mutation (p.R277G) associated



with a severe phenotype.

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Comment in

Gene. 2015 Mar 15;559(1):99-101.

Hyperimmunoglobulinemia D and periodic fever syndrome (HIDS; MIM# 260920) is a rare recessively-inherited autoinflammatory condition caused by mutations in the MVK gene, which encodes for mevalonate kinase, an essential enzyme in the isoprenoid pathway. HIDS is clinically characterized by recurrent episodes of fever and inflammation. Here we report on the case of a 2 year-old Portuguese boy with recurrent episodes of fever, malaise, massive cervical lymphadenopathy and hepatosplenomegaly since the age of 12 months. Rash, arthralgia, abdominal pain and diarrhea were also seen occasionally. During attacks a vigorous acute-phase response was detected, including elevated erythrocyte sedimentation rate, C-reactive protein, serum amyloid A and leukocytosis. Clinical and laboratory improvement was seen between attacks. Despite normal serum IgD level, HIDS was clinically suspected. Mutational MVK analysis revealed the homozygous genotype with the novel p.Arg277Gly (p.R277G) mutation, while the healthy non-consanguineous parents were heterozygous. Short nonsteroidal anti-inflammatory drugs and corticosteroid courses were given during attacks with poor benefits, whereas anakinra showed positive responses only at high doses. The p.R277G mutation here described is a novel missense MVK mutation, and it has been detected in this case with a severe HIDS phenotype. Further studies are needed to evaluate a co-relation genotype, enzyme activity and phenotype, and to define the best therapeutic strategies.

2085. Exp Clin Transplant. 2015 Apr;13(2):188-92. doi: 10.6002/ect.2013.0244. Epub 2014 Mar 19.

Protracted febrile myalgia syndrome in a kidney transplant recipient with familial Mediterranean fever.

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Drug-induced toxic myopathy is a complication of familial Mediterranean fever in patients who receive colchicine, especially when combined with cyclosporine. Protracted febrile myalgia syndrome is a severe form of familial Mediterranean fever. A 34-year-old man who had familial Mediterranean fever for > 15 years developed kidney failure because of secondary amyloidosis. He received living-unrelated-donor kidney transplant that functioned normally. He was on colchicine prophylaxis that was continued after transplant, and he received immuno-suppression induction with antithymocyte globulin and maintenance with prednisolone, mycophenolate mofetil, and cyclosporine. After 2 months, he presented with severe myopathy and elevated creatine kinase. Muscle biopsy showed evidence of drug-induced toxic myopathy, most likely caused by cyclosporine in combination with colchicine. Cyclosporine was replaced with sirolimus and colchicine was stopped. Symptoms partially improved and creatine kinase decreased to normal. The prednisolone dosage was reduced gradually to 5 mg daily. At 8 months after transplant, he was readmitted because of severe arthralgia, prolonged fever, pleuritic chest pain, diffuse abdominal pain, purpuric rash, macroscopic hematuria, proteinuria, and diarrhea. The C-reactive protein and erythrocyte sedimentation rate were elevated. The clinical diagnosis was recurrent familial Mediterranean fever presenting as protracted febrile myalgia syndrome. Despite the history of toxic myopathy, he was restarted on colchicine

(0.5 mg, twice daily), and colchicine was well tolerated. There was marked improvement of most symptoms within several days. Follow-up 5 years later showed normal kidney graft function and no familial Mediterranean fever activity on colchicine prophylaxis. In summary, familial Mediterranean fever reactivation and protracted febrile myalgia syndrome after kidney transplant may be treated with colchicine and modulation of immunosuppressive therapy.

DOI: 10.6002/ect.2013.0244

PMID: 24650330 [Indexed for MEDLINE]

2086. Biomed Rep. 2014 Mar;2(2):292-296. Epub 2014 Jan 17.

Association of Toll-like receptor 2 polymorphisms with gout.

Cai Y(1), Peng YH(2), Tang Z(3), Guo XL(1), Qing YF(4), Liang SH(5), Jiang H(6), Dang WT(4), Ma Q(3), He C(3), Zhou JG(4).

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Gout is the most common autoinflammatory arthritis characterized by elevated

serum urate and recurrent attacks of intra-articular crystal deposition of monosodium urate (MSU) in tissues. The pathogenesis of gout has not been fully determined, although certain genetic factors are involved in the development of gout. Accumulated data suggested that MSU crystal-induced inflammation is a paradigm of innate immunity. As Toll-like receptors (TLRs) are the underlying mechanisms of the innate immune response, the present study aimed to investigate whether TLR2 polymorphisms are associated with gout. Two single-nucleotide polymorphisms (Arg677Trp and Arg753Gln, rs5743708) in TLR2 were genotyped by polymerase chain reaction-restriction fragment length polymorphism and the -196 to -174 del polymorphism was investigated using the allele-specific polymerase chain reaction in 431 individuals (215 patients with gout and 216 healthy controls). TLR2 Arg677Trp and Arg753Gln genotyping indicated that all the positive samples were of the wild-type genotype. No significant differences in genotype ( $\chi^2=1.686$ ,  $P=0.430$ ) and allele ( $\chi^2=1.430$ ,  $P=0.232$ ) frequencies of the -196 to -174 del polymorphism between the patients with gout and the control groups was observed. Our results suggested that the TLR2 Arg677Trp, Arg753Gln and the -196 to -174 del polymorphisms were not associated with susceptibility to primary gouty arthritis.

DOI: 10.3892/br.2014.224

PMCID: PMC3917755

PMID: 24649113

2087. *Dermatology*. 2014;228(3):211-4. doi: 10.1159/000358125. Epub 2014 Mar 12.

Inhibition of interleukin-1 by canakinumab as a successful mono-drug strategy for the treatment of refractory Behçet's disease: a case series.

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Recommendations related to ocular, mucosal and cutaneous involvement of Behçet's disease (BD) are mainly evidence-based, but in cases of vascular, neurological and gastrointestinal involvement there are no guidelines to define the best

treatment strategy. We report three adult patients with BD, who received an interleukin-1 $\beta$  inhibitor by subcutaneous injections, canakinumab (at the dosage of 150 mg every 6 weeks), after failure shown by corticosteroids and different combinations of immunosuppressant agents. The prompt and sustained clinical efficacy demonstrated by canakinumab as a monotherapy supports the opportunity of using this specific anti-interleukin-1 $\beta$  agent as a valid therapeutic option for resistant or refractory BD. Open trials and observational studies should be performed to test canakinumab efficacy on a larger number of patients. The most appropriate dosage and intervals between administrations should be decided according to the individual patient, severity or recurrence of clinical manifestations and major organ involvement.

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DOI: 10.1159/000358125

PMID: 24642905 [Indexed for MEDLINE]

2088. Int J Rheum Dis. 2017 Dec;20(12):2106-2112. doi: 10.1111/1756-185X.12339. Epub 2014 Mar 19.

Assessment of sleep problems in children with familial Mediterranean fever.

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AIMS: This study aimed to investigate sleep patterns, sleep disturbances and possible factors that are associated with sleep disturbances among children with familial Mediterranean fever (FMF).

PATIENTS AND METHODS: Fifty-one patients with FMF and 84 age- and sex-matched healthy controls were enrolled in the study. The patients who had an attack during the last 2 weeks were not included. Demographic data, FMF symptoms, disease duration, dose of colchicine, disease severity score, number of attacks

in the last year, MEFV mutation and serum C-reactive protein (CRP) levels were recorded for each patient. A Children's Sleep Habits Questionnaire was performed.

**RESULTS:** The total sleep scores of the patients with FMF were significantly higher than the control group. Total sleep durations were similar between FMF patients and controls. Children with FMF had significantly higher scores regarding sleep-onset delay, sleep anxiety, night wakings and sleep-disordered breathing when compared to healthy controls. There was a significant positive correlation between number of attacks in the last year and sleep onset delay, night wakings and sleep disordered-breathing. Disease severity score and CRP levels were not associated with any of the subscale scores. The patients with exertional leg pain had significantly higher total sleep scores than the ones without. Furthermore, patients with exertional leg pain had significantly higher subscale scores regarding sleep onset delay, parasomnias and sleep-disordered breathing.

**CONCLUSION:** This study showed for the first time that children with FMF had more sleep disturbances than their healthy peers. Higher numbers of attacks and exertional leg pain were associated with poor sleep quality. In conclusion, this study underlines the need to assess and manage sleep problems in children with FMF.

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DOI: 10.1111/1756-185X.12339

PMID: 24641439 [Indexed for MEDLINE]

2089. Clin Rheumatol. 2014 May;33(5):677-83. doi: 10.1007/s10067-014-2542-1. Epub 2014 Mar 13.

Markedly elevated CD64 expressions on neutrophils and monocytes are useful for diagnosis of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome during flares.

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Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is the most commonly encountered autoinflammatory disease in children, but its pathogenesis and diagnostic biomarkers are unknown. In this study, we examined the utility of CD64, a member of the Fc $\gamma$  receptors, expressions on neutrophils and monocytes in diagnosing patients with PFAPA, along with other autoinflammatory diseases exhibiting periodic fever, and bacterial infections. Although CD64 was expressed at a similar level in the attack-free period of PFAPA and in controls, CD64 expressions on both neutrophils and monocytes were dramatically increased during attacks. Serum IFN- $\gamma$  also increased in some PFAPA patients during flares, suggesting the involvement of T cell activation. Our findings demonstrate that remarkable CD64 expression during PFAPA flares serves as a potential biomarker for the diagnosis. We also suspect that IFN- $\gamma$ , possibly from retention of activated T cells in peripheral tissues, increases CD64 synthesis in such cases.

DOI: 10.1007/s10067-014-2542-1

PMID: 24623459 [Indexed for MEDLINE]

2090. Rom J Intern Med. 2013 Jul-Dec;51(3-4):125-30.

Urticaria--an allergologic, dermatologic or multidisciplinary disease?

Leru P.

Urticaria is a frequent disease, with complex etiopathogeny, raising important problems in clinical practice. The life-time prevalence for any subtype of urticaria is about 20%. Urticaria and/or angioedema is a heterogeneous group of diseases that result from a large variety of underlining causes, are elicited by a great diversity of factors and present clinically in a high variable way. In the past few decades an increasing understanding of the pathomechanisms involved in urticaria has highlighted the heterogeneity of different subtypes. According to the clinical picture and associated signs and symptoms, urticaria can be a simple, self-limited disease or a very complicated and debilitating one.

Urticaria is frequently caused by allergic reactions, but there are also many nonallergic causes. The majority cases of chronic urticaria have unknown (idiopathic) causes, with about 30-40% possibly having an autoimmune substrate.

An autoimmune subset of chronic spontaneous urticaria is increasingly being recognized internationally, based on laboratory and clinical evidence that accrued over the last 20 years. Urticarial rash may be part of clinical picture of autoinflammatory diseases, a group of rare disorders of the innate immune system, mediated by Interleukin-1. Since urticaria is an early and prominent symptom of a complex clinical picture, the awareness of these disorders may help the diagnostic in early stages and prevent severe long-term complications. Management of urticaria is based on recommendations of EAACI/GA2LEN/EDF/WAO Guideline published in 2009 and updated during the 4th International Consensus Meeting on Urticaria (Berlin, November 2012).

PMID: 24620623 [Indexed for MEDLINE]

2091. J Clin Immunol. 2014 May;34(4):398-424. doi: 10.1007/s10875-014-0003-x. Epub 2014 Mar 12.

ICON: the early diagnosis of congenital immunodeficiencies.

Routes J(1), Abinun M, Al-Herz W, Bustamante J, Condino-Neto A, De La Morena MT, Etzioni A, Gambineri E, Haddad E, Kobrynski L, Le Deist F, Nonoyama S, Oliveira JB, Perez E, Picard C, Rezaei N, Sleasman J, Sullivan KE, Torgerson T.

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Primary immunodeficiencies are intrinsic defects in the immune system that result in a predisposition to infection and are frequently accompanied by a propensity to autoimmunity and/or immunodysregulation. Primary immunodeficiencies can be divided into innate immunodeficiencies, phagocytic deficiencies, complement deficiencies, disorders of T cells and B cells (combined immunodeficiencies), antibody deficiencies and immunodeficiencies associated with syndromes. Diseases of immune dysregulation and autoinflammatory disorder are many times also included although the immunodeficiency in these disorders are often secondary to the autoimmunity or immune dysregulation and/or secondary immunosuppression used to control these disorders. Congenital primary immunodeficiencies typically manifest early in life although delayed onset are increasingly recognized. The



early diagnosis of congenital immunodeficiencies is essential for optimal management and improved outcomes. In this International Consensus (ICON) document, we provide the salient features of the most common congenital immunodeficiencies.

DOI: 10.1007/s10875-014-0003-x

PMID: 24619621 [Indexed for MEDLINE]

2092. Clin Rheumatol. 2015 Apr;34(4):807-9. doi: 10.1007/s10067-014-2556-8. Epub 2014 Mar 11.

Tumor necrosis factor receptor-associated periodic syndrome managed with the couple canakinumab-alendronate.

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Management of tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is puzzling, and therapeutic choices can be complicated, due to both wide genetic heterogeneity and protean clinical phenotype. We report on a 35-year-old female who was diagnosed with TRAPS, after finding the V95M mutation on the TNFRSF1A gene; who was treated in order with etanercept, anakinra, and canakinumab (150 mg/every 8 weeks by subcutaneous injection, then increased to 150 mg every 4 weeks); and who started therapy with oral alendronate (70 mg/weekly) to control her osteoporosis. Alendronate combined with canakinumab led to the optimal clinical control of all TRAPS manifestations and normalization of inflammatory markers. Further studies should be performed to clarify bisphosphonates' role in the scenery of autoinflammatory disorders.

DOI: 10.1007/s10067-014-2556-8

PMID: 24609716 [Indexed for MEDLINE]

2093. Nihon Naika Gakkai Zasshi. 2014 Jan 10;103(1):149-51.

[Case report; a case of familial Mediterranean fever identified by periodic fever associated with the menstrual cycle].

[Article in Japanese]

Sato H(1), Sumi H(1), Sato L(1), Tanaka M(1), Nishiwaki A(1), Tsuruta S(1), Haraoka H(1).

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PMID: 24605501 [Indexed for MEDLINE]

2094. Pharmazie. 2014 Jan;69(1):43-7.

Effect of colchicine on rat hepatic cytochrome P450 enzymes by cocktail probe drugs.

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Colchicine (COL), an alkaloid derived from plants, has been used to treat gout, pseudogout and familial Mediterranean fever for several decades. The purpose of this study was to investigate the in vivo effect of COL on rat cytochrome P450 enzymes (CYP1A2, CYP2C9, CYP2C19 and CYP2D6) to assess its potential to interact with co-administered drugs. This was a randomized, double-blind, two-way crossover study with a 4-week washout period between the phases. Rats received COL via an irrigation stomach needle at a dose of 0.4 mg/kg once daily for consecutive 10 days. On the eleventh day, a cocktail solution at a dose of 4 ml/kg, which contained phenacetin (15.0 mg/kg), tolbutamide (3.0 mg/kg), omeprazole (15.0 mg/kg) and dextromethorphan (15.0mg/kg), was oral administered to all rats. Then 0.3 ml blood samples were collected at a set of time-points. The plasma concentrations of probe drugs were simultaneously determined by

HPLC-MS/MS. Pharmacokinetic parameters simulated by DAS software were used for the evaluation of COL on the activities of rat CYP1A2, CYP2C9, CYP2C19 and CYP2D6 enzymes. Our study showed that COL administration induced CYP2C9 activity, causing a significant decrease in AUC(0-infinity) ( $P < 0.01$ ) and  $t_{1/2}$  ( $P < 0.05$ ) of tolbutamide, and a distinct increase in CL ( $P < 0.01$ ). Many pharmacokinetic parameters of dextromethorphan in COL-treated rats were affected significantly, which indicated that the metabolism of dextromethorphan in these treatment groups was evidently slowed down. However, there was no significant influence of pharmacokinetic parameters of phenacetin and omeprazole in COL-treated rats. The results from the present in vivo study suggested that COL showed no effects on rat CYP1A2 and CYP2C19, however, it demonstrated potential inductive effects on CYP2C9 and inhibitory effects on CYP2D6. Therefore, caution is needed when COL is co-administered with drugs metabolized by CYP2C9 or CYP2D6, which may result in altered plasma concentrations of these drugs and relevant drug-drug interactions.

PMID: 24601222 [Indexed for MEDLINE]

2095. J Invest Dermatol. 2014 Jul;134(7):1805-1810. doi: 10.1038/jid.2014.76. Epub 2014 Mar 6.

The inflammasomes in autoinflammatory diseases with skin involvement.

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During the past years, significant progress in the understanding of the complexity, regulation, and relevance of innate immune responses underlying several inflammatory conditions with neutrophilic skin involvement has been made. These diseases belong to the novel class of autoinflammatory diseases, and several are caused by mutations in genes regulating the function of innate immune complexes, termed inflammasomes, leading to enhanced secretion of the proinflammatory cytokine IL-1 $\beta$ . Consequently, targeting of IL-1 $\beta$  has proven successful in the treatment of these diseases, and the identification of related

pathogenic mechanisms in other more common skin diseases characterized by autoinflammation and neutrophilic tissue damage also provides extended opportunities for therapy by interfering with IL-1 signaling.

DOI: 10.1038/jid.2014.76

PMID: 24599175 [Indexed for MEDLINE]

2096. Mod Rheumatol. 2014 Mar;24(2):349-52. doi: 10.3109/14397595.2013.852844.

Amyloid A amyloidosis in a Japanese patient with familial Mediterranean fever associated with homozygosity for the pyrin variant M694I/M694I.

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Familial Mediterranean fever (FMF) is an autoinflammatory disease common in eastern Mediterranean populations. The most severe complication is the development of secondary amyloid A (AA) amyloidosis. A 51-year-old Japanese male who had been suffering from periodic fever since in his twenties was referred to our hospital for proteinuria. Histological findings from renal biopsy revealed the deposition of AA amyloid fibrils, suggesting that renal dysfunction was due to AA amyloidosis. Gene analysis of the patient and his mother showed that both were homozygous for the M694I mutation in the MEFV gene. His mother was also a carrier of the SAA1.3 allele, which is not only a univariate predictor of survival but also a risk factor for the association of AA amyloidosis with rheumatoid arthritis in Japanese patients, and the SAA1-13T allele in the 13T/C polymorphism on the 5'-flanking region of the SAA1 gene. The patient was also a carrier of the SAA-13T allele. Colchicine resulted in not only an amelioration of the acute febrile attacks of FMF inflammation, but also an improvement in kidney dysfunction due to AA amyloidosis.

DOI: 10.3109/14397595.2013.852844

PMID: 24593212 [Indexed for MEDLINE]

2097. Autoimmune Dis. 2014;2014:238931. doi: 10.1155/2014/238931. Epub 2014 Jan 30.

Idiopathic uveitis and familial mediterranean Fever: is there any relationship?

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**Introduction.** Familial Mediterranean fever (FMF) is an auto-inflammatory disease characterized by attacks of fever and polyserositis. FMF is often associated with other autoimmune diseases such as rheumatoid arthritis, polyarteritis nodosa (PAN), and Behcet. Uveitis is an inflammatory process caused by underlying infectious and inflammatory disorders. This study investigates the probable relationship between idiopathic uveitis and FMF. **Methods.** Patients with idiopathic uveitis were analyzed for the 12 most common MEFV mutations (P369S, F479L, M680I(G/C), M680I(G/A), I692del, M694V, M694I, K695R, V726A, A744S, R761H, E148Q) by a reverse hybridization assay (FMF StripAssay, Vienna lab, Vienna, Austria). **Results.** 12 patients with idiopathic uveitis were enrolled in this study. 10 of them were female. The youngest patient was a 7-year-old child and the oldest was 57. The most common complaints of patients were blurred vision and then eye redness. One patient was heterozygous for R761H. Genetic analysis of the 12 most common MEFV mutations in the patients with idiopathic uveitis did not have any positive results. **Conclusion.** According to the analysis of the 12 most common MEFV gene mutations, FMF is not an underlying cause of idiopathic uveitis. On the other hand, uveitis merely could not be the first presentation of FMF.

DOI: 10.1155/2014/238931

PMCID: PMC3926436

PMID: 24592325

2098. Rheumatol Int. 2014 Sep;34(9):1275-80. doi: 10.1007/s00296-014-2972-8. Epub 2014 Mar 4.

## Fibromyalgia in patients with other rheumatic diseases: prevalence and relationship with disease activity.

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Fibromyalgia (FM) is a syndrome characterized by chronic widespread pain and the presence of specific tender points. The prevalence of FM has been estimated at 2-7 % of the general global population. The presence of FM in several rheumatic diseases with a structural pathology has been reported as 11-30 %. The objectives of this study were to determine the prevalence of FM and to evaluate the possible relationship between FM existence and disease activity among rheumatic diseases. The study group included 835 patients--197 rheumatoid arthritis (RA), 67 systemic lupus erythematosus (SLE), 119 ankylosing spondylitis (AS), 238 osteoarthritis (OA), 14 familial Mediterranean fever (FMF), 53 Behçet's disease (BD), 71 gout, 25 Sjögren's syndrome (SS), 20 vasculitis, 29 polymyalgia rheumatica (PMR), and two polymyositis (PM)--with or without FM. Recorded information included age, gender, laboratory parameters, presence of fatigue, and disease activity indexes. The prevalence of FM in patients with rheumatologic diseases was found to be 6.6 % for RA, 13.4 % for SLE, 12.6 % for AS, 10.1 % for OA, 5.7 % for BD, 7.1 % for FMF, 12 % for SS, 25 % for vasculitis, 1.4 % for gout, and 6.9 % for PMR. One out of two patients with PM was diagnosed with FM. Some rheumatologic cases (AS, OA) with FM were observed mostly in female patients ( $p = 0.000$ ). Also, there were significant correlations between disease activity indexes and Fibromyalgia Impact Questionnaire scores for most rheumatologic patients (RA, AS, OA, and BD) ( $p < 0.05$ ; respectively,  $r = 0.6, 0.95, 0.887, \text{ and } 1$ ). Concomitant FM is a common clinical problem in rheumatologic diseases, and its recognition is important for the optimal management of these diseases. Increased pain, physical limitations, and fatigue may be interpreted as increased activity of these diseases, and a common treatment option is the prescription of higher doses of biologic agents or corticosteroids. Considerations of the FM component in the management of rheumatologic diseases increase the likelihood of the success of the treatment.

DOI: 10.1007/s00296-014-2972-8

PMID: 24589726 [Indexed for MEDLINE]

2099. Rinsho Shinkeigaku. 2014;54(2):124-9.

[A case of colchicine-responsive Mollaret's meningitis with MEFV gene mutation].

[Article in Japanese]

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A 66-year-old woman was admitted to our hospital with recurrent meningitis. She presented with 10 episodes of meningitis in 10 months. Examination of cerebrospinal fluid demonstrated pleocytosis, with neutrophils dominant at the early stage, and lymphocytes dominant at the late stage. Mollaret cells were found and the level of IL-6 was increased in cerebrospinal fluid. Several antibiotics and antiviral agents failed to prevent relapse. However, colchicine therapy successfully prevented the recurrence of meningitis. Genetic testing for familial Mediterranean fever (FMF) showed a mutation in the MEFV gene. It is difficult to diagnose the cause of Mollaret's meningitis in some patients. FMF, neuro-Behçet's disease, and neuro-Sweet disease should be included in the differential diagnosis of recurrent meningitis. In addition, colchicine therapy can prevent the relapse of meningitis in such cases.

PMID: 24583586 [Indexed for MEDLINE]

2100. Ren Fail. 2014 Jun;36(5):743-7. doi: 10.3109/0886022X.2014.886935. Epub 2014 Mar 3.

Higher thrombin activatable fibrinolysis inhibitor levels are associated with inflammation in attack-free familial Mediterranean fever patients.

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**BACKGROUND:** Coagulation abnormalities have been reported in familial Mediterranean fever (FMF) patients with amyloidosis and nephrotic syndrome; but there is not enough data about the continuity of the thrombogenic activity in FMF patients in clinical remission. The purpose of this study was to assess thrombin activatable fibrinolysis inhibitor (TAFI) levels and its relationship with fibrinolytic activity and also evaluate relationships between mutations and clinical signs in attack-free patients without amyloidosis.

**METHODS:** Seventy-nine FMF patients and 40 healthy adults were included. The study group was divided into five groups as follows: first group, homozygote M694V; second group, homozygote M680I; third group, M694V in one allele, the other allele have other mutations or not; fourth group, other mutations; and fifth group, no mutation.

**RESULTS:** Serum TAFI levels were significantly increased in patients compared with healthy individuals ( $116.64 \pm 21.8$  vs.  $78.48 \pm 19.7$   $\mu\text{g/mL}$ ,  $p < 0.001$ ) and a positive correlation was detected between TAFI antigen level and erythrocyte sedimentation rate and C-reactive protein levels ( $r = 0.247$ ,  $p = 0.029$  and  $r = 0.252$ ,  $p = 0.032$ , respectively). Mean fibrinogen and TAFI levels were significantly higher in Group 1 than the other groups ( $p = 0.04$  and  $p = 0.001$ , respectively) and in Group 3 it was higher than Groups 2, 4 and 5 ( $p = 0.04$  and  $p = 0.001$ , respectively).

**CONCLUSIONS:** High level of TAFI antigen in attack-free period of FMF disease shows ongoing subclinical inflammation and hypercoagulability. Clinicians should be careful about thrombosis even in patients at clinical remission. Also, genetic tests must be considered to predict clinical outcome and to reduce complications of FMF disease.

DOI: 10.3109/0886022X.2014.886935

PMID: 24580410 [Indexed for MEDLINE]

2101. Int J Rheum Dis. 2014 Feb;17(2):212-3. doi: 10.1111/1756-185X.12118. Epub 2013 Jun 20.

Protracted febrile myalgia in an afebrile child with familial Mediterranean fever.

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DOI: 10.1111/1756-185X.12118

PMID: 24576277 [Indexed for MEDLINE]

2102. Eur J Rheumatol. 2014 Mar;1(1):21-33. Epub 2014 Mar 1.

Familial Mediterranean fever: An updated review.

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Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory disorder characterised by acute attacks of fever and serosal inflammation. FMF primarily affects Jewish, Armenian, Turkish, and Arab populations. The disease is accompanied by a marked decrease in quality of life due to the effects of attacks and subclinical inflammation in the attack-free periods. Untreated or inadequately treated patients run the risk of amyloidosis, which is an important cause of morbidity and mortality. In this review, the current information available on FMF is summarised.

DOI: 10.5152/eurjrheum.2014.006

PMCID: PMC5042258

PMID: 27708867

2103. Eur J Rheumatol. 2014 Mar;1(1):11-13. Epub 2014 Mar 1.

Evaluation of arterial stiffness with plasma GGT levels and pulse wave velocity

measurement in patients with FMF.

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**OBJECTIVE:** Pulse wave velocity (PWV) is a non-invasive technique used to evaluate the arterial elasticity, which is an early indicator of atherosclerosis. Lately, gamma glutamyl transferase (GGT) is considered a determiner of arterial stiffness (AS). In this study, we aimed to evaluate the relationship between GGT levels and AS with PWV in patients with Familial Mediterranean fever (FMF).

**MATERIAL AND METHODS:** The study was conducted with 60 patients with FMF and 40 controls. Genetic analysis of the patients were performed. AS was assessed by PWV and, after the measurement of PWV, the presence of AS was determined.

**RESULTS:** Mean PWV values and AS frequency were significantly higher in patients with FMF compared with the control group ( $p<0.001$  and  $p=0.004$ , respectively). Mean GGT levels of FMF patients were higher than in the control group but the difference was not statistically different. In the correlation analysis, PWV and AS were positively correlated with FMF ( $r=0.349$ ,  $p<0.001$ ;  $r=0.435$ ,  $p<0.001$ , respectively). FMF duration and FMF were associated with GGT ( $r=0.300$ ,  $p=0.02$ ;  $r=0.199$ ,  $p=0.047$ , respectively).

**CONCLUSION:** Increased PWV values in FMF patients may indicate arterial stiffness. These patients may be followed closely with PWV as an early indicator of atherosclerosis. Therefore, the cardiovascular risk can be determined in the early stages of disease and it may be possible to take necessary precautions.

DOI: 10.5152/eurjrheum.2014.003

PMCID: PMC5042255

PMID: 27708864

2104. Ann Rheum Dis. 2014 May;73(5):897-901. doi: 10.1136/annrheumdis-2013-204719.  
Epub  
2014 Feb 25.

FMF50: a score for assessing outcome in familial Mediterranean fever.

Ozen S(1), Demirkaya E, Duzova A, Erdogan O, Erken E, Gul A, Kasapcopur O, Kasifoglu T, Kisacik B, Ozdogan H, Tunca M, Acikel C; FMF Arthritis Vasculitis and Orphan disease Research in pediatric rheumatology (FAVOR) and Turkish FMF study group.

Collaborators: Direskeneli H, Basbozkurt G, Sayarlioglu M, Yuksel S, Yildiz F, Donmez O, Berdeli A, Senel S, Ayaz N, Polat A, Sozeri B, Tabel Y, Akar S, Onat A, Ozkaya O, Emre S, Akinci N, Ozcelik G, Yavuz S, Yesilkaya S, Ugurlu S, Gok F, Poyrazoglu H, Bakkaloglu S, Erten S, Tufan A, Goker B, Kavukcu S, Cakar N, Saldir M, Delibas A, Makay B, Kisaarslan A, Unsal S, Topaloglu R, Erdem H.

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**BACKGROUND:** Colchicine is the main treatment for familial Mediterranean fever (FMF). However, biological agents and other treatments are available for patients who are unable to receive optimal treatment.

**OBJECTIVE:** To develop outcome criteria that define response to treatment.

**METHODS:** Two rounds of Delphi exercise were followed by a consensus conference enabling the definition of the criteria to be employed. Data for patients with FMF responding and resistant to their treatment were obtained from the FMF Arthritis Vasculitis and Orphan disease Research in paediatric rheumatology (FAVOR) website. The suggested criteria were analysed and validated in this patient cohort. Sensitivity/specificity measures and the ability of the score to discriminate between patients with active and inactive disease via the best cut-off score were calculated by a receiver operating characteristic analysis.

**RESULTS:** Compliance with the maximum dose of the drug was considered essential for evaluation of the patients. Seven criteria were suggested in the consensus conference. The performance of each criterion, in differentiating between resistant and responsive patients, was tested. The final set of criteria was defined as at least 50% improvement in five of six criteria, without worsening in any one defined response to treatment with a very high sensitivity and specificity. The items of this FMF50 included: 1. Percentage change in the frequency of attacks with the treatment. 2. Percentage change in the duration of attacks with the treatment. 3. Patients/parents' global assessment of disease severity (10 cm visual analogue scale (VAS)). 4. Physicians' global assessment of

disease severity (10 cm VAS). 5. Percentage change in arthritis attacks with the treatment. 6. Percentage change in C-reactive protein, erythrocyte sedimentation rate or serum amyloid A level with the treatment.

CONCLUSIONS: The FMF50 produced is a user-friendly measurement tool to guide physicians and can be used in clinical trials.

DOI: 10.1136/annrheumdis-2013-204719

PMID: 24570027 [Indexed for MEDLINE]

2105. Clin Exp Rheumatol. 2014 Jul-Aug;32(4 Suppl 84):S160-4. Epub 2014 Feb 24.

Are MEFV mutations susceptibility factors in enthesitis-related arthritis patients in the eastern Mediterranean?

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OBJECTIVES: Enthesitis-related arthritis (ERA), is a complex genetic disease.

Although HLA-B27 is well established, it does not explain all the genetic load in ERA. Familial Mediterranean fever (FMF), caused by mutations in the MEFV gene, is a frequent autoinflammatory disorder in the eastern Mediterranean.

METHODS: We investigated the clinical and imaging features of 53 ERA patients, as well as the frequency of MEFV gene mutations in those who were HLA-B27 negative.

RESULTS: The mean age of the patients was  $13.3 \pm 2.2$  years and 49 were boys.

Peripheral arthritis was present in all and sacroileitis in 26 patients.

Ultrasonography showed enthesitis in 6 patients of the tendons, whereas these were assessed to be normal by physical examination. Forty patients (75.5%) were positive for HLA-B27. MEFV analysis was performed for patients who were HLA-B27 negative. One patient refused MEFV analysis. 9 patients carried MEFV mutations: 2 patients were homozygous for M694V (both patients were subsequently started colchicine along with ERA treatment), 5 patients were heterozygous for M694V mutation, 1 patient was heterozygous for E148Q, and 1 patient was heterozygous for K695R mutation. None of the patients had features suggesting FMF at diagnosis of ERA; 1 patient subsequently developed typical FMF attacks.

CONCLUSIONS: Our findings suggest that MEFV mutations may represent a

susceptibility factor for ERA in the populations of the eastern Mediterranean.

PMID: 24564907 [Indexed for MEDLINE]

2106. Vnitr Lek. 2014 Jan;60(1):80-5.

[Familial Mediterranean fever - first experiences in Slovakia].

[Article in Czech]

Dallos T, Gálová LL, Macejková E, Sedlačko J, Toplak N, Debeljak M, Sargsyan H, Ilenčíková D, Kovács L.

Comment in

Vnitr Lek. 2014 Jan;60(1):17-9.

Familial Mediterranean fever (FMF) is the most prevalent genetically determined autoinflammatory disease. FMF significantly decreases the quality of life and limits life expectancy due to the development of amyloidosis in affected individuals. Prevalence of FMF is highest in the south-eastern Mediterraneans. In other parts of the world, its occurrence is often restricted to high-risk ethnic groups. In Central Europe, experience with FMF is scarce to none, as in the case of Slovakia, where no cases have been reported, so far. Herein we report the first five patients (3 adults and 2 children, 4 native Slovaks) in whom the diagnosis of FMF could be confirmed in Slovakia. Our experience demonstrates that FMF does occur in low-risk populations in Central Europe. Due to low prevalence and lack of experience, FMF diagnosis may be significantly delayed (4.5-30 years) and undiagnosed cases are to be expected in our population.

PMID: 24564780 [Indexed for MEDLINE]

2107. Vnitr Lek. 2014 Jan;60(1):30-7.

[Familial Mediterranean fever - clinical picture, diagnosis and treatment].

[Article in Czech]

Dallos T, Ilenčíková D, Kovács L.

Comment in

Vnitr Lek. 2014 Jan;60(1):17-9.

Familial mediterranean fever (FMF) is the most prevalent genetically determined autoinflammatory disease. FMF significantly decreases the quality of life and limits life expectancy due to the development of amyloidosis in affected individuals. Prevalence of FMF is highest in the south-eastern Mediterraneans. In other parts of the world, its occurrence is often restricted to high-risk ethnic groups. In Central Europe, experience with FMF is scarce. As for Slovakia, we have reported the first cases of FMF in ethnic Slovaks only recently. Along with their complicated fates, this has led us to compile a comprehensive overview of the clinical picture, diagnosis and treatment of this elusive disease. Hereby we hope to be able to promote the awareness about this disease and possibly aid the diagnosis in new patients.

PMID: 24564774 [Indexed for MEDLINE]

2108. Vnitr Lek. 2014 Jan;60(1):25-9.

[Familiar Mediterranean fever in Czech Republic].

[Article in Czech]

Sedivá A, Maňásek V, Gřegořová A, Plevová P, Toplak N, Debeljak M.

Comment in

Vnitr Lek. 2014 Jan;60(1):17-9.

Familiar Mediterranean fever (FMF) is a well defined autosomal recessive disease occurring mostly in Mediterranean regions. Here we present the experience from one center from Czech Republic, where we follow 4 families with patients with genetically proven FMF. Three out of these 4 families cluster to one limited region in Moravia, in the heart of Europe, without any linkage to Mediterranean

origin. Furthermore, majority of these patients are heterozygots presenting with well defined typical clinical symptoms. Potential pseudodominant inheritance and/or epigenetic and environmental factors might influence clinical presentation of the disease.

PMID: 24564773 [Indexed for MEDLINE]

2109. Clin Rheumatol. 2016 Jan;35(1):265-70. doi: 10.1007/s10067-014-2535-0. Epub 2014 Feb 23.

A rare cause for lower back pain: a case of an IgG4-related periaortitis.

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IgG4-related disease (IgG4-RD) are a group of autoinflammatory diseases often presenting as tumor-like lesions because of their infiltrative or mass forming behavior. They are characterized by a typical histology consisting of storiform fibrosis, high numbers of infiltrating IgG4-positive plasma cells, obliterative phlebitis, and a moderate presence of eosinophilic cells. Serum IgG4 levels can be elevated. We present a case of a 57 year-old male patient with immobilizing lower back pain, fever, and night sweats. We diagnosed IgG4-related periaortitis using serum IgG4 levels, abdominal ultrasound, PET/CT, and histology. We successfully treated the patient with glucocorticoids (GC) and azathioprine. Periaortitis is a rare presentation of IgG4-RD and therefore noteworthy. It has to be considered in patients with a retroperitoneal mass.

DOI: 10.1007/s10067-014-2535-0

PMID: 24562718 [Indexed for MEDLINE]

2110. Indian Pediatr. 2014 Jan;51(1):55-7.

Modified regimen of etanercept for tumor necrosis factor receptor associated periodic syndrome (TRAPS) like illness.

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**BACKGROUND:** TRAPS, an autosomal dominant autoinflammatory disorder occurs due to mutations of the TNFRSF1A gene. Mutation negative TRAPS (TRAPS like illness) is also known. Anti TNF molecules (etanercept) is the mainstay of therapy.

**CASE CHARACTERISTICS:** A 11-year-old boy with a 5 year clinical profile indicative of a TRAPS like illness and with negative mutation studies is described. He has been followed up for nearly 2 years after starting etanercept.

**OUTCOME:** He had sustained response to etanercept which has subsequently been titrated (0.4 mg/kg subcutaneously every 23-24 days) to keep him symptom free.

**MESSAGE:** Mutation negative cases of TRAPS can be diagnosed with a high index of suspicion. Treatment with etanercept is expensive but possibly intervals between doses could be titrated to reduce cost.

PMID: 24561467 [Indexed for MEDLINE]

2111. J Clin Rheumatol. 2014 Mar;20(2):103-5. doi: 10.1097/01.RHU.0000442576.41537.de.

Interleukin 6 blockade for hyperimmunoglobulin D and periodic fever syndrome.

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Hyperimmunoglobulin D and periodic fever syndrome (HIDS) is a rare, autoinflammatory condition caused by mutations in the mevalonate kinase gene. There is no standard treatment for HIDS, and randomized controlled trials are lacking. Corticosteroids, colchicine, nonsteroidal anti-inflammatory drugs, statins, and cyclosporine are of limited efficacy in controlling this condition. Recent case reports suggest that most patients respond to etanercept or anakinra. Interleukin 6 blockade in HIDS has not been described. We report the case of a 13-year-old girl with HIDS, who failed to respond to colchicine, corticosteroids, etanercept, and anakinra but was successfully treated with the anti-IL-6 monoclonal antibody, tocilizumab.

DOI: 10.1097/01.RHU.0000442576.41537.de

PMID: 24561416 [Indexed for MEDLINE]

2112. Rheumatol Int. 2014 Aug;34(8):1185-6. doi: 10.1007/s00296-014-2970-x. Epub 2014 Feb 20.

Evaluation of platelet indices in children with familial Mediterranean fever: confounding factors should be considered.

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Comment on

Rheumatol Int. 2012 Nov;32(11):3559-63.

DOI: 10.1007/s00296-014-2970-x

PMID: 24553679 [Indexed for MEDLINE]

2113. Proc Natl Acad Sci U S A. 2014 Mar 4;111(9):3526-31. doi: 10.1073/pnas.1322831111. Epub 2014 Feb 18.

IL-1 receptor blockade restores autophagy and reduces inflammation in chronic granulomatous disease in mice and in humans.

de Luca A(1), Smeekens SP, Casagrande A, Iannitti R, Conway KL, Gresnigt MS, Begun J, Plantinga TS, Joosten LA, van der Meer JW, Chamilos G, Netea MG, Xavier RJ, Dinarello CA, Romani L, van de Veerdonk FL.

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Comment in

Clin Infect Dis. 2014 Jul 15;59(2):iii.

Autophagy. 2014 Jun;10(6):1141-2.

Patients with chronic granulomatous disease (CGD) have a mutated NADPH complex resulting in defective production of reactive oxygen species; these patients can develop severe colitis and are highly susceptible to invasive fungal infection. In NADPH oxidase-deficient mice, autophagy is defective but inflammasome activation is present despite lack of reactive oxygen species production. However, whether these processes are mutually regulated in CGD and whether defective autophagy is clinically relevant in patients with CGD is unknown. Here, we demonstrate that macrophages from CGD mice and blood monocytes from CGD patients display minimal recruitment of microtubule-associated protein 1 light chain 3 (LC3) to phagosomes. This defect in autophagy results in increased IL-1 $\beta$  release. Blocking IL-1 with the receptor antagonist (anakinra) decreases neutrophil recruitment and T helper 17 responses and protects CGD mice from colitis and also from invasive aspergillosis. In addition to decreased inflammasome activation, anakinra restored autophagy in CGD mice in vivo, with increased Aspergillus-induced LC3 recruitment and increased expression of autophagy genes. Anakinra also increased Aspergillus-induced LC3 recruitment from 23% to 51% ( $P < 0.01$ ) in vitro in monocytes from CGD patients. The clinical relevance of these findings was assessed by treating CGD patients who had severe colitis with IL-1 receptor blockade using anakinra. Anakinra treatment resulted in a rapid and sustained improvement in colitis. Thus, inflammation in CGD is due to IL-1-dependent mechanisms, such as decreased autophagy and increased inflammasome activation, which are linked pathological conditions in CGD that can be restored by IL-1 receptor blockade.

DOI: 10.1073/pnas.1322831111  
PMCID: PMC3948220  
PMID: 24550444 [Indexed for MEDLINE]

2114. Brain Dev. 2014 Nov;36(10):884-91. doi: 10.1016/j.braindev.2014.01.009. Epub 2014 Feb 15.

Primary headaches in pediatric patients with chronic rheumatic disease.

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**OBJECTIVES:** To assess the presence, prevalence and clinical characteristics of primary headaches in pediatric patients with chronic rheumatic diseases such as juvenile idiopathic arthritis (JIA) and familial Mediterranean fever (FMF), and to analyze the common pathophysiological mechanisms.

**STUDY DESIGN:** In this noncontrolled, cross-sectional study, a semi-structured 53 item headache questionnaire was administered to subjects with FMF and JIA, and interviewed a total sample size of 601 patients younger than 16 years of age. The questionnaires were then analyzed according to the International Headache Society's diagnostic criteria.

**RESULTS:** Children with FMF (n=378) and JIA (n=223) were studied. Each group was then divided into two subgroups according to whether the subjects reported headache or not. 29.5% of subjects with FMF reported having migraine, 37.6% probable migraine and 32.9% tension type headache (TTH). In JIA group 28.2% were diagnosed with migraine; 41.2% with probable migraine and 30.6% with TTH. No significant difference was found between all subjects with (n=258) and without

(n=343) headache for variables such as living in a crowded family ( $p=0.95$ ), being the first child in the family ( $p=0.63$ ), academic achievement of the child ( $p=0.63$ ), high education level (higher than high school) of the mother ( $p=0.52$ ) and father ( $p=0.46$ ). The presence of systemic disease was reported not to be effecting the daily life at the time of evaluation by 90.2% of the children with headache and 91.0% of the children without headache ( $p=0.94$ ). 81.4% of the children reported their headaches were not aggravating with the exacerbation periods of their systemic disease. Family history of hypertension was reported higher by the subjects with headache (13.5% with headache and 4.0% without headache  $p=0.001$ ). Diabetes mellitus was also reported higher (5.8% with headache; 0.5% without headache;  $p=0.006$ ). Family history of headache was reported in 28.2% of the patients with headache whereas it was 17.4% of the patients without headache ( $p<0.001$ ). Family history of headache was reported in 28.2% of the FMF subjects with headache whereas it was 17.4% of the patients without headache ( $p<0.001$ ). For JIA patients a positive family history for headache was obtained in 25.9% of children with headache notably in migraineurs (81.8%).

**CONCLUSION:** Patients with JIA and FMF should be asked specifically about accompanying primary headaches particularly migraine headaches as they may be additional disabilities for these patients.

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DOI: 10.1016/j.braindev.2014.01.009

PMID: 24534055 [Indexed for MEDLINE]

2115. Clin Exp Immunol. 2015 Jan;179(1):5-10. doi: 10.1111/cei.12296.

Anti-dsDNA antibodies as a classification criterion and a diagnostic marker for systemic lupus erythematosus: critical remarks.

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Antibodies to mammalian dsDNA have, for decades, been linked to systemic lupus erythematosus (SLE) and particularly to its most serious complication, lupus nephritis. This canonical view derives from studies on its strong association with disease. The dogma was particularly settled when the antibody was included in the classification criteria for SLE that developed during the 1970s, most prominently in the 1982 American College of Rheumatology (ACR), and recently in The Systemic Lupus International Collaborating Clinics (SLICC) classification criteria. There are several problems to be discussed before the anti-dsDNA antibody can be accepted without further distinction as a criterion to classify SLE. Old and contemporary knowledge make it clear that an anti-dsDNA antibody is not a unifying term. It embraces antibodies with a wide spectrum of fine molecular specificities, antibodies that are produced transiently in context of infections and persistently in the context of true autoimmunity, and also includes anti-dsDNA antibodies that have the potential to bind chromatin (accessible DNA structures) and not (specificity for DNA structures that are embedded in chromatin and therefore inaccessible for the antibodies). This critical review summarizes this knowledge and questions whether or not an anti-dsDNA antibody, as simply that, can be used to classify SLE.

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DOI: 10.1111/cei.12296

PMCID: PMC4260890

PMID: 24533624 [Indexed for MEDLINE]

2116. Mod Rheumatol. 2015 Mar;25(2):312-4. doi: 10.3109/14397595.2013.874756. Epub 2014 Feb 18.

Coexistence of two rare genetic disorders: Kartagener syndrome and familial Mediterranean fever.

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Primary ciliary dyskinesia (PCD) is a rare disease, predominantly inherited as an autosomal recessive, with ciliary dysfunction leading to impaired mucociliary clearance, chronic airway infection and inflammation. Situs inversus totalis occurs in ~50 % of PCD patients and it is known as Kartagener syndrome. Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent attacks of fever and peritonitis, pleuritis, arthritis, or erysipelas-like skin disease. FMF is caused by mutations in the MEFV gene which is located on chromosome 16p13.3. p.M680I, p.M694 V, p.M694I, p.V726A on exon 10 and p.E148Q on exon 2 are the most common mutations among FMF patients and these constitute 85 % of all. Homozygosity of R202Q polymorphism is strongly associated with FMF. We would like to present a case of Kartagener syndrome accompanied by FMF with R202Q polymorphism. Our case is the first in the literature indicating the accidental coexistence of FMF and Kartagener syndrome.

DOI: 10.3109/14397595.2013.874756

PMID: 24533546 [Indexed for MEDLINE]

2117. Mod Rheumatol. 2016;26(3):458-9. doi: 10.3109/14397595.2014.882221. Epub 2014 Feb 18.

Rapid resolution of protracted febrile myalgia syndrome with anakinra: Report of two cases.

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Protracted febrile myalgia syndrome (PFMS) is a very rare but severe manifestation of familial Mediterranean fever (FMF) which is characterized by severe debilitating pain in large muscle groups that may last for several weeks. Colchicine is ineffective and treatment is largely supportive. Demonstration of crucial role of interleukin-1 (IL-1) in the pathogenesis of FMF has increased the use of IL-1 blockers in colchicine resistant or intolerant patients. Herein, we

reported successful use of an IL-1 inhibitor, anakinra, in treatment of two patients with PFMS.

DOI: 10.3109/14397595.2014.882221

PMID: 24533541 [Indexed for MEDLINE]

2118. Clin Rheumatol. 2014 Nov;33(11):1681-4. doi: 10.1007/s10067-014-2523-4. Epub 2014 Feb 15.

Mevalonate kinase deficiency in two sisters with therapeutic response to anakinra: case report and review of the literature.

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Mevalonate kinase deficiency (MKD) is a rare, hereditary autoinflammatory condition characterized by recurrent inflammatory episodes. Depending on the residual mevalonate kinase activity, the clinical spectrum ranges from a relatively mild periodic fever syndrome to a lethal metabolic disease. Data on therapeutic options for MKD are currently limited and rely generally on case reports and small series. Recent reports show promising results with anakinra and etanercept to treat the attacks. We report two sisters treated with good, but partial response, to continuous daily anakinra (interleukin-1 receptor antagonist).

DOI: 10.1007/s10067-014-2523-4

PMID: 24531849 [Indexed for MEDLINE]

2119. Eur J Neurol. 2014 Mar;21(3):e27-8. doi: 10.1111/ene.12313.

Cryopyrin associated periodic syndrome with neurological involvement in a 50-year-old patient.

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DOI: 10.1111/ene.12313

PMID: 24517880 [Indexed for MEDLINE]

2120. Clin Rheumatol. 2015 Jul;34(7):1311-6. doi: 10.1007/s10067-013-2481-2. Epub 2014 Feb 9.

Renal involvement in secondary amyloidosis of Muckle-Wells syndrome: marked improvement of renal function and reduction of proteinuria after therapy with human anti-interleukin-1 $\beta$  monoclonal antibody canakinumab.

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Muckle-Wells syndrome (MWS) is a rare hereditary autoinflammatory disorder characterized by recurrent urticaria-like skin rashes, arthralgias, conjunctivitis, hypoacusia, and risk of reactive AA amyloidosis due to the progressive accumulation of amyloid fibrils in different organs. Its genetic defect lies in mutations in the NLRP3 gene, encoding the cryopyrin protein, and resulting in interleukin (IL)-1 $\beta$  oversecretion. Renal involvement, in terms of proteinuria or renal insufficiency, can be observed in up to 25% of patients. Herein, we describe our experience with two Caucasian patients, father and son, aged 52 and 26 years, respectively, heterozygous for both V198M and R260W NLRP3 mutations who had AA amyloid deposits on renal biopsy. The fully human monoclonal antibody canakinumab, providing selective and prolonged IL-1 $\beta$  blockade, was administered in both patients every 60 days over a period of 18 months. This treatment allowed to obtain amazing results: a rapid disappearance of any clinical symptoms, the stable normalization of serum amyloid-A and, furthermore,



a marked improvement of glomerular filtration rate and proteinuria with no adverse events. Our data, though limited to only two patients, emphasize that therapeutic intervention with canakinumab, suppressing both inflammation and IL-1 $\beta$ -mediated manifestations, can contribute to improve kidney function in MWS with overt renal amyloidosis.

DOI: 10.1007/s10067-013-2481-2

PMID: 24510061 [Indexed for MEDLINE]

2121. *Biochim Biophys Acta*. 2014 May;1843(5):836-45. doi: 10.1016/j.bbamcr.2014.01.033. Epub 2014 Feb 5.

Activation of inflammasomes in podocyte injury of mice on the high fat diet: Effects of ASC gene deletion and silencing.

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Inflammasome, an intracellular inflammatory machinery, has been reported to be involved in a variety of chronic degenerative diseases such as atherosclerosis, autoinflammatory diseases and Alzheimer's disease. The present study hypothesized that the formation and activation of inflammasomes associated with apoptosis associated speck-like protein (ASC) are an important initiating mechanism resulting in obesity-associated podocyte injury and consequent glomerular sclerosis. To test this hypothesis, Asc gene knockout (Asc(-/-)), wild type (Asc(+/+)) and intrarenal Asc shRNA-transfected wild type (Asc shRNA) mice were fed a high fat diet (HFD) or normal diet (ND) for 12 weeks to produce obesity and associated glomerular injury. Western blot and RT-PCR analyses demonstrated that

renal tissue Asc expression was lacking in Asc(-/-) mice or substantially reduced in Asc shRNA transfected mice compared to Asc(+/+) mice. Confocal microscopic and co-immunoprecipitation analysis showed that the HFD enhanced the formation of inflammasome associated with Asc in podocytes as shown by colocalization of Asc with Nod-like receptor protein 3 (Nalp3). This inflammasome complex aggregation was not observed in Asc(-/-) and local Asc shRNA-transfected mice. The caspase-1 activity, IL-1 $\beta$  production and glomerular damage index (GDI) were also significantly attenuated in Asc(-/-) and Asc shRNA-transfected mice fed the HFD. This decreased GDI in Asc(-/-) and Asc shRNA transfected mice on the HFD was accompanied by attenuated proteinuria, albuminuria, foot process effacement of podocytes and loss of podocyte slit diaphragm molecules. In conclusion, activation and formation of inflammasomes in podocytes are importantly implicated in the development of obesity-associated glomerular injury.

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DOI: 10.1016/j.bbamcr.2014.01.033

PMCID: PMC3986924

PMID: 24508291 [Indexed for MEDLINE]

2122. Rheumatology (Oxford). 2014 Jun;53(6):1125-9.

International periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis syndrome cohort: description of distinct phenotypes in 301 patients.

Hofer M, Pillet P, Cochard MM, Berg S, Krol P, Kone-Paut I, Rigante D, Hentgen V, Anton J, Brik R, Neven B, Touitou I, Kaiser D, Duquesne A, Wouters C, Gattorno M.

**OBJECTIVES:** The aims of this study were to describe the clinical features of periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) and identify distinct phenotypes in a large cohort of patients from different countries.

**METHODS:** We established a web-based multicentre cohort through an international collaboration within the periodic fevers working party of the Pediatric Rheumatology European Society (PReS). The inclusion criterion was a diagnosis of PFAPA given by an experienced paediatric rheumatologist participating in an international working group on periodic fever syndromes.

**RESULTS:** Of the 301 patients included from the 15 centres, 271 had pharyngitis,

236 cervical adenitis, 171 oral aphthosis and 132 with all three clinical features. A total of 228 patients presented with additional symptoms (131 gastrointestinal symptoms, 86 arthralgias and/or myalgias, 36 skin rashes, 8 neurological symptoms). Thirty-one patients had disease onset after 5 years and they reported more additional symptoms. A positive family history for recurrent fever or recurrent tonsillitis was found in 81 patients (26.9%). Genetic testing for monogenic periodic fever syndromes was performed on 111 patients, who reported fewer occurrences of oral aphthosis or additional symptoms. Twenty-four patients reported symptoms (oral aphthosis and malaise) outside the flares. The CRP was >50 mg/l in the majority (131/190) of the patients tested during the fever.

**CONCLUSION:** We describe the largest cohort of PFAPA patients presented so far. We confirm that PFAPA may present with varied clinical manifestations and we show the limitations of the commonly used diagnostic criteria. Based on detailed analysis of this cohort, a consensus definition of PFAPA with better-defined criteria should be proposed.

DOI: 10.1093/rheumatology/ket460

PMID: 24505122 [Indexed for MEDLINE]

2123. J Thromb Haemost. 2014 Apr;12(4):444-51. doi: 10.1111/jth.12523.

The risk of venous thromboembolism in patients with multiple sclerosis: the Clinical Practice Research Datalink.

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**BACKGROUND:** In patients with multiple sclerosis (MS), disability and autoinflammatory processes may result in an increased risk of venous thromboembolism (VTE) **OBJECTIVE:** To evaluate the risk of VTE associated with MS. **METHODS:** We conducted an observational-cohort study within the Clinical Practice Research Datalink (1987-2009) linked to the National Registry of Hospitalizations (1997-2008). At the time of MS diagnosis, a comparison cohort (N = 33 370) without a recorded MS diagnosis during the study period was matched (6:1) to the

MS cohort (n = 5566) by birth year, sex, and practice. Subjects were followed from the index date until the occurrence of VTE, end of data collection, migration, or death, whichever came first. Cox proportional-hazards models were used to derive adjusted hazard ratios and 95% confidence intervals for VTE associated with MS and VTE risk factors within the MS cohort. Time-dependent adjustments were made for age, comorbidity, and medication use.

RESULTS: Compared with the comparison cohort, a 2.6-fold increased risk of VTE was observed for MS patients (adjusted hazard ratio 2.56, 95% confidence interval 2.06-3.20). A prior VTE event, varicose veins, obesity, and major trauma were found to be associated with an increased risk of VTE within the MS population. Moreover, the risk of VTE was increased in MS patients with recent records indicating immobility, spasticity, glucocorticoid use, or disability.

CONCLUSIONS: Patients with MS had an increased risk of VTE. Furthermore, our results provide evidence that this association is, at least in part, mediated through an increased prevalence of VTE risk factors in MS patients.

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DOI: 10.1111/jth.12523

PMID: 24502649 [Indexed for MEDLINE]

2124. Scientifica (Cairo). 2013;2013:637629. doi: 10.1155/2013/637629. Epub 2013 Dec 30.

Genetics of proteasome diseases.

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The proteasome is a large, multiple subunit complex that is capable of degrading most intracellular proteins. Polymorphisms in proteasome subunits are associated with cardiovascular diseases, diabetes, neurological diseases, and cancer. One polymorphism in the proteasome gene PSMA6 (-8C/G) is associated with three different diseases: type 2 diabetes, myocardial infarction, and coronary artery

disease. One type of proteasome, the immunoproteasome, which contains inducible catalytic subunits, is adapted to generate peptides for antigen presentation. It has recently been shown that mutations and polymorphisms in the immunoproteasome catalytic subunit PSMB8 are associated with several inflammatory and autoinflammatory diseases including Nakajo-Nishimura syndrome, CANDLE syndrome, and intestinal M. tuberculosis infection. This comprehensive review describes the disease-related polymorphisms in proteasome genes associated with human diseases and the physiological modulation of proteasome function by these polymorphisms. Given the large number of subunits and the central importance of the proteasome in human physiology as well as the fast pace of detection of proteasome polymorphisms associated with human diseases, it is likely that other polymorphisms in proteasome genes associated with diseases will be detected in the near future. While disease-associated polymorphisms are now readily discovered, the challenge will be to use this genetic information for clinical benefit.

DOI: 10.1155/2013/637629

PMCID: PMC3892944

PMID: 24490108

2125. Int J Adolesc Med Health. 2014;26(4):541-9. doi: 10.1515/ijamh-2013-0332.

Quality of life measures and psychiatric symptoms in adolescents with systemic lupus erythematosus and familial Mediterranean fever.

Düzçeker Y, Kanbur NÖ, Demirkaya E, Derman O, Moorthy LN, Ozen S.

**PURPOSE:** To describe the relation between global Quality of Life (QL) and psychiatric symptoms in adolescents with systemic lupus erythematosus (SLE) and familial Mediterranean fever (FMF), and to analyze the perceptions of parents and adolescents.

**METHODS:** This study included 51 adolescents diagnosed with SLE (n=25) and FMF (n=26), and 51 healthy adolescents. The Health Related QL (HRQL) of SLE patients was rated by parents and adolescents using the Simple Measurement of Impact of Lupus Erythematosus in Youngsters© (SMILEY©). The global QL of FMF patients and healthy adolescents was rated by the response given to the first question of the SMILEY© by each parent and adolescent. All participants completed the Brief Symptom Inventory (BSI), which measures psychiatric symptoms.

**RESULTS:** In total, 92.3% with FMF, 56% with SLE and 76.5% of healthy adolescents reported their global QL as good and very good using the first question of the SMILEY©. The global QL perceptions of adolescents and their parents did not correlate (FMF,  $p=0.94$ ; SLE,  $p=0.16$ ). SLE patients had the highest rate of depression (54.2%), whereas hostility was detected among 54.9% of healthy adolescents. Significant relations were detected between BSI and SMILEY© scores.

**CONCLUSION:** The global QL perceptions of adolescents with FMF were better than those of healthy adolescents, which may be explained by their perceived relief of anguish they suffer during their short-lived attacks. The global QL perceptions of adolescents with SLE were the worst, most probably due to the chronic course resulting in an awareness of limitations and intense treatment. Adolescents with SLE had similar psychopathological symptom scores when compared with FMF patients and healthy adolescents. This could be explained by developing resilience. Differences in the perception of adolescents versus their parents regarding global QL emphasized the importance of adolescent-specific interviews for chronic illnesses and multidisciplinary follow-up with adolescent medicine.

DOI: 10.1515/ijamh-2013-0332

PMID: 24486727 [Indexed for MEDLINE]

2126. Neurologia. 2015 Jun;30(5):315-7. doi: 10.1016/j.nrl.2013.07.002. Epub 2014 Jan 31.

Polyradiculoneuritis, cryopyrin-associated periodic syndromes, and familial Mediterranean fever.

[Article in English, Spanish]

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DOI: 10.1016/j.nrl.2013.07.002

PMID: 24485591 [Indexed for MEDLINE]

2127. Pediatrics. 2014 Feb;133(2):e461-5. doi: 10.1542/peds.2012-1372. Epub 2014 Jan 27.

Periodic fever in MVK deficiency: a patient initially diagnosed with incomplete Kawasaki disease.

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Mevalonate kinase deficiency (MKD) is a rare autosomal recessive disorder causing 1 of 2 phenotypes, hyperimmunoglobulin D syndrome and mevalonic aciduria, presenting with recurrent fever episodes, often starting in infancy, and sometimes evoked by stress or vaccinations. This autoinflammatory disease is caused by mutations encoding the mevalonate kinase (MVK) gene and is classified in the group of periodic fever syndromes. There is often a considerable delay in the diagnosis among pediatric patients with recurrent episodes of fever. We present a case of an 8-week-old girl with fever of unknown origin and a marked systemic inflammatory response. After excluding infections, a tentative diagnosis of incomplete Kawasaki syndrome was made, based on the finding of dilated coronary arteries on cardiac ultrasound and fever, and she was treated accordingly. However, the episodes of fever recurred, and alternative diagnoses were considered, which eventually led to the finding of increased excretion of mevalonic acid in urine. The diagnosis of MKD was confirmed by mutation analysis of the MVK gene. This case shows that the initial presentation of MKD can be indistinguishable from incomplete Kawasaki syndrome. When fever recurs in Kawasaki syndrome, other (auto-)inflammatory diseases must be ruled out to avoid inappropriate diagnostic procedures, ineffective interventions, and treatment

delay.

DOI: 10.1542/peds.2012-1372

PMID: 24470648 [Indexed for MEDLINE]

2128. Mol Biol Rep. 2014;41(4):2601-7. doi: 10.1007/s11033-014-3118-5. Epub 2014 Jan 28.

Screening of common and novel familial mediterranean fever mutations in south-east part of Turkey.

Oztuzcu S(1), Ulaşlı M, Ergun S, Iğci YZ, Iğci M, Bayraktar R, Nacarkahya G, Tamer A, Cevik MO, Cakmak EA, Arslan A.

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Familial mediterranean fever (FMF) is an autosomal recessive autoinflammatory disorder (MIM# 249100), particularly common in populations of Mediterranean extraction. MEFV gene, responsible for FMF, encoding pyrin has recently been mapped to chromosome 16p13.3. In the present study, 3,341 unrelated patients with the suspicion of FMF in south-east part of Turkey between the years 2009 and 2013 were enrolled and genomic sequences of exon 2 and exon 10 of the MEFV gene were scanned for mutations by direct sequencing. We identified 43 different type of mutations and 9 of them were novel. DNA was amplified by PCR and subjected to direct sequencing for the detection of MEFV gene mutations. Among the 3,341 patients, 1,598 (47.8 %) were males and 1,743 (52.1 %) were females. The mutations were heterozygous in 806 (62.3 %), compound heterozygous in 188 (14.5 %), homozygous in 281 (21.8 %) and mutations had complex genotype in 17 (1.32 %) patients. No mutation was detected in 2,051 (61.4 %) patients. The most frequent mutations were M694V, E148Q, M680I(G/C) and V726A. We could not find any significant differences between the two common mutations according to the gender. Molecular diagnosis of MEFV is a useful tool in clinical practice, thus a future study relating to genotype/phenotype correlation of FMF in more and larger group in Turkish population involving the whole MEFV gene mutations is necessary.

DOI: 10.1007/s11033-014-3118-5



2129. Int J Rheum Dis. 2017 Dec;20(12):2093-2100. doi: 10.1111/1756-185X.12297. Epub 2014 Jan 28.

Anxiety and depression in adult patients with familial Mediterranean fever: a study comparing patients living in Germany and Turkey.

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(7)AID-NET Autoinflammatory Disorders (AID) in Children: Genetics, Disease Mechanisms, Diagnostic Markers and Therapeutic Targets, Essen, Germany.

AIM: To determine the prevalence of anxiety and depression among patients with familial Mediterranean fever (FMF) living in Germany or Turkey a prospective study was conducted.

METHODS: Forty FMF patients living in Turkey (T), 40 FMF patients living in Germany (G) and 40 healthy controls living in Germany (C) were included. Patients and controls were of Turkish ancestry. G were compared to T and C. The Hospital Anxiety and Depression Scale (HADS) was used with a cut-off of  $\geq 8$  for each subdomain score (HADS-A, HADS-D).

RESULTS: Baseline characteristics of G were comparable to T and C except for age (T: 30.5 years, G: 35.2 years, C: 34.6 years; T vs. G  $P = 0.045$ ), duration of disease (T: 14.4 years, G: 24;  $P < 0.001$ ), C-reactive protein (T: 0.78 mg/dL, G: 0.78 mg/dL, C: 0.35 mg/dL; G vs. C  $P = 0.03$ ). Prevalence of anxiety was higher in G compared to C (T: 65%, G: 52.5%, C: 22.5%; G vs. C  $P < 0.05$ ). No difference was

found for the prevalence of depression (T: 30%, G: 35%, C: 20%). The association between FMF and anxiety in subjects living in Germany persisted after adjusting for age and gender in a regression analysis and was robust to an adjustment for coexisting depression. Anxiety and depression did not correlate with FMF disease severity assessed with the Pras score.

CONCLUSION: Anxiety, but not depression is more common among FMF patients living in Germany compared to healthy controls. No significant difference could be found between FMF patients living in Germany or Turkey concerning the prevalence of anxiety or depression.

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DOI: 10.1111/1756-185X.12297

PMID: 24467729 [Indexed for MEDLINE]

2130. PLoS One. 2014 Jan 21;9(1):e85666. doi: 10.1371/journal.pone.0085666. eCollection 2014.

Chronic proliferative dermatitis in Sharpin null mice: development of an autoinflammatory disease in the absence of B and T lymphocytes and IL4/IL13 signaling.

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SHARPIN is a key regulator of NFkB and integrin signaling. Mice lacking Sharpin develop a phenotype known as chronic proliferative dermatitis (CPDM), typified by progressive epidermal hyperplasia, apoptosis of keratinocytes, cutaneous and systemic eosinophilic inflammation, and hypoplasia of secondary lymphoid organs.

Rag1(-/-) mice, which lack mature B and T cells, were crossed with Sharpin(-/-) mice to examine the role of lymphocytes in CPDM. Although inflammation in the lungs, liver, and joints was reduced in these double mutant mice, dermatitis was not reduced in the absence of functional lymphocytes, suggesting that lymphocytes are not primary drivers of the inflammation in the skin. Type 2 cytokine expression is increased in CPDM. In an attempt to reduce this aspect of the phenotype, Il4ra(-/-) mice, unresponsive to both IL4 and IL13, were crossed with Sharpin(-/-) mice. Double homozygous Sharpin(-/-) , Il4ra(-/-) mice developed an exacerbated granulocytic dermatitis, acute system inflammation, as well as hepatic necrosis and mineralization. High expression of CHI3L4, normally seen in CPDM skin, was abolished in Sharpin(-/-) , Il4ra(-/-) double mutant mice indicating the crucial role of IL4 and IL13 in the expression of this protein. Cutaneous eosinophilia persisted in Sharpin(-/-) , Il4ra(-/-) mice, although expression of Il5 mRNA was reduced and the expression of Ccl11 and Ccl24 was completely abolished. TSLP and IL33 were both increased in the skin of Sharpin(-/-) mice and this was maintained in Sharpin(-/-) , Il4ra(-/-) mice suggesting a role for TSLP and IL33 in the eosinophilic dermatitis in SHARPIN-deficient mice. These studies indicate that cutaneous inflammation in SHARPIN-deficient mice is autoinflammatory in nature developing independently of B and T lymphocytes, while the systemic inflammation seen in CPDM has a strong lymphocyte-dependent component. Both the cutaneous and systemic inflammation is enhanced by loss of IL4 and IL13 signaling indicating that these cytokines normally play an anti-inflammatory role in SHARPIN-deficient mice.

DOI: 10.1371/journal.pone.0085666

PMCID: PMC3897490

PMID: 24465642 [Indexed for MEDLINE]

2131. J Autoimmun. 2014 Feb-Mar;48-49:53-9. doi: 10.1016/j.jaut.2014.01.026. Epub 2014 Jan 24.

Diagnosis and classification of relapsing polychondritis.

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Relapsing polychondritis is a rare and potentially fatal autoimmune disease of unknown etiology, characterized by inflammation and destruction of different cartilaginous structures, including the ear, nose, larynx, trachea, bronchi, peripheral joints, eye, heart and skin, with high risk of misdiagnosis. The spectrum of clinical presentations is protean and may vary from intermittent episodes of painful and disfiguring auricular and nasal chondritis or polyarthritis to severe progressive multi-organ damage. A laryngotracheobronchial involvement appears in nearly half of patients and is complicated by local obstructions, which may be life-threatening. A highly medical specialized approach is required for diagnosis of relapsing polychondritis. This review comprehensively examines the literature related to the clinical sceneries of the disease and focuses on both diagnostic tools used in clinical studies and recent findings related to its etiopathogenesis.

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DOI: 10.1016/j.jaut.2014.01.026

PMID: 24461536 [Indexed for MEDLINE]

2132. J Autoimmun. 2014 Feb-Mar;48-49:31-3. doi: 10.1016/j.jaut.2014.01.009. Epub 2014 Jan 21.

Diagnosis and classification of juvenile idiopathic arthritis.

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In recent years, it has become increasingly clear that the term Juvenile Idiopathic Arthritis (JIA) comprises not one disease but several. Moreover, recent studies strongly suggest that some of these clinico-pathophysiologic entities appear to cross current diagnostic categories. The ultimate goal of the JIA classification is to facilitate development of better, more specific therapy for different forms of disease through improved understanding of pathophysiology. The past two decades have witnessed significant advances in treatment and improved outcomes for many children with chronic arthritis. However, understanding of the basic biologic processes underlying these diseases remains far from complete. As a result, even the best biologic agents of today represent "halfway technologies". Because they do not treat fundamental biologic processes, they are inherently expensive, need to be given for a long time in order to ameliorate the adverse effects of chronic inflammation, and do not cure the disease. Pediatric rheumatology is now entering an era in which diagnostic categories may need to change to keep up with discovery. A more precise, biologically based classification is likely to contribute to development of more specific and improved treatments for the various forms of childhood arthritis. In this review, we discuss how genetic, gene expression, and immunologic findings have begun to influence how these diseases are understood and classified.

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DOI: 10.1016/j.jaut.2014.01.009

PMID: 24461383 [Indexed for MEDLINE]

2133. Case Rep Rheumatol. 2013;2013:636713. doi: 10.1155/2013/636713. Epub 2013 Dec 22.

Rheumatoid Arthritis and Familial Mediterranean Fever or Sacroiliitis Accompanied by FMF.

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The coexistence of rheumatoid arthritis (RA) and familial Mediterranean fever (FMF) has been rarely seen in case reports in the literature. Herein, we wanted to present a patient who had been followed up and treated as RA, but on investigation we concluded that he really had FMF and its joint complaints associated with sacroiliitis. Recovery was achieved by etanercept administered as if he was an RA patient.

DOI: 10.1155/2013/636713

PMCID: PMC3881508

PMID: 24455383

2134. Immunol Lett. 2014 Oct;161(2):226-30. doi: 10.1016/j.imlet.2013.12.013. Epub 2014 Jan 19.

Autoinflammatory diseases.

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Autoinflammatory diseases represent an expanding spectrum of genetic and non-genetic inflammatory diseases characterized by recurrent episodes of fever and systemic inflammation affecting the eyes, joints, skin, and serosal surfaces. Thus, these syndromes are recognized as disorders of innate immunity. Confirming this view, most autoinflammatory diseases are uniquely responsive to IL-1 $\beta$  blockade. Although many autoinflammatory diseases have a genetic cause,

increasing evidence indicates that the degree of cell stress concurs to the severity of the disease phenotype. In this mini-review, I will discuss the recent advances on pathogenesis, pathophysiology and therapeutic approaches in autoinflammatory syndromes.

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DOI: 10.1016/j.imlet.2013.12.013

PMID: 24452074 [Indexed for MEDLINE]

2135. Clin Sci (Lond). 2014 May;126(9):593-612. doi: 10.1042/CS20130497.

Cytokine networking of innate immunity cells: a potential target of therapy.

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Innate immune cells, particularly macrophages and epithelial cells, play a key role in multiple layers of immune responses. Alarmins and pro-inflammatory cytokines from the IL (interleukin)-1 and TNF (tumour necrosis factor) families initiate the cascade of events by inducing chemokine release from bystander cells and by the up-regulation of adhesion molecules required for transendothelial trafficking of immune cells. Furthermore, innate cytokines produced by dendritic cells, macrophages, epithelial cells and innate lymphoid cells seem to play a critical role in polarization of helper T-cell cytokine profiles into specific subsets of Th1/Th2/Th17 effector cells or regulatory T-cells. Lastly, the innate immune system down-regulates effector mechanisms and restores homeostasis in injured tissue via cytokines from the IL-10 and TGF (transforming growth factor) families mainly released from macrophages, preferentially the M2 subset, which have a capacity to induce regulatory T-cells, inhibit the production of pro-inflammatory cytokines and induce healing of the tissue by regulating extracellular matrix protein deposition and angiogenesis. Cytokines produced by innate immune cells represent an attractive target for therapeutic intervention, and multiple molecules are currently being tested clinically in patients with inflammatory bowel disease, rheumatoid arthritis, systemic diseases,

autoinflammatory syndromes, fibrosing processes or malignancies. In addition to the already widely used blockers of TNF $\alpha$  and the tested inhibitors of IL-1 and IL-6, multiple therapeutic molecules are currently in clinical trials targeting TNF-related molecules [APRIL (a proliferation-inducing ligand) and BAFF (B-cell-activating factor belonging to the TNF family)], chemokine receptors, IL-17, TGF $\beta$  and other cytokines.

DOI: 10.1042/CS20130497

PMID: 24450743 [Indexed for MEDLINE]

2136. Rheumatology (Oxford). 2014 May;53(5):810-20. doi: 10.1093/rheumatology/ket438. Epub 2014 Jan 20.

Increased Notch pathway activation in Behçet's disease.

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**OBJECTIVE:** Behçet's disease (BD) is a refractory inflammatory disorder with unknown causes. Since the Notch pathway is critically involved in the immune response, the present study was undertaken to investigate the role of this pathway in BD.

**METHODS:** Hes-1, Notch 1-4, Jagged-1, DLL-1 and DLL-4 expression, frequency of IFN- $\gamma$  and IL-17 expressing Th cells, Notch intracellular domain (NICD), phosphorylation of signal transducer and activator of transcription 3 (STAT3) and the production of IFN- $\gamma$  and IL-17 were examined by real-time PCR, flow cytometry and ELISA. Notch blockade was performed using the  $\gamma$ -secretase inhibitor N-[N-(3,5-difluorophenacetyl)-1-alanyl]-S-phenylglycine t-butyl ester (DAPT). Transfection with miR-23b mimics and inhibitor was used to examine the effect of miR-23b on Notch pathway activation.

**RESULTS:** Active BD patients showed an increased activation of the Notch pathway in association with a higher Th17 response. Notch blockade preferentially inhibited Th17 responses. The effect of Notch blockade on the Th17 response was associated with a lower level of STAT3 phosphorylation. miR-23b was significantly



decreased in CD4(+) T cells from active BD patients. CD4(+) T cells transfected with miR-23b showed a reduced expression of NICD and a reduced frequency of IL-17- and IFN- $\gamma$ -expressing T cells.

**CONCLUSION:** The present study suggests that an increased activation of the Notch pathway may contribute to the pathogenesis of BD. Decreased expression of miR-23b may be involved in activation of the Notch pathway in BD. Manipulation of the Notch pathway may offer a novel therapeutic approach for BD.

DOI: 10.1093/rheumatology/ket438

PMID: 24446471 [Indexed for MEDLINE]

2137. Clin Rheumatol. 2015 Feb;34(2):391-5. doi: 10.1007/s10067-014-2493-6. Epub 2014 Jan 21.

Early-onset sarcoidosis caused by a rare CARD15/NOD2 de novo mutation and responsive to infliximab: a case report with long-term follow-up and review of the literature.

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Granulomatous autoinflammatory diseases are monogenic syndromes caused by mutations in the region encoding for the nucleotide-binding domain region of the NOD2/CARD15 gene with subsequent dysregulation of the inflammatory response and formation of noncaseous granulomas. They include Blau syndrome (BS) and early-onset sarcoidosis (EOS); both are clinically and genetically indistinguishable between them and they are the familial (autosomal dominantly inherited) and sporadic forms of the same disease, respectively. We describe a case of EOS, misdiagnosed for 30 years such as "juvenile rheumatoid arthritis" before and "classic sarcoidosis" later. In our patient, we found a new de novo mutation (E383G) in NOD2 that has been reported only in a family of Japanese patients with BS. After long-term follow-up (42 months), infliximab maintained good efficacy and safety without any sign of disease relapse and side effects.

DOI: 10.1007/s10067-014-2493-6

2138. Int J Rheum Dis. 2017 Dec;20(12):2101-2105. doi: 10.1111/1756-185X.12207. Epub 2013 Oct 29.

Functional gastrointestinal disorders in patients with familial Mediterranean fever.

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**AIM:** Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disease characterised by recurrent episodes of fever and polyserositis. To date, insufficient data regarding the prevalence of functional gastrointestinal disorders such as irritable bowel syndrome (IBS) and functional dyspepsia (FD) have been reported in patients with FMF. This study aimed to determine the prevalence of functional gastrointestinal disorders in patients with FMF.

**METHODS:** This study included 122 patients with FMF and a control group of 122 healthy volunteers who were similar with respect to age and sex. Clinical data were collected and gastrointestinal complaints were evaluated according to the Rome III criteria.

**RESULTS:** IBS was found in 18% of the patients and 10.7% of the controls ( $P > 0.05$ ). Dyspepsia was reported in 37.7% of the patients and 35.2% of the

controls. Constipation was significantly higher in the control group (15.6% vs. 7.4%,  $P = 0.045$ ), whereas diarrhoea was reported significantly more often in patients with FMF ( $P = 0.001$ ).

CONCLUSIONS: IBS and dyspepsia were not increased in patients with FMF, whereas diarrhoea was more frequently reported.

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DOI: 10.1111/1756-185X.12207

PMID: 24433546 [Indexed for MEDLINE]

2139. *Pediatr Rheumatol Online J.* 2014 Jan 16;12:5. doi: 10.1186/1546-0096-12-5.

MEFV gene mutations and cardiac phenotype in children with familial Mediterranean fever: a cohort study.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is the most common autoinflammatory disorder in the world. It is characterized by recurrent febrile inflammatory attacks of serosal and synovial membranes. MEFV gene mutations are responsible for the disease and its protein product, pyrin or marenostrin, plays an essential role in the regulation of the inflammatory reactions. Although the disease may carry a potential for cardiovascular disorders because of sustained inflammation during its course, the spectrum of cardiac involvement in children with FMF has not been well studied. We aimed at defining the frequency and spectrum of cardiac affection in children with FMF. The correlation between these affections and MEFV gene mutations was searched for to establish the relationship between cardiac phenotype and the patient's genotype in FMF.

**METHODS:** The present work is a cohort study including 55 patients with the clinical diagnosis of FMF based on the Tel-Hashomere criteria, confirmed by genetic analysis showing homozygous or compound heterozygous mutation of MEFV genes. Fifty age- and sex-matched normal children were included as controls. The

entire study group underwent detailed cardiac examination, 12-lead ECG and echocardiography. All data was statistically analysed using SPSS version-15.

RESULTS: Patients had an average age of 8.5+/-4.2 years; with an average disease duration of 2.1+/-2.2 years; 28 were males. All controls showed no MEVF gene mutations. The most frequent gene mutation of the studied cases was E148Q mutation seen in 34% of cases and the most frequent compound mutation was E148Q/V726A seen in 16.6% of cases. Echocardiographic examination revealed pericardial effusion in nine patients. Twelve had aortic regurgitation; nine had mitral regurgitation and six had pulmonary regurgitation. The most common mutation associated with pericardial effusion was E148Q/V726A in 5/9 of cases. Valvular involvement were significantly more common in FMF patients with gene mutations. Also cardiac involvement was more common in patients with positive consanguinity. However, these cardiac manifestations showed no correlation to age, family history of FMF, or response to therapy or laboratory data.

CONCLUSIONS: In our cohort of children with FMF, cardiac involvement appears to be common. Pericardial effusions are significantly related to presence of mutation types E48Q, P 369S, V726A. These associations may warrant genetic screening of children with FMF to detect cardiac risk.

DOI: 10.1186/1546-0096-12-5

PMCID: PMC3931676

PMID: 24433404 [Indexed for MEDLINE]

2140. Arthritis Rheumatol. 2014 Jan;66(1):197-202. doi: 10.1002/art.38217.

Brief Report: whole-exome sequencing revealing somatic NLRP3 mosaicism in a patient with chronic infantile neurologic, cutaneous, articular syndrome.

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OBJECTIVE: To identify the genetic cause of chronic infantile neurologic, cutaneous, articular syndrome (CINCA syndrome) using whole-exome sequencing in a child who had typical clinical features but who was NLRP3 mutation negative based on conventional Sanger sequencing.

**METHODS:** We performed whole-exome sequencing on DNA from peripheral blood, using Illumina TruSeq Exome capture and the HiSeq sequencing platform. Exome data were analyzed in the Galaxy Web-based suite. Whole-exome sequencing findings were confirmed by massively parallel sequencing.

**RESULTS:** Analysis of variants in known autoinflammatory genes led to the identification of the pathogenic p.F556L NLRP3 missense mutation in 17.7% of Illumina reads (25 of 141). No new candidate genes were identified. Massively parallel sequencing of DNA from peripheral blood (performed in duplicate) unequivocally confirmed the presence of this mutation in 14.5% of alleles. Reexamination of the original Sanger chromatograms revealed a small peak at nucleotide position c.1698 corresponding to the mutated allele. This had initially been regarded as background noise, but in retrospect is completely consistent with somatic mosaicism for the p.F556L NLRP3 mutation in this child with CINCA syndrome.

**CONCLUSION:** This is the first description of somatic NLRP3 mosaicism detected using whole-exome sequencing in a "mutation-negative" patient with CINCA syndrome. Our findings suggest that whole-exome sequencing could be an important diagnostic tool for detecting somatic mosaicism, as well as for the discovery of novel causative gene mutations, in patients with clinical features of cryopyrin-associated periodic syndromes who are NLRP3 mutation negative by conventional sequencing. This approach could also be applicable to patients with other autosomal-dominant autoinflammatory diseases characterized by gain-of-function mutations who are mutation negative by conventional Sanger sequencing.

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DOI: 10.1002/art.38217

PMCID: PMC3995009

PMID: 24431285 [Indexed for MEDLINE]

2141. Iran J Pediatr. 2013 Aug;23(4):489-90.

Hashimoto's Thyroiditis in a Child with Familial Mediterranean Fever: a Case Report.

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PMCID: PMC3883383

PMID: 24427507

2142. Curr Atheroscler Rep. 2014 Mar;16(3):391. doi: 10.1007/s11883-013-0391-z.

Colchicine for secondary prevention of cardiovascular disease.

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Preliminary evidence demonstrating that adding 0.5 mg of colchicine per day to statin and antiplatelet therapy reduced the risk of acute coronary events in patients with stable coronary artery disease has raised the hope that it may prove effective for the long-term secondary prevention of cardiovascular disease. The ability of colchicine to suppress blood levels of inflammatory mediators and prevent cholesterol-crystal-induced neutrophil-mediated inflammation implicated in the progression and instability of atherosclerosis adds plausibility to this clinical observation. Early intestinal intolerance in some patients is well recognized, but clinical experience gained over more than half a century with the continuous use of colchicine for the prevention of neutrophil-mediated inflammation in patients with familial Mediterranean fever and gout indicates that low-dose long-term therapy is safe. Nonetheless, before colchicine can be recommended for the secondary prevention of cardiovascular disease, further studies are required to confirm its safety and efficacy in a broad range of patients with coronary disease, and to determine whether doses of colchicine less

than 0.5 mg/day might be effective and even better tolerated. Trials exploring the role of colchicine in the treatment of patients with acute coronary syndromes would also be of special interest but may require the use of doses higher than those used for long-term secondary prevention.

DOI: 10.1007/s11883-013-0391-z

PMID: 24425060 [Indexed for MEDLINE]

2143. Autoimmun Rev. 2014 Apr-May;13(4-5):388-90. doi: 10.1016/j.autrev.2014.01.045. Epub 2014 Jan 11.

Diagnostic criteria of familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is the most prevalent monogenic autoinflammatory disease, mainly affecting ethnic groups living at Mediterranean basin. FMF is characterized by recurrent, self-limited episodes of fever and serositis. The diagnosis is difficult in the presence of atypical signs, which may result in significant delay in initiating treatment. As autoinflammatory diseases may have overlapping symptoms, strict diagnostic criteria are essential. Since the discovery that mutations in the gene MEFV underlie FMF, molecular genetic testing has been used as a diagnostic adjunct, especially in atypical cases. However, despite progress in the understanding of FMF disease mechanisms during the past 15 years; the diagnosis is still based on clinical criteria. Several sets of diagnostic criteria have been proposed and used. Existing diagnostic criteria should be modified to include genetic data, and need to be more widely validated.

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DOI: 10.1016/j.autrev.2014.01.045

2144. Annu Rev Med. 2014;65:223-44. doi: 10.1146/annurev-med-061512-150641.

IL-1 blockade in autoinflammatory syndromes.

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Monogenic autoinflammatory syndromes present with excessive systemic inflammation including fever, rashes, arthritis, and organ-specific inflammation and are caused by defects in single genes encoding proteins that regulate innate inflammatory pathways. Pathogenic variants in two interleukin-1 (IL-1)-regulating genes, NLRP3 and IL1RN, cause two severe and early-onset autoinflammatory syndromes, CAPS (cryopyrin associated periodic syndromes) and DIRA (deficiency of IL-1 receptor antagonist). The discovery of the mutations that cause CAPS and DIRA led to clinical and basic research that uncovered the key role of IL-1 in an extended spectrum of immune dysregulatory conditions. NLRP3 encodes cryopyrin, an intracellular "molecular sensor" that forms a multimolecular platform, the NLRP3 inflammasome, which links "danger recognition" to the activation of the proinflammatory cytokine IL-1 $\beta$ . The success and safety profile of drugs targeting IL-1 in the treatment of CAPS and DIRA have encouraged their wider use in other autoinflammatory syndromes including the classic hereditary periodic fever syndromes (familial Mediterranean fever, TNF receptor-associated periodic syndrome, and hyperimmunoglobulinemia D with periodic fever syndrome) and additional immune dysregulatory conditions that are not genetically well defined, including Still's, Behcet's, and Schnitzler diseases. The fact that the accumulation of metabolic substrates such as monosodium urate, ceramide, cholesterol, and glucose can trigger the NLRP3 inflammasome connects metabolic stress to IL-1 $\beta$ -mediated inflammation and provides a rationale for therapeutically targeting IL-1 in prevalent diseases such as gout, diabetes mellitus, and coronary artery disease.



PMCID: PMC4178953

PMID: 24422572 [Indexed for MEDLINE]

2145. Blood. 2014 Apr 24;123(17):2703-14. doi: 10.1182/blood-2013-07-516948. Epub 2014 Jan 13.

The F-BAR protein PSTPIP1 controls extracellular matrix degradation and filopodia formation in macrophages.

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Comment in

Blood. 2014 Apr 24;123(17):2597-9.

PSTPIP1 is a cytoskeletal adaptor and F-BAR protein that has been implicated in autoinflammatory disease, most notably in the PAPA syndrome: pyogenic sterile arthritis, pyoderma gangrenosum, and acne. However, the mechanism by which PSTPIP1 regulates the actin cytoskeleton and contributes to disease pathogenesis remains elusive. Here, we show that endogenous PSTPIP1 negatively regulates macrophage podosome organization and matrix degradation. We identify a novel PSTPIP1-R405C mutation in a patient presenting with aggressive pyoderma gangrenosum. Identification of this mutation reveals that PSTPIP1 regulates the balance of podosomes and filopodia in macrophages. The PSTPIP1-R405C mutation is in the SRC homology 3 (SH3) domain and impairs Wiskott-Aldrich syndrome protein (WASP) binding, but it does not affect interaction with protein-tyrosine phosphatase (PTP)-PEST. Accordingly, WASP inhibition reverses the elevated F-actin content, filopodia formation, and matrix degradation induced by PSTPIP1-R405C. Our results uncover a novel role for PSTPIP1 and WASP in orchestrating different types of actin-based protrusions. Our findings implicate the cytoskeletal regulatory functions of PSTPIP1 in the pathogenesis of pyoderma gangrenosum and suggest that the cytoskeleton is a rational target for therapeutic intervention in autoinflammatory disease.

DOI: 10.1182/blood-2013-07-516948

PMCID: PMC3999755

PMID: 24421327 [Indexed for MEDLINE]

2146. Acta Derm Venereol. 2014 Sep;94(5):512-6. doi: 10.2340/00015555-1775.

Calcipotriol increases hCAP18 mRNA expression but inhibits extracellular LL37 peptide production in IL-17/IL-22-stimulated normal human epidermal keratinocytes.

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Interleukins (IL)-17A and -22 are involved in the patho-genesis of psoriasis. Cathelicidin LL37 serves as not only antimicrobial peptide but also as autoinflammatory mediator. 1,25-Dihydroxyvitamin D3 analogues, such as calcipotriol, are used as topical treatment for psoriasis. However, the effect of calcipotriol on the mRNA expression/production of human cathelicidin antimicrobial protein (hCAP18) and LL37 peptide by IL-17A/IL-22-stimulated keratinocytes remains controversial. To evaluate the modulatory action of calcipotriol on the production of hCAP18 and LL37, we analysed hCAP18 mRNA expression and hCAP18/LL37 peptide production in IL-17A/IL-22-stimulated cultured human keratinocytes by real-time qPCR, ELISA, western blotting, and immunocytochemical staining. By western blotting, hCAP18 protein was detected in keratinocytes cultured for 72 h with IL-17/IL-22. Calcipotriol increased hCAP18 mRNA expression in IL-17/IL-22-stimulated keratinocytes. However, LL37 peptide in the culture supernatants was reduced by calcipotriol. Immunostaining revealed that the overproduced LL37 resides within the cells. LL37 promotes psoriasis via interaction with extracellular DNA, but may suppress psoriasis by interfering cytosolic DNA.

DOI: 10.2340/00015555-1775

PMID: 24419155 [Indexed for MEDLINE]

2147. Int J Rheum Dis. 2014 Mar;17(3):321-6. doi: 10.1111/1756-185X.12253. Epub 2014 Jan 11.

Decreased vitamin D levels in children with familial Mediterranean fever.

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**OBJECTIVES:** To determine the frequency of vitamin D deficiency in children with familial Mediterranean fever (FMF) and to investigate the factors associated with low vitamin D status.

**DESIGN AND METHODS:** Forty-four patients with FMF and 39 age- and sex-matched healthy controls were enrolled in this study. Demographic data, FMF symptoms, disease duration, time to delay for diagnosis, duration of follow-up, disease severity score, MEFV gene mutation, cumulative colchicine dose, compliance to treatment and serum C-reactive protein levels were recorded for each patient. Serum 25-hydroxyvitamin D levels were measured by an original commercial kit based on chemiluminescent microparticle immunoassay (CMIA).

**RESULTS:** The serum 25-hydroxyvitamin D levels were significantly lower in FMF patients than the healthy controls ( $12.9 \pm 3.6$  and  $16.3 \pm 5.5$  ng/mL, respectively,  $P = 0.001$ ). Vitamin D levels were similar in patients homozygous for M694V and other genotypes ( $11.8 \pm 3.7$  and  $13.2 \pm 3.6$  ng/mL, respectively,  $P = 0.21$ ). Stepwise multiple linear regression analysis confirmed that the cumulative colchicine dose was the strongest independent variable correlating with vitamin D levels ( $r(2) = 0.194$ ,  $P = 0.001$ ).

**CONCLUSION:** Our results suggest that serum 25-hydroxyvitamin D levels are decreased in children with FMF. Cumulative colchicine dose appears to negatively affect vitamin D levels. The role of colchicine on vitamin D metabolism needs to be elicited.

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DOI: 10.1111/1756-185X.12253

PMID: 24410734 [Indexed for MEDLINE]

2148. Clin Lab. 2013;59(11-12):1271-6.

Absence of autoantibodies against oral and vascular-related cell lines in the sera of patients with Behcet's disease.

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**BACKGROUND:** Behcet's disease (BD) is an autoinflammatory disease with unclear pathogenesis. The oral and vascular tissue are the main target organs in BD. The role of humoral immunity in pathogenesis of oral and vascular lesions in BD patients has not been well studied. Therefore, the aim of this study was to investigate the presence of autoantibodies in the sera of BD patients using oral and vascular tissue related cell lines.

**METHODS:** Proteins from oral (KB, HGF-1) and vascular (HUVEC) related cell lines as well as C2C12 (a muscle myoblast cell line) were extracted as representatives of oral and vascular tissue antigens and the presence of autoantibodies in BD's sera were investigated using high throughput two dimensional electrophoresis (2DE) and immunoblotting techniques. Sera of other autoimmune diseases (RA and SLE) and normal individuals were used as controls.

**RESULTS:** After silver staining of 2DE gels, 2831, 2195, 1732, and 1839 spots were detectable in the proteome map of HUVEC, KB, HGF-1, and C2C12 cell lines, respectively. The majority of spots were in the pH range of 5 - 8 and the molecular weight range of 14 - 66 Kd. The immunoreactivity of BD, RA, SLE, and normal sera were not different with separated proteins of the cell lines.

**CONCLUSIONS:** According to our results, it seems that humoral immunity is not significantly involved in BD pathogenesis. Therefore, investigation of the role of cellular immunity, especially TH1 and TH17 cells and their cytokine profiles, in the pathogenesis of BD is recommended for future studies.

PMID: 24409661 [Indexed for MEDLINE]

2149. Orphanet J Rare Dis. 2014 Jan 9;9:3. doi: 10.1186/1750-1172-9-3.

Colchicine-free remission in familial Mediterranean fever: featuring a unique subset of the disease-a case control study.

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**BACKGROUND:** To demonstrate and clinically, genetically and demographically characterize familial Mediterranean fever (FMF) patients, maintaining remission despite colchicine abstinence.

**METHODS:** FMF patients were screened for an endurance of prolonged remission ( $\geq 3$  years), despite refraining from colchicine. Clinical, demographic and genetic parameters were collected. Data were compared with those of consecutive control FMF subjects, coming to the clinic for their periodic follow up examination.

**RESULTS:** Of 1000 patients screened over 5 years, 33 manifested colchicine-free remission. The mean duration of the remission period was  $12.6 \pm 8.1$  years.

Patients in the remission group had milder severity of FMF, compared to the control group (22 vs. 11 patients with mild disease, respectively,  $p=0.003$ ) and a longer diagnosis delay ( $21 \pm 15.7$  vs.  $13.4 \pm 13.5$  years, respectively,  $p=0.04$ ).

Patients experiencing remission suffered mostly of abdominal attacks, low rate of attacks in other sites and low rate of chronic and non-attack manifestations.

When the disease resumed activity, it responded well to colchicine, despite using a lower dose, as compared to the control subjects ( $p<0.001$ ). None of the patients in this group was homozygous for the M694V mutation ( $p=0.0008$ ).

**CONCLUSIONS:** Prolonged colchicine-free remission defines a rare and milder form of FMF with unique clinical, demographic, and molecular characteristics.

DOI: 10.1186/1750-1172-9-3

PMCID: PMC3895771

PMID: 24401676 [Indexed for MEDLINE]

2150. Nihon Naika Gakkai Zasshi. 2013 Oct 10;102(10):2653-666; quiz 2667-70.

[Organ damage in collagen vascular diseases: toward the understanding of the

complicated conditions (discussion)].

[Article in Japanese]

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PMID: 24400547 [Indexed for MEDLINE]

2151. Proc Natl Acad Sci U S A. 2014 Jan 21;111(3):1072-7. doi: 10.1073/pnas.1318685111. Epub 2014 Jan 6.

Inflammasome-independent IL-1 $\beta$  mediates autoinflammatory disease in Pstpip2-deficient mice.

Cassel SL(1), Janczy JR, Bing X, Wilson SP, Olivier AK, Otero JE, Iwakura Y, Shayakhmetov DM, Bassuk AG, Abu-Amer Y, Brogden KA, Burns TL, Sutterwala FS, Ferguson PJ.

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Chronic recurrent multifocal osteomyelitis (CRMO) is a human autoinflammatory

disorder that primarily affects bone. Missense mutation (L98P) of proline-serine-threonine phosphatase-interacting protein 2 (Pstpip2) in mice leads to a disease that is phenotypically similar to CRMO called chronic multifocal osteomyelitis (cmo). Here we show that deficiency of IL-1RI in cmo mice resulted in a significant reduction in the time to onset of disease as well as the degree of bone pathology. Additionally, the proinflammatory cytokine IL-1 $\beta$ , but not IL-1 $\alpha$ , played a critical role in the pathology observed in cmo mice. In contrast, disease in cmo mice was found to be independent of the nucleotide-binding domain, leucine-rich repeat-containing family, pyrin domain-containing 3 (NLRP3) inflammasome as well as caspase-1. Neutrophils, but not bone marrow-derived macrophages, from cmo mice secreted increased IL-1 $\beta$  in response to ATP, silica, and *Pseudomonas aeruginosa* compared with neutrophils from WT mice. This aberrant neutrophil response was sensitive to inhibition by serine protease inhibitors. These results demonstrate an inflammasome-independent role for IL-1 $\beta$  in disease progression of cmo and implicate neutrophils and neutrophil serine proteases in disease pathogenesis. These data provide a rationale for directly targeting IL-1RI or IL-1 $\beta$  as a therapeutic strategy in CRMO.

DOI: 10.1073/pnas.1318685111

PMCID: PMC3903222

PMID: 24395802 [Indexed for MEDLINE]

2152. Proc Natl Acad Sci U S A. 2014 Jan 21;111(3):1066-71. doi: 10.1073/pnas.1318688111. Epub 2014 Jan 6.

Critical role for inflammasome-independent IL-1 $\beta$  production in osteomyelitis.

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The immune system plays an important role in the pathophysiology of many acute and chronic bone disorders, but the specific inflammatory networks that regulate

individual bone disorders remain to be elucidated. Here, we characterized the osteoimmunological underpinnings of osteolytic bone disease in *Pstpip2(cmo)* mice. These mice carry a homozygous L98P missense mutation in the Pombe Cdc15 homology family phosphatase PSTPIP2 that is responsible for the development of a persistent autoinflammatory disease resembling chronic recurrent multifocal osteomyelitis in humans. We found that improper regulation of IL-1 $\beta$  production resulted in secondary induction of inflammatory cytokines, inflammatory cell infiltration in the bone, and unremitting bone inflammation. Aberrant IL1 $\beta$  expression precedes the development of osteolytic damage in young *Pstpip2(cmo)* mice, and genetic deletion of *Il1r* and *Il1 $\beta$* , but not *Il1 $\alpha$* , rescued osteolytic bone disease in mutant mice. Intriguingly, caspase-1 and nucleotide-binding oligomerization domain (NOD)-like receptor family, pyrin domain containing 3 activation in the inflammasome complex were dispensable for *Pstpip2(cmo)*-mediated bone disease. Thus, our findings establish a critical role for inflammasome-independent production of IL-1 $\beta$  in osteolytic bone disease and identify PSTPIP2 as a negative regulator of caspase-1-autonomous IL-1 $\beta$  production.

DOI: 10.1073/pnas.1318688111

PMCID: PMC3903206

PMID: 24395792 [Indexed for MEDLINE]

2153. Semin Arthritis Rheum. 2014 Jun;43(6):818-23. doi: 10.1016/j.semarthrit.2013.12.002. Epub 2013 Dec 12.

The expanding spectrum of low-penetrance TNFRSF1A gene variants in adults presenting with recurrent inflammatory attacks: clinical manifestations and long-term follow-up.

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**OBJECTIVE:** To analyze the clinical manifestations and response to treatment in a cohort of adult patients presenting with recurrent inflammatory attacks and carrying low-penetrance TNFRSF1A variants, as well as to provide data on their long-term follow-up.

**METHODS:** We performed a retrospective chart review of 36 patients carrying low-penetrance TNFRSF1A variants. Moreover, 60 genetically negative patients treated for recurrent inflammatory attacks and 13 patients with structural TNFRSF1A mutations were also analyzed. Detailed demographic and clinical data were collected at the time of molecular screening and at each follow-up visit. Treatments and markers of inflammation were also assessed.

**RESULTS:** Individuals with low-penetrance TNFRSF1A variants have a lower family history for inflammatory attacks and present with a later disease onset compared with patients with structural mutations, but do not differ, in this respect, with genetically negative individuals. Moreover, low-penetrance variants are less frequently associated with a chronic disease course, with clinical manifestations such as abdominal pain and myalgia, and with amyloidosis. A distinctive clinical feature is a higher rate of pericarditis. Interestingly, mutation-negative patients were found to present with a significant history of recurrent pharyngitis during childhood. Patients with low-penetrance variants are mostly managed with short courses of steroids or non-steroidal anti-inflammatory drugs on attacks. Although the need for a biological treatment is significantly lower compared with patients with structural mutations, still approximately 20% of individuals with recurrent inflammatory attacks carrying low-penetrance variants ultimately require these therapies.

**CONCLUSIONS:** Our study confirms that low-penetrance TNFRSF1A variants can be associated with an autoinflammatory phenotype. Although a chronic disease course is rarely observed, some patients ultimately benefit from a biological treatment.

DOI: 10.1016/j.semarthrit.2013.12.002

PMID: 24393624 [Indexed for MEDLINE]

2154. Inflammation. 2014 Jun;37(3):833-4. doi: 10.1007/s10753-013-9803-z.

Assessing disease severity and activity in patients with familial Mediterranean fever.

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Comment on

Inflammation. 2013 Dec;36(6):1357-62.

DOI: 10.1007/s10753-013-9803-z

PMID: 24390269 [Indexed for MEDLINE]

2155. Asian Pac J Allergy Immunol. 2013 Dec;31(4):325-9. doi: 10.12932/AP0244.31.4.2013.

Three Japanese patients (mother and two children) with familial Mediterranean fever associated with compound heterozygosity for L110P/E148Q/M694I and an autosomal true dominant inheritance pattern.

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Familial Mediterranean fever (FMF) is characterized by repeated episodes of fever, peritonitis, pleuritis, and synovitis. We describe here 3 Japanese patients (a mother and 2 children) in whom FMF was diagnosed on analysis of MEFV. A 40-year-old woman presented with fever and abdominal pain. The patient had had these symptoms on and off since childhood and consulted many hospitals. A

38-year-old man had abdominal pain and fever since the age of 30 years. A 59-year-old woman had had episodes of fever, abdominal pain, and chest pain for more than 20 years. MEFV gene analysis showed compound heterozygosity for L110P, E148Q, and M694I in all three patients. In Japanese patients with FMF, this mode of autosomal true dominant inheritance has not yet been reported. FMF is difficult to diagnose unless it is included in the differential diagnosis by physicians. We hope that our valuable experience will promote increased awareness and understanding of FMF.

DOI: 10.12932/AP0244.31.4.2013

PMID: 24383976 [Indexed for MEDLINE]

2156. J Rheumatol. 2014 Jan;41(1):140. doi: 10.3899/jrheum.130689.

An unusual clinical presentation of amyloidosis: auricular concha involvement.

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DOI: 10.3899/jrheum.130689

PMID: 24382925 [Indexed for MEDLINE]

2157. Mol Biol Rep. 2014 Mar;41(3):1419-26. doi: 10.1007/s11033-013-2986-4. Epub 2014 Jan 1.

The frequency of Familial Mediterranean fever gene mutations and genotypes at Kirikkale and comparison with the mean of regional MEFV mutation frequency of Turkey.

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In this study we have retrospectively analysed the mutation spectrum of the 351 Familial Mediterranean fever patients referred to Kırıkkale University Faculty of Medicine, Department of Medical Genetics Laboratory over a period of 5 years and compared them with Turkey's mean. We have found 11 different mutations, including rare mutations such as F479L, K695R, M680I(G/A) and 45 different genotypes showing the heterogeneity of MEFV mutations in Central Anatolia. The most three prevalent mutations were M694V (14.8%), E148Q (7.1%) and M680I(G/C) (4.1%) in accordance with the literature. We have also investigated R202Q in our routine molecular diagnosis. Mutation causing R202Q (c.605G > A) change was described as a frequent polymorphism and G allele was found in linkage disequilibrium (LD) with M694V. There are limited number of studies investigating R202Q, some of them implicate that its homozygote state is disease causing. We showed the high frequency of R202Q (23.7%) with and without M694V in all the groups analysed and its high LD rate with M694V in the diagnosed group. Our study is reflecting the mutational heterogeneity of MEFV and summarize mutational spectrum of Turkey's geographical regions and overall Turkey.

DOI: 10.1007/s11033-013-2986-4

PMID: 24381109 [Indexed for MEDLINE]

2158. J Am Acad Dermatol. 2014 Mar;70(3):555-61. doi: 10.1016/j.jaad.2013.10.043. Epub 2013 Dec 24.

Specific targeting of interleukin-23p19 as effective treatment for psoriasis.

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Interleukin (IL)-23 is a heterodimeric cytokine composed of a distinct p19 subunit and a p40 subunit, which it shares with IL-12. The dermatology and rheumatology communities have long surmised that anti-IL-12/23p40 antibodies

suppress autoinflammatory disease owing to their effect on IL-12. The aim of this review is to bring to light new data from murine and human studies demonstrating that in fact IL-23 and its resulting Th17 pathway mediate the inflammatory cascade that induces psoriatic plaque formation. Evidence derives from lesional immunohistochemical analyses, genetic studies, and research in other autoimmune diseases. Although current IL-12/23p40 inhibitors have shown good efficacy and safety, data regarding the functional role of IL-12 in immune defense suggest that preserving this cytokine would be beneficial. To date, evidence from mouse models and preliminary data in human beings show that specifically targeting IL-23p19 may be a safer but equally efficacious treatment option.

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DOI: 10.1016/j.jaad.2013.10.043

PMID: 24373779 [Indexed for MEDLINE]

2159. Allergy Asthma Clin Immunol. 2013 Dec 27;9(1):50. doi: 10.1186/1710-1492-9-50.

Spectrum of primary immunodeficiency disorders in Sri Lanka.

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**BACKGROUND:** While primary immunodeficiencies (PID) has been recognized in the west for decades, recognition has been delayed in the third world. This study attempts to detail the spectrum of PID, the therapy provided, and constraints in the diagnosis and treatment in a middle income country such as Sri Lanka.

**METHODS:** Nine hundred and forty two patients with recurrent infections and features suggestive of immune deficiency, referred from the entire country in a 4 year period, to the sole immunology unit in Sri Lanka were included. The following tests were performed. Full blood counts, serum Immunoglobulin and complement C3 and C4 levels, functional antibody levels, enumeration of lymphocyte subsets, in vitro and in vivo T cell functional assays,, nitroblue tetrazolium assay to diagnose chronic granulomatous disease, hair shaft assay to

diagnose Griscelli syndrome. Sequencing of the common gamma chain to identify x linked severe combined immune deficiency, and X linked agammaglobulinemia was confirmed by assaying for Btk mutations by single sequence conformation polymorphism. HIV/AIDS was excluded in all patients.

RESULTS: Seventy three patients were diagnosed with a primary immune deficiency. The majority (60.27%) had antibody deficiency. Common variable immune deficiency was the commonest (28.76%), followed by X linked agammaglobulinemia (XLA) (20.54%). Five patients had possible hyper IgM syndrome. Ten patients had severe combined immune deficiency (SCID), including 2 with x linked SCID, in addition to DiGeorge syndrome (2), ataxia telangiectasia (6), autosomal dominant hyper IgE syndrome (2), chronic granulomatous disease (4), leucocyte adhesion deficiency type 1 (2) and Griscelli syndrome (3). Patients with autoinflammatory, innate immune and complement defects could not be identified due to lack of facilities.

CONCLUSIONS: Antibody deficiency is the commonest PID, as in the west. IgA deficiency is rare. Autoinflammatory diseases, innate immune and complement deficiencies could not be identified due to lack of diagnostic facilities. Lack of awareness of PID among adult physicians result in delay in treatment of adult patients. While treatment of antibody deficiencies provided in state hospitals has extended life expectancy, there is no treatment available for severe T cell defects.

DOI: 10.1186/1710-1492-9-50

PMCID: PMC3880003

PMID: 24373416

2160. Bull Acad Natl Med. 2014 Jan;198(1):17-29; discussion 29-30.

[Psoriasis: how the epithelium influences the immune response: keratinocytes, dendritic cells and T lymphocytes].

[Article in French]

Nicolas JF.

Psoriasis is an autoinflammatory skin disease mediated by interactions between keratinocytes, dendritic cells and T lymphocytes, which create a vicious circle of cell activation and lead to the development and persistence of skin lesions. Inflammatory cytokines produced by these three cell types, especially TNF $\alpha$ , IL-23

and IL-17, are central to the disease and are the targets of new, highly effective immunobiological therapies. Advances in the pathophysiology and treatment of psoriasis have applications far beyond the skin disease itself. Indeed, psoriasis serves as a model for studies of the mechanisms of chronic inflammation such as rheumatoid arthritis, Crohn's disease, atherosclerosis and type 2 diabetes, and for developing new targeted therapies for autoinflammatory diseases.

PMID: 26259283 [Indexed for MEDLINE]

2161. Cent Eur J Immunol. 2014;39(3):331-7. doi: 10.5114/ceji.2014.45944. Epub 2014 Oct 14.

Cutaneous expressions of interleukin-6 and neutrophil elastase as well as levels of serum IgA antibodies to gliadin nonapeptides, tissue transglutaminase and epidermal transglutaminase: implications for both autoimmunity and autoinflammation involvement in dermatitis herpetiformis.

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**INTRODUCTION:** Dermatitis herpetiformis (DH) seems to be a chronic immune-mediated inflammatory disease of partially known origin. In light of its known biological functions and its involvement in tissue pathology in other disease states, particularly in nickel-induced allergic contact dermatitis coexisting with DH, it would appear that the central and peripheral response by neutrophils and their mediators (e.g. neutrophil elastase - NE) in DH may be partially mediated by interleukin-6 (IL-6). The aim of the study was to assess the role of IL -6 in DH lesions by examining the relationships between IL -6/NE cutaneous expression and

levels of serum anti-nonapeptides of gliadin (npG) IgA, anti-tissue transglutaminase (tTG) immunoglobulin A (IgA), anti-epidermal transglutaminase (eTG) IgA in DH.

**MATERIAL AND METHODS:** In total, 24 DH patients having IgA cutaneous deposition were studied. Immunohistochemistry on paraffin-embedded sections with quantitative digital morphometry was used to measure the intensity of IL -6 and NE cutaneous expressions. Levels of serum anti-npG IgA, anti-tTG IgA and anti-eTG IgA were evaluated with ELISA.

**RESULTS:** We found no statistically significant correlation between the NE and IL -6 expression intensities. Our results revealed also a lack of correlations between NE/IL -6 expressions and levels of anti-npG IgA, anti-tTG IgA, anti-eTG IgA in DH. However, the IL -6 expression level was significantly lower than that of NE.

**CONCLUSIONS:** The lack of correlations suggested no substantial interactions between IL -6, NE, IgA/npG, IgA/tTG or IgA/eTG in DH. Presented results might indicate the heterogenetic nature of DH pathogenesis suggesting further that both autoimmune and autoinflammatory phenomena may be involved in DH cutaneous pathology.

DOI: 10.5114/ceji.2014.45944

PMCID: PMC4440002

PMID: 26155144

2162. Clin Transl Allergy. 2014 Dec 5;4:41. doi: 10.1186/2045-7022-4-41. eCollection 2014.

Schnitzler's syndrome: lessons from 281 cases.

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Schnitzler's syndrome is an autoinflammatory disorder characterized by the association of a monoclonal IgM (or IgG) gammopathy, a chronic urticarial rash,



and signs and symptoms of systemic inflammation, including fever, arthralgias and bone pain. It was first described in 1972. This review summarizes the clinical features, efficacy of therapies, and follow-up data of the 281 cases that have been reported to date. Also, the results of skin histology, bone imaging, laboratory investigations, and studies of the pathogenesis will be discussed, including the pivotal role of interleukin-1 beta in this disorder.

DOI: 10.1186/2045-7022-4-41

PMCID: PMC4405827

PMID: 25905009

2163. Uirusu. 2014;64(1):83-94. doi: 10.2222/jsv.64.83.

[Innate immune DNA sensing pathways].

[Article in Japanese]

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How the cells triggers the induction of innate immune genes in response to nucleic acids derived from microbes, such as DNA viruses, intracellular bacteria, and parasites, or self DNA, has not been elucidated fully. We have previously shown that an endoplasmic reticulum (ER)-associated multiple transmembrane protein, so-called STING (stimulator of interferon genes), functions as an essential molecules for triggering DNA-mediated gene induction. STING may directly associate with stimulatory ligands, which include DNA, as well as with cyclic dinucleotides (CDNs), which are secreted by intracellular bacteria. After DNA or CDN stimulation, STING traffics with kinase TBK1 in an autophagic signaling complex, from ER to perinuclear endosomal compartments harboring IRF3 and NF- $\kappa$ B. STING may involve in autoinflammatory disease manifested by aberrant self-DNA. Understanding of STING function may conceivably lead to the development of potent adjuvants for vaccine development or conversely therapeutics that could control inflammation aggravated disease.

DOI: 10.2222/jsv.64.83

PMID: 25765984 [Indexed for MEDLINE]

2164. Rheumatology (Oxford). 2014 May;53(5):828-33. doi: 10.1093/rheumatology/ket436. Epub 2013 Dec 24.

No appreciable decrease in fertility in Behçet's syndrome.

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**OBJECTIVES:** Behçet's syndrome (BS) follows an active course during the childbearing years in both men and women. We formally surveyed the infertility rate and the effect of drugs and types of organ involvement on fertility in BS.

**METHODS:** We compared fertility among BS patients with and without major organ involvement with those with FMF, AS and healthy controls. A structured interview was performed and the medical records of the patients were reviewed to confirm the sites of involvement and drugs they used during their entire follow-up.

**RESULTS:** The number of female patients who were not able to ever conceive, who were not able to conceive before or after disease onset or who were able to conceive late or only with assisted reproductive technology was not increased among the BS group. The same was true for the male patients to successfully achieve a conception and/or father a child. The average number of children, miscarriages, terminations and ectopic pregnancies were similar among the groups. Infertility was more common in BS patients with major organ involvement who used cyclophosphamide (CYC) compared with those who did not ( $P = 0.009$ ).

**CONCLUSION:** Infertility is not appreciably increased among BS patients attending a dedicated outpatient clinic. Major organ involvement does not increase the risk of infertility and CYC is the only drug that seems to compromise fertility in BS.

DOI: 10.1093/rheumatology/ket436

PMID: 24369417 [Indexed for MEDLINE]

2165. Rheumatology (Oxford). 2014 Apr;53(4):741-5. doi: 10.1093/rheumatology/ket400.

Epub 2013 Dec 24.

Amyloidosis and its related factors in Turkish patients with familial Mediterranean fever: a multicentre study.

Kasifoglu T(1), Bilge SY, Sari I, Solmaz D, Senel S, Emmungil H, Kilic L, Oner SY, Yildiz F, Yilmaz S, Bakirli DE, Tufan MA, Yilmaz S, Yazisiz V, Pehlivan Y, Bes C, Cetin GY, Erten S, Gonullu E, Temel T, Sahin F, Akar S, Aksu K, Kalyoncu U, Direskeneli H, Erken E, Kisacik B, Sayarlioglu M, Korkmaz C.

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**OBJECTIVE:** The primary aim of this study was to investigate the prevalence of amyloidosis and its related factors in a large number of FMF patients.

**METHODS:** Fifteen centres from the different geographical regions of Turkey were included in the study. Detailed demographic and medical data based on a structured questionnaire and medical records were collected. The diagnosis of amyloidosis was based on histological proof of congophilic fibrillar deposits in tissue biopsy specimens.

**RESULTS:** There were 2246 FMF patients. The male/female ratio was 0.87 (1049/1197). The mean age of the patients was 34.5 years (S.D. 11.9). Peritonitis was the most frequent clinical finding and it was present in 94.6% of patients. Genetic testing was available in 1719 patients (76.5%). The most frequently observed genotype was homozygous M694V mutation, which was present in 413 (24%) patients. Amyloidosis was present in 193 patients (8.6%). Male sex, arthritis, delay in diagnosis, M694V genotype, patients with end-stage renal disease (ESRD) and family history of amyloidosis and ESRD were significantly more prevalent in patients with amyloidosis compared with the amyloidosis-negative subjects. Patients with homozygous M694V mutations had a 6-fold higher risk of amyloidosis compared with the other genotypes (95% CI 4.29, 8.7,  $P < 0.001$ ).

**CONCLUSION:** In this nationwide study we found that 8.6% of our FMF patients had amyloidosis and homozygosity for M694V was the most common mutation in these patients. The latter finding confirms the association of homozygous M694V mutation with amyloidosis in Turkish FMF patients.

DOI: 10.1093/rheumatology/ket400

PMID: 24369413 [Indexed for MEDLINE]

2166. JAMA Dermatol. 2014 Feb;150(2):213-4. doi: 10.1001/jamadermatol.2013.6095.

Neutrophilic lobular panniculitis as an expression of a widened spectrum of familial mediterranean fever.

Leiva-Salinas M(1), Betlloch I(1), Arribas MP(1), Francés L(1), Pascual JC(1).

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DOI: 10.1001/jamadermatol.2013.6095

PMID: 24369338 [Indexed for MEDLINE]

2167. Ann Dermatol Venereol. 2013 Nov;140 Suppl 3:S263-72. doi: 10.1016/S0151-9638(13)70142-X.

[What's new in internal medicine?].

[Article in French]

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In this paper based on a review of medical articles from September 2012 to September 2013, new data were selected about IgG4-related disease, connections between vitamin D and systemic lupus erythematosus, revised nomenclature of vasculitis, effects of salt on autoimmunity, new autoinflammatory syndromes and some diseases as systemic sclerosis and thrombangiitis obliterans.

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DOI: 10.1016/S0151-9638(13)70142-X

PMID: 24365498 [Indexed for MEDLINE]

2168. An Pediatr (Barc). 2015 Jan;82(1):e82-5. doi: 10.1016/j.anpedi.2013.11.005. Epub 2013 Dec 21.

[Cardiac tamponade as first manifestation in Mediterranean fever with autosomal dominant form].

[Article in Spanish]

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Familial Mediterranean fever (FMF) is a hereditary disease characterized by brief, recurring and self-limited episodes of fever and pain with inflammation, of one or several serous (peritoneum, pleura, pericardium, synovial or vaginal tunic of the testicle). Amyloidosis is its more important complication and the principal reason of death in the cases in which it appears. Diagnosis is based on the clinic and is confirmed by genetic tests. The treatment with Colchicine (0,02-0,03 mg/kg/day) prevents the recurrence of FMF attacks and the development of secondary (AA) amyloidosis. We report a case of a 13-year-old child in which FMF was diagnosed after several coincidental episodes with fever, pericarditis and cardiac tamponade. The genetic confirmation showed an autosomal dominant inheritance that is less frequent than the recessive form, in this disease.

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DOI: 10.1016/j.anpedi.2013.11.005

PMID: 24365392 [Indexed for MEDLINE]

2169. Dermatol Online J. 2013 Dec 16;19(12):20720.

Muckle-Wells treatment with anakinra.

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A 35-year-old man initially was referred for management of recalcitrant urticaria. Owing to his long history of arthritis and sensorineural hearing loss, genetic testing was performed. The test showed a D305N heterozygous mutation in the NLRP3 gene, which is consistent with the diagnosis of Muckle-Wells syndrome. We discussed the rationales behind the use of the interleukin-1 antagonist anakinra in this autoinflammatory disorder.

PMID: 24365011 [Indexed for MEDLINE]

2170. BMJ Open. 2013 Dec 20;3(12):e003971. doi: 10.1136/bmjopen-2013-003971.

Diagnostic workup for fever of unknown origin: a multicenter collaborative retrospective study.

Naito T(1), Mizooka M, Mitsumoto F, Kanazawa K, Torikai K, Ohno S, Morita H, Ukimura A, Mishima N, Otsuka F, Ohyama Y, Nara N, Murakami K, Mashiba K, Akazawa K, Yamamoto K, Senda S, Yamanouchi M, Tazuma S, Hayashi J.

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**OBJECTIVE:** Fever of unknown origin (FUO) can be caused by many diseases, and varies depending on region and time period. Research on FUO in Japan has been limited to single medical institution or region, and no nationwide study has been conducted. We identified diseases that should be considered and useful diagnostic testing in patients with FUO.

**DESIGN:** A nationwide retrospective study.

**SETTING:** 17 hospitals affiliated with the Japanese Society of Hospital General

Medicine.

**PARTICIPANTS:** This study included patients  $\geq 18$  years diagnosed with 'classical fever of unknown origin' (axillary temperature  $\geq 38^{\circ}\text{C}$  at least twice over a  $\geq 3$ -week period without elucidation of a cause at three outpatient visits or during 3 days of hospitalisation) between January and December 2011.

**RESULTS:** A total of 121 patients with FUO were enrolled. The median age was 59 years (range 19-94 years). Causative diseases were infectious disease in 28 patients (23.1%), non-infectious inflammatory disease in 37 (30.6%), malignancy in 13 (10.7%), other in 15 (12.4%) and unknown in 28 (23.1%). The median interval from fever onset to evaluation at each hospital was 28 days. The longest time required for diagnosis involved a case of familial Mediterranean fever. Tests performed included blood cultures in 86.8%, serum procalcitonin in 43.8% and positron emission tomography in 29.8% of patients.

**CONCLUSIONS:** With the widespread use of CT, FUO due to deep-seated abscess or solid tumour is decreasing markedly. Owing to the influence of the ageing population, polymyalgia rheumatica was the most frequent cause (9 patients). Four patients had FUO associated with HIV/AIDS, an important cause of FUO in Japan. In a relatively small number of cases, cause remained unclear. This may have been due to bias inherent in a retrospective study. This study identified diseases that should be considered in the differential diagnosis of FUO.

DOI: 10.1136/bmjopen-2013-003971

PMCID: PMC3884594

PMID: 24362014

2171. Orphanet J Rare Dis. 2013 Dec 20;8:196. doi: 10.1186/1750-1172-8-196.

Weekly oral alendronate in mevalonate kinase deficiency.

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**BACKGROUND:** Mevalonate kinase deficiency (MKD) is caused by mutations in the MVK

gene, encoding the second enzyme of mevalonate pathway, which results in subsequent shortage of downstream compounds, and starts in childhood with febrile attacks, skin, joint, and gastrointestinal symptoms, sometimes induced by vaccinations.

**METHODS:** For a history of early-onset corticosteroid-induced reduction of bone mineral density in a 14-year-old boy with MKD, who also had presented three bone fractures, we administered weekly oral alendronate, a drug widely used in the management of osteoporosis and other high bone turnover diseases, which blocks mevalonate and halts the prenylation process.

**RESULTS:** All of the patient's MKD clinical and laboratory abnormalities were resolved after starting alendronate treatment.

**CONCLUSIONS:** This observation appears enigmatic, since alendronate should reinforce the metabolic block characterizing MKD, but is crucial because of the ultimate improvement shown by this patient. The anti-inflammatory properties of bisphosphonates are a new question for debate among physicians across various specialties, and requires further biochemical and clinical investigation.

DOI: 10.1186/1750-1172-8-196

PMCID: PMC3880037

PMID: 24360083 [Indexed for MEDLINE]

2172. *Pediatr Rheumatol Online J.* 2013 Dec 23;11(1):47. doi: 10.1186/1546-0096-11-47.

Autoinflammatory bone disorders with special focus on chronic recurrent multifocal osteomyelitis (CRMO).

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Sterile bone inflammation is the hallmark of autoinflammatory bone disorders, including chronic nonbacterial osteomyelitis (CNO) with its most severe form chronic recurrent multifocal osteomyelitis (CRMO). Autoinflammatory osteopathies are the result of a dysregulated innate immune system, resulting in immune cell infiltration of the bone and subsequent osteoclast differentiation and



activation. Interestingly, autoinflammatory bone disorders are associated with inflammation of the skin and/or the intestine. In several monogenic autoinflammatory bone disorders mutations in disease-causing genes have been reported. However, regardless of recent developments, the molecular pathogenesis of CNO/CRMO remains unclear. Here, we discuss the clinical presentation and molecular pathophysiology of human autoinflammatory osteopathies and animal models with special focus on CNO/CRMO. Treatment options in monogenic autoinflammatory bone disorders and CRMO will be illustrated.

DOI: 10.1186/1546-0096-11-47

PMCID: PMC3881012

PMID: 24359092

2173. J Biol Chem. 2014 Feb 21;289(8):5000-12. doi: 10.1074/jbc.M113.536920. Epub 2013 Dec 19.

Defects in mitochondrial clearance predispose human monocytes to interleukin-1 $\beta$  hypersecretion.

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Most hereditary periodic fever syndromes are mediated by deregulated IL-1 $\beta$  secretion. The generation of mature IL-1 $\beta$  requires two signals: one that induces synthesis of inflammasome components and substrates and a second that activates inflammasomes. The mechanisms that mediate autoinflammation in mevalonate kinase deficiency, a periodic fever disease characterized by a block in isoprenoid biosynthesis, are poorly understood. In studying the effects of isoprenoid shortage on IL-1  $\beta$  generation, we identified a new inflammasome activation signal that originates from defects in autophagy. We find that hypersecretion of IL-1 $\beta$  and IL-18 requires reactive oxygen species and is associated with an oxidized redox status of monocytes but not lymphocytes. IL-1 $\beta$  hypersecretion by monocytes involves decreased mitochondrial stability, release of mitochondrial content into

the cytosol and attenuated autophagosomal degradation. Defective autophagy, as established by ATG7 knockdown, results in prolonged cytosolic retention of damaged mitochondria and increased IL-1 $\beta$  secretion. Finally, activation of autophagy in healthy but not mevalonate kinase deficiency patient cells reduces IL-1 $\beta$  secretion. Together, these results indicate that defective autophagy can prime monocytes for mitochondria-mediated NLRP3 inflammasome activation, thereby contributing to hypersecretion of IL-1 $\beta$  in mevalonate kinase deficiency.

DOI: 10.1074/jbc.M113.536920

PMCID: PMC3931060

PMID: 24356959 [Indexed for MEDLINE]

2174. Curr Allergy Asthma Rep. 2014 Jan;14(1):407. doi: 10.1007/s11882-013-0407-3.

Complexities in the relationship between infection and autoimmunity.

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The possible role of infections in driving autoimmune disease (AD) has long been debated. Many theories have emerged including release of hidden antigens, epitope spread, anti-idiotypes, molecular mimicry, the adjuvant effect, antigenic complementarity, or simply that AD could be a direct consequence of activation or subversion of the immune response by microbes. A number of issues are not adequately addressed by current theories, including why animal models of AD require adjuvants containing microbial peptides in addition to self tissue to induce disease, and why ADs occur more often in one sex than the other. Reviews published in the past 3 years have focused on the role of the innate immune response in driving AD and the possible role of persistent infections in altering immune responses. Overall, recent evidence suggests that microbes activating specific innate immune responses are critical, while antigenic cross-reactivity may perpetuate immune responses leading to chronic autoinflammatory disease.

DOI: 10.1007/s11882-013-0407-3

PMCID: PMC3926441

2175. Rheumatology (Oxford). 2014 Apr;53(4):665-70. doi: 10.1093/rheumatology/ket415. Epub 2013 Dec 17.

Efficacy and safety of canakinumab therapy in paediatric patients with cryopyrin-associated periodic syndrome: a single-centre, real-world experience.

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**OBJECTIVE:** The aim of this study was to determine the short- and long-term efficacy and safety of 8-weekly canakinumab therapy in children with cryopyrin-associated periodic syndromes (CAPS) in routine clinical practice.

**METHODS:** A single-centre observational study was performed. Patients were assessed every 8 weeks at a dedicated clinic. Standardized assessments were the 10-domains DAS for CAPS, acute phase reactants (APRs), physician's global assessment of disease activity, Child Health Assessment Questionnaire (CHAQ) and Child Health Questionnaire Parent Form 28 (CHQPF-28). The primary endpoint was clinical improvement, defined as a reduction of DAS score 8 weeks after commencing therapy. Secondary endpoints included sustained clinical improvement in APRs, relapses, CHAQ score and CHQPF-28 score.

**RESULTS:** Ten children with CAPS [eight Muckle-Wells syndrome (MWS), two chronic infantile cutaneous neurological articular (CINCA); median age 6.3 years] received 8-weekly canakinumab treatments at 2-8.7 mg/kg for a median of 21 months (range 12-31 months). Nine of 10 patients improved after the first dose: baseline median DAS of 7.5/20 decreased to 3.5/20 at 8 weeks ( $P = 0.04$ ). This clinical improvement was sustained at a median follow-up of 21 months (range 12-31 months). Children with CINCA required higher doses of canakinumab than those with MWS. CHAQ and CHQ scores indicated improvement in functioning and health-related quality of life (HRQoL). Treatment was well tolerated, with no injection site reactions and no serious infections.

**CONCLUSION:** Canakinumab, although costly, is a safe and effective treatment for CAPS in children, leading to sustained improvement in disease activity,

serological markers, functional ability and HRQoL.

DOI: 10.1093/rheumatology/ket415

PMID: 24352339 [Indexed for MEDLINE]

2176. J Ophthalmic Vis Res. 2013 Jul;8(3):291-3.

Behçet's Disease: Autoimmune or Autoinflammatory?

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PMCID: PMC3853784

PMID: 24349676

2177. Indian J Nephrol. 2013 Nov;23(6):469-70. doi: 10.4103/0971-4065.120355.

Is bullous skin lesion a risk factor for renal amyloidosis in patients with familial mediterranean fever?

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DOI: 10.4103/0971-4065.120355

PMCID: PMC3841526

PMID: 24339536

2178. Eur J Ophthalmol. 2014 Jul-Aug;24(4):593-8. doi: 10.5301/ejo.5000398. Epub 2013 Dec 5.

# Ophthalmic manifestations in familial Mediterranean fever: a case series of 6 patients.

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**PURPOSE:** To describe the ocular involvement of patients with familial Mediterranean fever (FMF) followed in a tertiary referral center.

**METHODS:** The data of 6 patients with FMF were retrospectively reviewed. Detailed ophthalmologic examinations, type of inflammation, course of the disease, number of recurrences, treatment regimens, complications, and comorbid ocular or systemic diseases were noted.

**RESULTS:** The mean age  $\pm$  SD at diagnosis was  $29.3 \pm 19.3$  (4-53) years. A total of 66.7% of the patients were male and 66.7% of the patients had bilateral disease. The anatomical distribution of the ophthalmic involvement was as follows: posterior uveitis in 2 (33.3%), anterior uveitis in 2 (33.3%), posterior scleritis in 1 (16.7%), and intermediate uveitis in 1 (16.7%) patient. The course was recurrent in 50% of the patients. Final visual acuities were favorable except in the patients with chronic course uveitis. Cystoid macula edema, epiretinal membrane, retinal ischemia, cataract, glaucoma, and band keratopathy were complications noted in the follow-up period. Both cataract and glaucoma patients (50%) needed a surgical intervention. In 33.3% of patients, Behçet disease was present as a concurrent disease. In patients with posterior uveitis and the patient with intermediate uveitis (50%), systemic immunosuppression was required.

**CONCLUSIONS:** There was a male and bilateral involvement predominance. The course of the inflammation was recurrent in half of the patients. Since ocular involvement in FMF is very rare, it should be considered as diagnosis of exclusion.

DOI: 10.5301/ejo.5000398

PMID: 24338581 [Indexed for MEDLINE]

[Self-medication to treat pain in attacks of familial Mediterranean fever: aiming to find a new approach to pain management].

[Article in German]

Giese A(1), Ornek A, Kurucay M, Kilic L, Şendur SN, Münker A, Puchstein C, Lainka E, Wittkowski H, Henning BF.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is an autoinflammatory disease characterized by bouts of fever and serositis. Morbidity caused by bouts as well as self-medication were assessed among patients of Turkish ancestry living in Germany (D) or Turkey (T) in order to evaluate current analgetic concepts from a patient's perspective.

**MATERIAL AND METHODS:** D and T were asked about the 3 months preceding the interview.

**RESULTS:** A total of 40 D and 40 T were included; 35/40 D and 40/40 T were on colchicine. In the last 3 months, 61.3 % had  $\geq 1$  bout and suffered from peritonitis (87.8 %), fever (61.2 %), myalgia (45 %), pleuritis (42.8 %), arthralgia (36.7 %), and cephalgia (32.6 %). Of the patients, 65.3 % were bedridden during bouts, 61.2 % sought the attention of a physician, 53.1 % were unable to work or attend school, and 38.8 % were hospitalized. The following drugs were taken: NSAIDs (45.6 %), NSAIDs and paracetamol (42.6 %), and combinations of NSAIDs with other analgesics. NSAIDs (58.6 %) and paracetamol (20.7 %) were considered the most potent substances.

**CONCLUSION:** FMF inflicts substantial morbidity. Patients most commonly rely on NSAIDs and paracetamol to relieve symptoms of FMF bouts.

DOI: 10.1007/s00482-013-1367-1

PMID: 24337427 [Indexed for MEDLINE]

2180. Arerugi. 2013 Aug;62(8):942-9.

[Autoinflammatory diseases reach adolescence].

[Article in Japanese]

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PMID: 24335420 [Indexed for MEDLINE]

2181. *Pediatr Int.* 2013 Dec;55(6):801-2. doi: 10.1111/ped.12225.

Development of Kawasaki disease in a patient with PFAPA.

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Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA) is one of the autoinflammatory diseases of unknown etiology characterized by regularly recurrent fever episodes with attacks lasting 3-6 days every 3-8 weeks associated with at least one of the three cardinal clinical signs: aphthous stomatitis, pharyngitis, and cervical adenitis. Kawasaki disease (KD) is an acute, self-limited systemic vasculitis that occurs predominantly in infants and young children. In most KD patients, i.v. immunoglobulin leads to a rapid amelioration of clinical symptoms and significantly decreases the risk of coronary artery aneurysms. Although the etiology of KD is still unknown, it was reported that innate immunity was activated in the patients. Described herein is a patient with PFAPA who developed KD. This is the first report of KD development in a PFAPA patient. The association between KD and PFAPA may represent a genetic predisposition to dysregulated innate immune response.

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DOI: 10.1111/ped.12225

2182. Am J Respir Cell Mol Biol. 2014 Jun;50(6):1021-30. doi: 10.1165/rcmb.2013-0234OC.

Interleukin-32 $\gamma$  suppresses allergic airway inflammation in mouse models of asthma.

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Asthma is a chronic airway inflammatory disease typically associated with T helper cell type 2 (Th2) cytokines. IL-32, first reported as an inducer of tumor necrosis factor (TNF)- $\alpha$ , is an inflammatory cytokine involved in various autoinflammatory diseases, viral infection, and cancer-related inflammation. However, the role of IL-32 $\gamma$  in asthma has not been clearly elucidated. In this study, the levels of IL-32 $\gamma$  in sputum from patients with asthma were measured by ELISA, and IL-32 $\gamma$  function was investigated in murine models of asthma with human IL-32 $\gamma$ -overexpressed transgenic (IL-32 $\gamma$  TG) mice. The therapeutic effect of recombinant IL-32 $\gamma$  (rIL-32 $\gamma$ ) on allergic inflammation was also evaluated through bronchoalveolar lavage fluid analysis and histopathologic examinations. Sputum IL-32 $\gamma$  levels from patients with asthma were lower than those from healthy control subjects. In an acute mouse model of asthma, IL-32 $\gamma$  TG mice exhibited significantly reduced airway inflammation compared with that in wild-type mice. The production of Th1 cytokines, such as TNF- $\alpha$  and IFN- $\gamma$ , and Th2 cytokines, such as IL-4, IL-5, and IL-13, was decreased in the lungs of IL-32 $\gamma$ TG mice. On the contrary, the expression of IL-10 and IL-10-producing CD11b(+) monocytic cells was significantly increased in the lungs of ovalbumin-sensitized IL-32 $\gamma$  TG mice. In addition, rIL-32 $\gamma$  treatment revealed a suppressive effect on the airway inflammation in a chronic mouse model of asthma. The results of this study suggest that IL-32 $\gamma$  may have a preventive role in the development of allergic airway inflammation and could be a potential novel therapeutic target for bronchial asthma.

DOI: 10.1165/rcmb.2013-0234OC

PMID: 24328857 [Indexed for MEDLINE]



2183. Ann Rheum Dis. 2015 Mar;74(3):603-10. doi: 10.1136/annrheumdis-2013-204361. Epub 2013 Dec 10.

Somatic NLRP3 mosaicism in Muckle-Wells syndrome. A genetic mechanism shared by different phenotypes of cryopyrin-associated periodic syndromes.

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: Familial cold autoinflammatory syndrome, Muckle-Wells syndrome (MWS), and chronic, infantile, neurological, cutaneous and articular (CINCA) syndrome are dominantly inherited autoinflammatory diseases associated to gain-of-function NLRP3 mutations and included in the cryopyrin-associated periodic syndromes (CAPS). A variable degree of somatic NLRP3 mosaicism has been detected in  $\approx 35\%$  of patients with CINCA. However, no data are currently available regarding the relevance of this mechanism in other CAPS phenotypes. **OBJECTIVE:** To evaluate somatic NLRP3 mosaicism as the disease-causing mechanism in patients with clinical CAPS phenotypes other than CINCA and NLRP3 mutation-negative. **METHODS:** NLRP3 analyses were performed by Sanger sequencing and by massively parallel sequencing. Apoptosis-associated Speck-like protein containing a CARD (ASC)-dependent nuclear factor kappa-light chain-enhancer of activated B cells (NF- $\kappa$ B) activation and transfection-induced THP-1 cell death assays determined

the functional consequences of the detected variants.

**RESULTS:** A variable degree (5.5-34.9%) of somatic NLRP3 mosaicism was detected in 12.5% of enrolled patients, all of them with a MWS phenotype. Six different missense variants, three novel (p.D303A, p.K355T and p.L411F), were identified. Bioinformatics and functional analyses confirmed that they were disease-causing, gain-of-function NLRP3 mutations. All patients treated with anti-interleukin1 drugs showed long-lasting positive responses.

**CONCLUSIONS:** We herein show somatic NLRP3 mosaicism underlying MWS, probably representing a shared genetic mechanism in CAPS not restricted to CINCA syndrome. The data here described allowed definitive diagnoses of these patients, which had serious implications for gaining access to anti-interleukin 1 treatments under legal indication and for genetic counselling. The detection of somatic mosaicism is difficult when using conventional methods. Potential candidates should benefit from the use of modern genetic tools.

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DOI: 10.1136/annrheumdis-2013-204361

PMID: 24326009 [Indexed for MEDLINE]

2184. Ren Fail. 2014 Apr;36(3):339-44. doi: 10.3109/0886022X.2013.865486. Epub 2013 Dec 9.

Do neutrophil gelatinase-associated lipocalin and interleukin-18 predict renal dysfunction in patients with familial Mediterranean fever and amyloidosis?

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**BACKGROUND:** The aim of this study was to evaluate whether neutrophil gelatinase-associated lipocalin (NGAL) and interleukin-18 (IL-18) predict renal dysfunction in patients with familial Mediterranean fever (FMF).

**METHODS:** This prospective study consisted of 102 patients with FMF in attack-free period, and 40 matched healthy controls. Of the patients, nine were diagnosed as amyloidosis. The patients were divided into two groups according to eGFR as below 120 mL per minute and above 120 mL per minute. Also, patients were divided into three groups according to the degree of urinary albumin excretion as normoalbuminuric, microalbuminuric, and macroalbuminuric. The serum levels of IL-18 (sIL-18) and NGAL (sNGAL), and urinary levels of IL-18 (uIL-18) and NGAL (uNGAL) were measured by using ELISA kits.

**RESULTS:** The levels of sIL-18, sNGAL, uIL-18, and uNGAL were detected significantly higher in FMF patients, particularly in patients with amyloidosis, when compared to controls. sNGAL, uIL-18, and uNGAL were significantly higher in patients with eGFR < 120 mL per minute than in patients with eGFR ≥ 120 mL per minute. sNGAL, uIL-18, and uNGAL were correlated significantly with urinary albumin excretion, additionally, were inverse correlated with eGFR. The most remarkable findings of this study are of the higher values of sIL-18, sNGAL, uIL-18, and uNGAL in both normoalbuminuric FMF patients and patients with eGFR ≥ 120 mL per minute.

**CONCLUSIONS:** The results of this study suggest that sIL-18, uIL-18, sNGAL, and uNGAL are reliable markers of early renal dysfunction in FMF patients, and may let us take measures from the early stage of renal involvement.

DOI: 10.3109/0886022X.2013.865486

PMID: 24320110 [Indexed for MEDLINE]

2185. Hematology Am Soc Hematol Educ Program. 2013;2013:605-11. doi: 10.1182/asheducation-2013.1.605.

Hemophagocytic lymphohistiocytosis: pathogenesis and treatment.

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Hemophagocytic lymphohistiocytosis (HLH) is not an independent disease but rather a life-threatening clinical syndrome that occurs in many underlying conditions and in all age groups. HLH is the consequence of a severe, uncontrolled hyperinflammatory reaction that in most cases is triggered by an infectious

agent. Persistent stimulation of lymphocytes and histiocytes results in hypercytokinemia, leading to the characteristic symptoms of HLH. Genetic defects in familial HLH and in immunodeficiency syndromes associated with albinism affect the transport, processing, and function of cytotoxic granules in natural killer cells and cytotoxic T lymphocytes. This leads to defective killing of target cells and a failure to contract the immune response. The defects are increasingly found also in adolescents and adults. Acquired HLH occurs in autoinflammatory and autoimmune diseases (macrophage activation syndrome) and in patients with iatrogenic immunosuppression or with malignancies, but also in otherwise healthy persons with infections. Treatment of HLH aims at suppressing hypercytokinemia and eliminating the activated and infected cells. In genetic HLH, hematopoietic stem cell transplantation (HSCT) is needed for the correction of the immune defect. Treatment modalities include immunosuppressive, immunomodulatory, and cytostatic drugs; T-cell antibodies; and anticytokine agents. Using immunochemotherapy, familial HLH, which had been invariably fatal, has become a curable disease with more than 50% survivors. Reduced intensity conditioning for HSCT, which is associated with less transplantation-related mortality, will further improve cure rates.

DOI: 10.1182/asheducation-2013.1.605

PMID: 24319239 [Indexed for MEDLINE]

2186. Mol Biol Rep. 2014 Jan;41(1):545-53. doi: 10.1007/s11033-013-2890-y. Epub 2013 Dec 7.

Defect of suppression of inflammasome-independent interleukin-8 secretion from SW982 synovial sarcoma cells by familial Mediterranean fever-derived pyrin mutations.

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Familial Mediterranean fever (FMF) is a recessive inherited autoinflammatory syndrome. Patients with FMF have symptoms such as recurrent fever and abdominal

pain, sometimes accompanied by arthralgia. Biopsy specimens have revealed substantial neutrophil infiltration into synovia. FMF patients have a mutation in the Mediterranean fever gene, encoding pyrin, which is known to regulate the inflammasome, a platform for processing interleukin (IL)-1 $\beta$ . FMF patients heterozygous for E148Q mutation, heterozygous for M694I mutation, or combined heterozygous for E148Q and M694I mutations, which were found to be major mutations in an FMF study group in Japan, suffer from arthritis, the severity of which is likely to be lower than in FMF patients with M694V mutations. Expression plasmids of wild-type (WT) pyrin and mutated pyrin, such as E148Q, M694I, M694V, and E148Q+M694I, were constructed, and SW982 synovial sarcoma cells were transfected with these expression plasmids. IL-8 and IL-6 were spontaneously secreted from the culture supernatant of SW982 cells without any stimulation, whereas IL-1 $\beta$  and TNF- $\alpha$  could not be detected even when stimulated with lipopolysaccharide. Notably, two inflammasome components, ASC and caspase-1, could not be detected in SW982 cells by Western blotting. IL-8 but not IL-6 secretion from SW982 cells was largely suppressed by WT pyrin, but less suppressed by mutated pyrin, which appeared to become weaker in the order of E148Q, M694I, E148Q+M694I, and M694V mutations. As for IL-8 and IL-6, similar results were obtained using stable THP-1 cells expressing the WT pyrin or mutated pyrans, such as M694V or E148Q, when stimulated by LPS. In addition, IL-8 secretion from mononuclear cells of FMF patients was significantly higher than that of healthy volunteers when incubated on a culture plate. Thus, our results suggest that IL-8 secretion from SW982 synovial sarcoma cells suppressed by pyrin independently of inflammasome is affected by pyrin mutations, which may reflect the activity in FMF arthritis.

DOI: 10.1007/s11033-013-2890-y

PMID: 24318677 [Indexed for MEDLINE]

2187. Transplant Proc. 2013;45(10):3502-4. doi: 10.1016/j.transproceed.2013.09.021.

Long-term outcome of renal transplantation in patients with familial Mediterranean fever amyloidosis: a single-center experience.

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**INTRODUCTION:** Familial Mediterranean fever (FMF) is an autosomal-recessive disorder, affecting multiple organs. The AA type of amyloidosis is most common and serious complication cause nephropathy and end-stage renal disease (ESRD). Renal transplantation (RTX) remains treatment of choice for ESRD. We aimed to investigate long-term results of RTX in patients with FMF amyloidosis.

**PATIENTS AND METHODS:** We compared the outcomes of 18 patients (12 men and 6 women) with FMF amyloidosis among 601 (2.9%) transplants with 200 control patients. Demographic data and gene analysis were evaluated.

**RESULTS:** In our study the 1-year graft and patient survivals were 94.44% and 100%, respectively. At 5 years after RTX, they were 94.73% and 88.88%, respectively, in the FMF group without difference from controls. Mean creatinine level at 1 and 5 years were  $1.43 \pm 0.54$  and  $1.73 \pm 0.89$ , respectively. The results of MEFV mutation analyses were: M694V/M694V homozygote in 1 patient, M694V/EQ148 in 3, M694V/V726A in 2, 680M-I/E148Q in 3, M694V/M680I in 5, R202Q/M680I in 2, and M694V/R202Q in 2. Recurrence was noticed in 1 patient with M694V/M680I. One patient died because of graft loss and cardiac complications with M694V/M680I gene analysis. Colchicine was reduced in 4 patients owing to side effects.

**CONCLUSION:** Long-term outcomes of transplantation in patients with amyloidosis secondary to FMF is similar to that in the general transplant population and maintenance colchicine, even after decreasing its dose, effectively prevents recurrence of amyloidosis in the allograft.

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DOI: 10.1016/j.transproceed.2013.09.021

PMID: 24314942 [Indexed for MEDLINE]

2188. Dermatol Online J. 2013 Nov 15;19(11):20405.

Recurrent migratory angioedema as cutaneous manifestation in a familiar case of TRAPS: dramatic response to Anakinra.

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**BACKGROUND:** Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) is a hereditary autoinflammatory syndrome characterized by recurrent episodes of fever and localized inflammation. Clinical presentation can be very variable in terms of duration of fever attacks, periodicity, and accompanying manifestations. One of the most characteristic symptoms is the occurrence of migrating skin rash with myalgia that is sustained by monocytic inflammation.

**OBSERVATIONS:** We herein present the case of a family suffering from TRAPS who had been misdiagnosed for a long period of time and whose main symptom was migrating angioedema. Skin biopsy from one of the patients documented a monocytic panniculitis. All the living patients responded dramatically to anakinra treatment.

**CONCLUSIONS:** The classic symptom of migratory angioedema with myalgia in TRAPS can be produced by monocytic panniculitis. This manifestation is so characteristic of TRAPS that its occurrence, even in the absence of other manifestations, should prompt genetic analysis. Our patient's condition responded promptly to anakinra treatment.

PMID: 24314780 [Indexed for MEDLINE]

2189. Front Immunol. 2013 Nov 20;4:396. doi: 10.3389/fimmu.2013.00396. eCollection 2013.

Ligands and receptors of the interleukin-1 family in immunity and disease.

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DOI: 10.3389/fimmu.2013.00396

PMCID: PMC3834610

PMID: 24312101



2190. Expert Rev Clin Immunol. 2014 Jan;10(1):7-18. doi: 10.1586/1744666X.2014.861325. Epub 2013 Nov 21.

Anakinra for cryopyrin-associated periodic syndrome.

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Cryopyrin-associated periodic syndrome (CAPS) is a very rare auto-inflammatory syndrome, which has recently served as a pure model of IL-1 $\beta$ -driven diseases. CAPS is caused by mutations into the NLRP3 gene that encodes cryopyrin, which serves as a receptor of the innate immunity that senses danger signals and pathogens. Constitutive activation of cryopyrin in CAPS leads to an excessive secretion of IL-1 $\beta$ . CAPS patients experience symptoms of systemic inflammation, intense fatigue and have poor quality of life. In the most severe forms, they may develop serious organ damage such as visual and hearing impairment, neurological deterioration and renal insufficiency. Anti-IL-1 drugs are effective in treating symptoms of almost all CAPS patients and have radically transformed their lives. We describe the history of the 'revival' of CAPS patients through anti-IL-1 treatments with a special focus on anakinra, the first drug used in cohorts with variable disease severity and number of patients.

DOI: 10.1586/1744666X.2014.861325

PMID: 24308832 [Indexed for MEDLINE]

2191. Clin Rheumatol. 2015 Jul;34(7):1293-301. doi: 10.1007/s10067-013-2443-8. Epub 2013 Dec 5.

Anakinra treatment in drug-resistant Behcet's disease: a case series.

Cantarini L(1), Vitale A, Scalini P, Dinarello CA, Rigante D, Franceschini R, Simonini G, Borsari G, Caso F, Lucherini OM, Frediani B, Bertoldi I, Punzi L,

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The study objective was to report treatment with an interleukin (IL)-1 receptor antagonist, anakinra, in patients with multiorgan Behcet's disease (BD). Comparison of clinical manifestations, previous treatments, markers of inflammation, concomitant medications, treatment regimen modifications, relapses, and adverse events before and during anakinra administration among patients with BD were evaluated. Nine BD patients (mean age  $34.55 \pm 16.30$  years) refractory to tumor necrosis factor blockers and standardized therapies are reported in our survey. Their mean age at disease onset was  $25 \pm 13.88$  years and their overall disease duration was  $9.55 \pm 5.33$  years. All patients were positive for the HLA-B51 allele. Within 1 or 2 weeks following the initiation of anakinra, eight out of nine patients promptly responded, and most of them were maintained on 100 mg of daily anakinra with low doses of prednisone. However, most patients experienced a relapse in one or more clinical manifestations over time (mean time to relapse  $29 \pm 21.65$  weeks), and only one patient remained completely under control on anakinra monotherapy. Despite a relapse in one or more disease manifestations, treatment was continued in most patients for a mean period of  $13.75 \pm 6.49$  months. No serious adverse events occurred. Eight out of nine refractory BD patients showed a prompt improvement after starting anakinra, supporting the concept that IL-1 plays a pathological role in this disease. Nevertheless, after several months, most patients experienced a relapse. It remains unclear whether increasing the dose of anakinra would have prevented the reoccurrence of disease activity.

DOI: 10.1007/s10067-013-2443-8

PMID: 24305945 [Indexed for MEDLINE]

2192. Eur Rev Med Pharmacol Sci. 2013 Nov;17(22):3024-30.

Thyroid autoimmunity in patients with Familial Mediterranean Fever: preliminary results.

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AIM: We investigated whether there was a significant increase in thyroid autoimmunity in patients with Familial Mediterranean fever (FMF).

PATIENTS AND METHODS: In total, 220 patients, consisting of 42 with FMF, 75 with rheumatoid arthritis (RA), and 103 healthy controls, were enrolled. Serum thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), and thyroid autoantibodies (anti-thyroid peroxidase and anti-thyroglobulin) were measured in all participants.

RESULTS: After adjustment for age, gender, and smoking status, statistically significant differences between serum levels of anti-thyroglobulin antibody, anti-thyroid peroxidase antibody, and fT3 were found between the groups (all  $p < 0.001$ ). Serum TSH level did not differ between the groups ( $p > 0.05$ ). The frequency of autoimmune thyroiditis in FMF group is higher than control group. However, this difference did not reached the level of statistical significance ( $p > 0.05$ ).

CONCLUSIONS: Although statistically not significant, thyroid autoimmunity was observed more frequently in patients with FMF than in healthy controls. Thyroid autoantibodies were significantly higher in patients with FMF. Studies with greater number of patients are required for evaluating the frequency of the autoimmune thyroiditis in patients with FMF.

PMID: 24302182 [Indexed for MEDLINE]

2193. Genet Mol Res. 2013 Oct 29;12(4):5152-9. doi: 10.4238/2013.October.29.9.

Spectrum of mutations in the familial Mediterranean fever gene (MEFV) in Turkish patients of the Central Anatolia region: a comparison of two mutation detection system.

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The purpose of this study was to determine the spectrum of the most common mutations in the familial Mediterranean fever gene (MEFV) in Turkish patients from the Central Anatolia region, by using two different methods for detecting FMF-associated mutations with different screening panels, and compare our results with other diagnostic molecular genetics centers. A total of 1579 patients were analyzed. Genomic DNA from 304 patients was tested for 6 common mutations located in exon 2 (E148Q), and exon 10 (M680I, M694V, M694I, V726A, R761H) by real-time PCR while 1275 patients were tested for 17 mutations located in exon 2 (E148Q), and exon10 [M680I (G/C), M680I (G/A), I692del, M694V, M694I, K695R, V726A, S675N, G678E, M680L, T681I, M694L, K695M, R717S, I720M, V722M] by pyrosequencing. The most frequent mutation was M694V, followed by M680I, E148Q, and V726A. Ten mutations in the panel were not detected in any patients. Finally, we compared our results with those of other centers in Turkey to contribute to the identified spectrum of Turkish MEFV mutations and we discuss which MEFV mutations are informative for evaluating an FMF patient.

DOI: 10.4238/2013.October.29.9

PMID: 24301775 [Indexed for MEDLINE]

2194. J Rheumatol. 2013 Dec;40(12):1948-50. doi: 10.3899/jrheum.131135.

The kidney in familial Mediterranean fever.

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Comment on

J Rheumatol. 2013 Dec;40(12):2083-7.

DOI: 10.3899/jrheum.131135

PMID: 24293619 [Indexed for MEDLINE]

2195. Ann Rheum Dis. 2014 Mar;73(3):483-91. doi: 10.1136/annrheumdis-2013-203844. Epub 2013 Nov 29.

Citrullination of autoantigens implicates NETosis in the induction of autoimmunity.

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Tolerance blocks the expression of autoantibodies, whereas autoimmunity promotes it. How tolerance breaks and autoantibody production begins thus are crucial questions for understanding and treatment of autoimmune diseases. Evidence implicates cell death and autoantigen modifications in the initiation of autoimmune reactions. One form of neutrophil cell death called NETosis deserves attention because it requires the post-translational modification of histones and results in the extracellular release of chromatin. NETosis received its name from NET, the acronym given to Neutrophil Extracellular Trap. The extracellular chromatin incorporates histones in which arginines have been converted to citrullines by peptidylarginine deiminase IV (PAD4). The deiminated chromatin may function to capture or 'trap' bacterial pathogens, thus generating an extracellular complex of deiminated histones and bacterial cell adjuvants. The complex of bacterial antigens and deiminated chromatin may be internalised by host phagocytes during acute inflammatory conditions, as arise during bacterial infections or chronic autoinflammatory disorders. The uptake and processing of deiminated chromatin together with bacterial adjuvants by phagocytes may induce the presentation of modified histone epitopes and co-stimulation, thus yielding a powerful stimulus to break tolerance. Autoantibodies to deiminated histones are prevalent in Felty's syndrome patients and are present in systemic lupus erythematosus (SLE) and patients with rheumatoid arthritis (RA). These observations clearly implicate histone deimination as an epigenetic mark that can act as an autoantibody stimulant.

DOI: 10.1136/annrheumdis-2013-203844

PMID: 24291655 [Indexed for MEDLINE]

2196. Mod Rheumatol. 2016;26(2):286-7. doi: 10.3109/14397595.2013.857801. Epub 2013 Dec 2.

The first case of adult-onset PFAPA syndrome in Japan.

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A 26-year-old woman presented with fever and pharyngitis. She previously experienced four periodic febrile episodes at 30- to 40-day intervals. We suspected periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome, and prescribed prednisolone, thereby her fever rapidly subsided. Her febrile episodes improved after daily cimetidine treatment. Genetic testing results of genomic DNA for periodic fever syndromes were negative, although she was heterozygous for p.Glu148Gln variation in MEFV, supporting the diagnosis of PFAPA syndrome.

DOI: 10.3109/14397595.2013.857801

PMID: 24289199 [Indexed for MEDLINE]

2197. Clin Kidney J. 2013 Dec;6(6):665-6. doi: 10.1093/ckj/sft129.

Colchicine-induced rhabdomyolysis following a concomitant use of clarithromycin in a haemodialysis patient with familial Mediterranean fever.

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DOI: 10.1093/ckj/sft129

PMCID: PMC4438377

PMID: 26120465

2198. Clin Kidney J. 2013 Dec;6(6):613-617. Epub 2013 Sep 24.

Secondary amyloidosis in a patient carrying mutations in the familial Mediterranean fever (FMF) and tumour necrosis factor receptor-1 syndrome (TRAPS) genes.

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Secondary amyloidosis (AA) is characterized by the extracellular tissue deposition of fibrils composed of fragments of an acute-phase reactant protein, serum amyloid A (SAA), due to chronic inflammatory diseases, infections and several neoplasms. AA amyloidosis may also complicate several hereditary diseases, where genetic factors play a pivotal role in the expression of amyloidosis. Familial Mediterranean fever (FMF) and tumour necrosis factor receptor-1 syndrome (TRAPS) are the most frequently involved. We describe a case of a 21-year-old Romanian woman who presented at the 35th week of gestation with acute abdominal pain, nausea and vomiting. The laboratory workup performed after delivery showed proteinuria in the nephrotic range and increased SAA protein.

Kidney amyloid deposits were detected and genetic testing for secondary amyloidosis was performed identifying two mutations, one involving the gene of FMF (MEFV), and the other involving the tumour necrosis factor receptor-1 gene (TNFRSF1A). To our knowledge, this is the first case in the literature where secondary amyloidosis develops in a patient carrying mutations involving the genes of both FMF and TRAPS.

DOI: 10.1093/ckj/sft112

PMCID: PMC3842151

PMID: 24286006

2199. Int J Rheumatol. 2013;2013:513782. doi: 10.1155/2013/513782. Epub 2013 Oct 24.

Monogenic autoinflammatory syndromes: state of the art on genetic, clinical, and therapeutic issues.

Caso F(1), Rigante D, Vitale A, Lucherini OM, Costa L, Atteno M, Compagnone A, Caso P, Frediani B, Galeazzi M, Punzi L, Cantarini L.

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Monogenic autoinflammatory syndromes (MAISs) are caused by innate immune system dysregulation leading to aberrant inflammasome activation and episodes of fever and involvement of skin, serous membranes, eyes, joints, gastrointestinal tract, and nervous system, predominantly with a childhood onset. To date, there are twelve known MAISs: familial Mediterranean fever, tumor necrosis factor receptor-associated periodic syndrome, familial cold urticaria syndrome, Muckle-Wells syndrome, CINCA syndrome, mevalonate kinase deficiency, NLRP12-associated autoinflammatory disorder, Blau syndrome, early-onset sarcoidosis, PAPA syndrome, Majeed syndrome, and deficiency of the interleukin-1 receptor antagonist. Each of these conditions may manifest itself with more or less severe inflammatory symptoms of variable duration and frequency, associated with findings of increased inflammatory parameters in laboratory investigation. The purpose of this paper is to describe the main genetic, clinical, and therapeutic aspects of MAISs and their most recent classification with the ultimate goal of increasing awareness of autoinflammation among various internal



medicine specialists.

DOI: 10.1155/2013/513782

PMCID: PMC3824558

PMID: 24282415

2200. J Pediatr Gastroenterol Nutr. 2013 Dec;57(6):817-21. doi: 10.1097/MPG.0b013e3182a9083b.

Colonic lymphoid nodular hyperplasia in childhood: causes of familial Mediterranean fever need extra attention.

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**OBJECTIVES:** The clinical importance and etiology of colonic lymphoid nodular hyperplasia (LNH) are not clear. It has been considered a response to some antigenic stimuli. Although food allergies, infections, inflammatory bowel diseases, and immunodeficiencies may be listed in the etiology of colonic LNH, the etiology has remained unclear in many cases. This study investigated the etiology of colonic LNH and its relation to familial Mediterranean fever (FMF) in children. FMF as an etiologic factor for colonic LNH has not been reported before in the literature.

**METHODS:** Medical files of patients who underwent colonoscopy between 2007 and 2011 were examined retrospectively. Demographic features, presenting symptoms, colonoscopy indications, colonoscopic findings, and final diagnoses of patients were evaluated. According to etiologies, patients with colonic LNH were divided into 2 groups: group A consisted of patients with FMF and group B consisted of diseases other than FMF.

**RESULTS:** A total of 311 patients were included in the study. Forty (12.6%) patients had isolated colonic LNH. In 23 (57.5%) patients, isolated LNH was observed in some colonic segments and total colonic LNH was noted in 17 (42.5%) patients. FMF was the etiologic factor in 6 (15%) patients. Thirty-four patients (85%) had etiologic factors other than FMF. We did not find any etiologic factor for LNH in 3.53% (11/311) of patients.

CONCLUSIONS: FMF may be an etiologic factor for colonic LNH in children besides food allergies, infections, inflammatory bowel diseases, and immunodeficiencies.

DOI: 10.1097/MPG.0b013e3182a9083b

PMID: 24280993 [Indexed for MEDLINE]

2201. Semin Immunol. 2013 Dec 15;25(6):469-84. doi: 10.1016/j.smim.2013.10.008. Epub 2013 Nov 23.

Treating inflammation by blocking interleukin-1 in humans.

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IL-1 is a master cytokine of local and systemic inflammation. With the availability of specific IL-1 targeting therapies, a broadening list of diseases has revealed the pathologic role of IL-1-mediated inflammation. Although IL-1, either IL-1 $\alpha$  or IL-1 $\beta$ , was administered to patients in order to improve bone marrow function or increase host immune responses to cancer, these patients experienced unacceptable toxicity with fever, anorexia, myalgias, arthralgias, fatigue, gastrointestinal upset and sleep disturbances; frank hypotension occurred. Thus it was not unexpected that specific pharmacological blockade of IL-1 activity in inflammatory diseases would be beneficial. Monotherapy blocking IL-1 activity in a broad spectrum of inflammatory syndromes results in a rapid and sustained reduction in disease severity. In common conditions such as heart failure and gout arthritis, IL-1 blockade can be effective therapy. Three IL-1 blockers have been approved: the IL-1 receptor antagonist, anakinra, blocks the IL-1 receptor and therefore reduces the activity of IL-1 $\alpha$  and IL-1 $\beta$ . A soluble decoy receptor, rilonacept, and a neutralizing monoclonal anti-interleukin-1 $\beta$  antibody, canakinumab, are also approved. A monoclonal antibody directed against the IL-1 receptor and a neutralizing anti-IL-1 $\alpha$  are in clinical trials. By specifically blocking IL-1, we have learned a great deal

about the role of this cytokine in inflammation but equally important, reducing IL-1 activity has lifted the burden of disease for many patients.

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DOI: 10.1016/j.smim.2013.10.008

PMCID: PMC3953875

PMID: 24275598 [Indexed for MEDLINE]

2202. J Clin Rheumatol. 2013 Dec;19(8):452-3. doi: 10.1097/RHU.0000000000000044.

Novel double heterozygous mutations in MEFV and NLRP3 genes in a patient with familial Mediterranean fever.

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DOI: 10.1097/RHU.0000000000000044

PMID: 24263150 [Indexed for MEDLINE]

2203. Immunol Allergy Clin North Am. 2014 Feb;34(1):169-79. doi: 10.1016/j.iac.2013.08.001. Epub 2013 Sep 26.

Hereditary disorders presenting with urticaria.

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The latest clinical guideline includes three major hereditary disorders presenting with urticaria: urticaria pigmentosa (mastocytosis), hereditary

angioedema, and cryopyrin-associated periodic syndromes. Understanding the genetic cause and the consequent pathogenesis of such disorders helps in providing disease-specific essential therapeutic regimens. In recent years, distinct hereditary autoinflammatory syndromes with cold urticaria have been reported: NLRP12-associated periodic syndrome, and PLCG2-associated antibody deficiency and immune dysregulation. Moreover, some familial cases with urticaria still remain to be genetically defined. Rapid progress in genetic analysis and further insights into undefined hereditary urticaria promise the development of novel therapeutics in the near future.

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DOI: 10.1016/j.iac.2013.08.001

PMID: 24262697 [Indexed for MEDLINE]

2204. Mod Rheumatol. 2014 Jan;24(1):212-6. doi: 10.3109/14397595.2013.852843.

Coexistence of familial Mediterranean fever and rheumatoid arthritis.

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Familial Mediterranean fever (FMF) is an autoinflammatory disorder characterized by recurrent febrile polyserositis and arthritis. Although accompanying seronegative spondyloarthropathy has been reported in FMF, coexistence with rheumatoid arthritis (RA) is very rare. This case report describes a Japanese female RA patient who presented with periodic fever. Genetic analysis revealed compound heterozygous mutations in exon 2 and 3 of the MEFV gene (E148Q/G304R/P369S/R408Q). The patient was successfully treated with colchicine with 3-year follow-up.

DOI: 10.3109/14397595.2013.852843

PMID: 24261781 [Indexed for MEDLINE]

2205. Mod Rheumatol. 2014 Jan;24(1):93-6. doi: 10.3109/14397595.2013.854049.

MEFV gene variations in patients with systemic lupus erythematosus.

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**OBJECTIVE:** The aim of this study was to investigate the frequency of familial Mediterranean fever (FMF)-associated MEFV gene variations in patients with systemic lupus erythematosus (SLE).

**METHODS:** The study group comprised 190 SLE patients and 101 healthy controls of Turkish origin with no clinical features of FMF. All individuals were genotyped for the four most common MEFV gene variations (M694V, M680I, V726A and E148Q) by PCR-restriction fragment length polymorphism analysis.

**RESULTS:** The frequency of carrying any of the four MEFV gene variations under study was 15 % in patients with SLE and 10 % in the healthy controls ( $p = 0.23$ ).

After the exclusion of the less penetrant E148Q variation, re-analysis for the three penetrant mutations revealed a significant association between exon 10 variations and pericarditis [ $p = 0.038$ , odds ratio (OR) 3.5, 95 % confidence interval (CI) 1.0-12.1], and pleural effusion ( $p = 0.043$ , OR 5.2, 95 % CI 0.8-30.9). No significant association was detected between the MEFV gene variations and a higher acute phase response.

**CONCLUSIONS:** The MEFV gene variations analyzed in our study do not seem to increase the overall susceptibility to SLE and do not have any strong association with its clinical manifestations. The possibility of a modest effect of penetrant exon 10 MEFV variants on the development of serosal effusions needs to be explored in a larger series of patients.

DOI: 10.3109/14397595.2013.854049

PMID: 24261764 [Indexed for MEDLINE]

2206. Pan Afr Med J. 2013 Aug 7;15:123. doi: 10.11604/pamj.2013.15.123.1434. eCollection 2013.

[Multiple myeloma occurring in a familial Mediterranean fever].

[Article in French]

Salem B(1), Afef F, Nadia B, Nabil A, Zouhir B, Maher B.

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DOI: 10.11604/pamj.2013.15.123.1434

PMCID: PMC3830460

PMID: 24255729 [Indexed for MEDLINE]

2207. Rheumatology (Oxford). 2014 May;53(5):958-60. doi: 10.1093/rheumatology/ket384. Epub 2013 Nov 19.

NOD2-associated autoinflammatory disease: an exploratory study of its pathogenesis.

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DOI: 10.1093/rheumatology/ket384

PMID: 24255163 [Indexed for MEDLINE]

2208. J R Army Med Corps. 2015 Mar;161(1):69-70. doi: 10.1136/jramc-2013-000185. Epub 2013 Nov 19.

An unusual cause of peritonitis in a deployed environment.

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Acute abdominal pain is a common presenting complaint to both primary and secondary care, and is a frequent cause of hospital admission among deployed personnel. Identification of generalised peritonism on abdominal examination is a classical indicator of intra-abdominal pathology that may warrant exploratory laparotomy. Negative findings at laparotomy should serve as a diagnostic prompt to consider other non-surgical mimics of an acute abdomen.

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DOI: 10.1136/jramc-2013-000185

PMID: 24254746 [Indexed for MEDLINE]

2209. Mod Rheumatol. 2015 Sep;25(5):806-9. doi: 10.3109/14397595.2013.844398. Epub 2015 Jul 29.

Pulmonary Necrotizing Granulomas in a patient with familial mediterranean fever.

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We herein report a case of familial Mediterranean fever (FMF) presenting with granulomatous lung lesions with neuronal apoptosis inhibitory protein (NAIP), MHC

class II transcription activator (CIITA), incompatibility locus protein from *Podospora anserina* (HET-E), and telomerase-associated protein (TP1) (NACHT) leucine-rich-repeat 1-positive inflammatory cell infiltrates. FMF is an autoinflammatory disorder characterized by recurrent and self-limited attacks of pyrexia, arthritis and erysipelas-like skin lesions. Lung disorders associated with FMF are extremely rare. This is the first report of an immunologically-confirmed case of pulmonary manifestations of this disease.

DOI: 10.3109/14397595.2013.844398

PMID: 24252001 [Indexed for MEDLINE]

2210. Mod Rheumatol. 2014 May;24(3):381-9. doi: 10.3109/14397595.2013.843755. Epub 2013 Oct 18.

Working the endless puzzle of hereditary autoinflammatory disorders.

Caso F(1), Cantarini L, Lucherini OM, Sfriso P, Fioretti M, Costa L, Vitale A, Atteno M, Galeazzi M, Muscari I, Magnotti F, Frediani B, Punzi L, Rigante D.

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Hereditary autoinflammatory disorders encompass manifold dysfunctions of innate immunity caused by mutations in genes coding for the main characters of the inflammatory scene: most of these conditions have an early onset, ranging from the first days of life to the first decades, and include hereditary periodic fevers, NLRP-related diseases, granulomatous and pyogenic syndromes, which are basically characterized by upturned inflammasome activity and overproduction of bioactive interleukin (IL)-1 $\beta$  and other proinflammatory cytokines. The discovery of a causative link between autoinflammation and IL-1 $\beta$  release has improved our understanding of the intimate mechanisms of innate immunity, and has likewise led to the identification of extraordinary treatments for many of these disorders.

DOI: 10.3109/14397595.2013.843755

PMID: 24251993 [Indexed for MEDLINE]



2211. Clin Genet. 2014 Dec;86(6):564-9. doi: 10.1111/cge.12323. Epub 2013 Dec 20.

Cluster of patients with Familial Mediterranean fever and heterozygous carriers of mutations in MEFV gene in the Czech Republic.

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Familial Mediterranean fever (FMF) is a well-described monogenic autosomal recessive disorder with highest occurrence in the Mediterranean region. In this article, we describe the experience of a center in the Czech Republic that follows four families with members bearing mutations in MEFV gene without provable ancestry from the Mediterranean region. We also discuss the clinical picture of the heterozygous variants that were present in our cohort. The typical clinical presentation in heterozygotes corresponds to data described in the international literature. The possibility of combination of mutations and/or polymorphisms in different genes and epigenetic or environmental influences on the clinical symptoms are taken into account.

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DOI: 10.1111/cge.12323

PMID: 24251727 [Indexed for MEDLINE]

2212. Nat Rev Rheumatol. 2014 Mar;10(3):135-47. doi: 10.1038/nrrheum.2013.174. Epub 2013 Nov 19.

A clinical guide to autoinflammatory diseases: familial Mediterranean fever and next-of-kin.

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Autoinflammatory diseases are associated with abnormal activation of the innate immune system, leading to clinical inflammation and high levels of acute-phase reactants. The first group to be identified was the periodic fever diseases, of which familial Mediterranean fever (FMF) is the most common. In FMF, genetic results are not always straightforward; thus, flowcharts to guide the physician in requesting mutation analyses and interpreting the findings are presented in this Review. The other periodic fever diseases, which include cryopyrin-associated periodic syndromes (CAPS), TNF receptor-associated periodic syndrome (TRAPS) and mevalonate kinase deficiency/hyperimmunoglobulin D syndrome (MKD/HIDS), have distinguishing features that should be sought for carefully during diagnosis. Among this group of diseases, increasing evidence exists for the efficacy of anti-IL-1 treatment, suggesting a major role of IL-1 in their pathogenesis. In the past decade, we have started to learn about the other rare autoinflammatory diseases in which fever is less pronounced. Among them are diseases manifesting with pyogenic lesions of the skin and bone; diseases associated with granulomatous lesions; diseases associated with psoriasis; and diseases associated with defects in the immunoproteasome. A better understanding of the pathogenesis of these autoinflammatory diseases has enabled us to provide targeted biologic treatment at least for some of these conditions.

DOI: 10.1038/nrrheum.2013.174

PMID: 24247370 [Indexed for MEDLINE]

2213. Immunol Lett. 2014 Jan-Feb;157(1-2):51-9. doi: 10.1016/j.imlet.2013.11.006. Epub 2013 Nov 12.

Epigallocatechin-3-gallate ameliorates both obesity and autoinflammatory arthritis aggravated by obesity by altering the balance among CD4<sup>+</sup> T-cell subsets.

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Epigallocatechin-3-gallate (EGCG) is the most biologically active catechin in green tea. EGCG has been shown to have therapeutic effects in autoinflammatory diseases and obesity. Obesity is currently regarded-partly-as an inflammatory condition because of the inflammatory cytokines and higher Th1 cell differentiation detected in obese animal models and human cohort studies. In this work, the effects of EGCG on diet-induced obesity (DIO) mice and obese collagen-induced arthritis (CIA) mice were investigated. EGCG reduced the body weight and fat infiltration in liver tissue while improving serum lipid profiles in DIO mice. EGCG also induced a higher Treg/Th17 cell ratio in CD4(+) T-cell differentiation by decreasing the ratio of STAT3/STAT5 expression in DIO mice. EGCG was also effective in obese CIA mice. Reducing Th17 cells and increasing regulatory T (Treg) cells by affecting the STAT protein ratio were important effects of EGCG that might result in improved arthritic scores and levels of several inflammatory indicators. Thus, EGCG has an anti-inflammatory effect by suppressing STAT3 proteins and Th17-cell differentiation. EGCG thus shows promise for treating autoimmune conditions related to STAT3 or Th17 cells, such as metabolic syndrome, inflammatory arthritis, and some neoplastic diseases.

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DOI: 10.1016/j.imlet.2013.11.006

PMID: 24239847 [Indexed for MEDLINE]

2214. Acta Orthop. 2013 Dec;84(6):585-92. doi: 10.3109/17453674.2013.854666. Epub 2013 Nov 18.

Toll-like receptors in human chondrocytes and osteoarthritic cartilage.

Sillat T(1), Barreto G, Clarijs P, Soininen A, Ainola M, Pajarinen J, Korhonen M, Konttinen YT, Sakalyte R, Hukkanen M, Ylinen P, Nordström DC.

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**BACKGROUND AND PURPOSE:** Degenerating cartilage releases potential danger signals that react with Toll-like receptor (TLR) type danger receptors. We investigated the presence and regulation of TLR1, TLR2, and TLR9 in human chondrocytes.

**METHODS:** We studied TLR1, TLR2, TLR4, and TLR9 mRNA (qRT-PCR) and receptor proteins (by immunostaining) in primary mature healthy chondrocytes, developing chondrocytes, and degenerated chondrocytes in osteoarthritis (OA) tissue sections of different OARSI grades. Effects of a danger signal and of a pro-inflammatory cytokine on TLRs were also studied.

**RESULTS:** In primary 2D-chondrocytes, TLR1 and TLR2 were strongly expressed. Stimulation of 2D and 3D chondrocytes with a TLR1/2-specific danger signal increased expression of TLR1 mRNA 1.3- to 1.8-fold, TLR2 mRNA 2.6- to 2.8-fold, and TNF- $\alpha$  mRNA 4.5- to 9-fold. On the other hand, TNF- $\alpha$  increased TLR1 mRNA expression 16-fold, TLR2 mRNA expression 143- to 201-fold, and TNF- $\alpha$  mRNA expression 131- to 265-fold. TLR4 and TLR9 mRNA expression was not upregulated. There was a correlation between worsening of OA and increased TLR immunostaining in the superficial and middle cartilage zones, while chondrocytes assumed a CD166(+) progenitor phenotype. Correspondingly, TLR expression was high soon after differentiation of mesenchymal stem cells to chondrocytes. With maturation, it declined (TLR2, TLR9).

**INTERPRETATION:** Mature chondrocytes express TLR1 and TLR2 and may react to cartilage matrix/chondrocyte-derived danger signals or degradation products. This leads to synthesis of pro-inflammatory cytokines, which stimulate further TLR and cytokine expression, establishing a vicious circle. This suggests that OA can act as an autoinflammatory disease and links the old mechanical wear-and-tear concept with modern biochemical views of OA. These findings suggest that the chondrocyte itself is the earliest and most important inflammatory cell in OA.

DOI: 10.3109/17453674.2013.854666

PMCID: PMC3851674

PMID: 24237425 [Indexed for MEDLINE]

2215. Bratisl Lek Listy. 2013;114(11):668.

Alterations in paraoxonase-1 activity.

Yalcinkaya E, Bagan B, Celik M, Yuksel UC.

Comment on

Bratisl Lek Listy. 2012;113(9):561-4.

PMID: 24236439 [Indexed for MEDLINE]

2216. Anadolu Kardiyol Derg. 2013 Sep;13(6):609.

Author's reply: To PMID 23531873.

Karakurt Arıtürk Ö.

Comment on

Anadolu Kardiyol Derg. 2013 Jun;13(4):357-62.

Anadolu Kardiyol Derg. 2013 Sep;13(6):608-9.

PMID: 24236304 [Indexed for MEDLINE]

2217. J Clin Immunol. 2014 Jan;34(1):104-13.

Clinical and genetic profile of children with periodic fever syndromes from a single medical center in South East Michigan.

Chandrakasan S, Chiwane S, Adams M, Fathalla BM.

**OBJECTIVE:** To report a cohort of children with periodic fever syndromes (PFS) from Southeast Michigan.

**METHODS:** A retrospective review of medical records for patients referred for periodic fever over 5 years.

**RESULTS:** Sixty-six patients including 21 FMF, 15 PFAPA, four TRAPS and one patient with combined HIDS and FMF were included. In addition, 25 patients were categorized as clinical PFS (cPFS) based on their clinical features however their genetic workup was either negative or inconclusive. Majority of the patients with

FMF were from Middle Eastern background (88 %), but positive family history was noted in only 55 % of cases. Mean age at diagnosis was 40.8 months with a mean delay in diagnosis of 24 months. Most common MEFV mutations were p.M694V and p.M694I. Four patients with TRAPS were from mixed European descent and age at onset of symptoms was 6, 12, 12, and 84 months respectively. TNFRSF1A sequence variants in the TRAPS patients included p.R121Q (R92Q) and p.C99G (C70G); one patient had a rare occurrence of a concurrent p.V726A/-MEFV mutation. One patient with HIDS and FMF presented with atypical overlapping PFS clinical manifestations and genetic evaluation showed a unique combination of p.I268T/p.V377I MVK mutations and p.E230K/-MEFV variant. All patients with PFAPA group were from mixed European descent, symptoms started at a mean age of 34.6 months with a mean delay in diagnosis of 23.3 months. Symptoms started during infancy in six patients. All patients fulfilled the diagnostic criteria for PFAPA. The mean age of onset of symptoms in cPFS group was 17.2 months. Empiric colchicine and glucocorticosteroids controlled flares in majority of patients with cPFS. No evidence of amyloidosis was found in this entire cohort of 66 patients after a mean of 29.2 months of follow-up.

CONCLUSION: PFS can present with atypical manifestations and should not be excluded based on a negative family history. Concomitant mutations in different autoinflammatory disorders genes can be present and possibly explain atypical manifestations. Various therapies may be considered even if genetic testing is inconclusive or negative.

DOI: 10.1007/s10875-013-9960-8

PMID: 24233262 [Indexed for MEDLINE]

2218. Rev Bras Reumatol. 2013 Aug;53(4):346-51.

Profile of paediatric rheumatology specialists and services in the state of São Paulo.

[Article in English, Portuguese]

Terreri MT, Campos LM, Okuda EM, Silva CA, Sacchetti SB, Marini R, Ferriani VP, Ventura MH, Fernandes T, Sato JO, Fernandes EC, Len C, Barbosa C, Lotito AP, Santos MC, Aikawa NE, Facó M, Piotto D, Bugni V, Kozu KT, Romanelli PR, Sallum AM, Febronio M, Fraga M, Magalhães CS.

**INTRODUCTION:** Paediatric rheumatology (PR) is an emerging specialty, practised by a limited number of specialists. Currently, there is neither a record of the profile of rheumatology patients being treated in Brazil nor data on the training of qualified rheumatology professionals in the country.

**OBJECTIVE:** To investigate the profile of PR specialists and services, as well as the characteristics of paediatric patients with rheumatic diseases, for estimating the current state of rheumatology in the state of São Paulo.

**PATIENTS AND METHODS:** In 2010, the scientific department of PR of the Paediatric Society of São Paulo administered a questionnaire that was answered by 24/31 accredited specialists in PR practising in state of São Paulo and by 8/21 institutions that provide PR care.

**RESULTS:** Most (91%) of the surveyed professionals practise in public institutions. Private clinics (28.6%) and public institutions (37.5%) reported not having access to nailfold capillaroscopy, and 50% of the private clinics reported not having access to acupuncture. The average duration of professional practise in PR was 9.4 years, and 67% of the physicians had attended postgraduate programmes. Seven (87.5%) public institutions perform teaching activities, in which new paediatric rheumatologists are trained, and five (62.5%) offer postgraduate programmes. Two-thirds of the surveyed specialists use immunosuppressants and biological agents classified as "restricted use" by the Health Secretariat. The disease most frequently reported was juvenile idiopathic arthritis (29.1-34.5%), followed by juvenile systemic lupus erythematosus (JSLE) (11.6-12.3%) and rheumatic fever (9.1-15.9%). The incidence of vasculitis (including Henoch-Schönlein purpura, Wegener's granulomatosis, and Takayasu's arteritis) and autoinflammatory syndromes was higher in public institutions compared to other institutions ( $P = 0.03$ ,  $P = 0.04$ ,  $P = 0.002$ , and  $P < 0.0001$ , respectively). Patients with JSLE had the highest mortality rate (68% of deaths), mainly due to infection.

**CONCLUSION:** The field of PR in the state of São Paulo has a significant number of specialists with postgraduate degrees who mostly practise at teaching institutions with infrastructures appropriate for the care of high-complexity patients.

PMID: 24217666 [Indexed for MEDLINE]

2219. Turk J Pediatr. 2013 May-Jun;55(3):315-8.

Diagnostic dilemma in autoinflammatory disease in two patients: does the name matter?

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The systemic autoinflammatory diseases are inflammatory disorders characterized by uncontrolled inflammation of the innate immune system. A common monogenic autoinflammatory disease is familial Mediterranean fever (FMF), associated with mutations in the MEFV gene. Another autoinflammatory disease group is cryopyrin-associated periodic syndromes (CAPS), which are characterized by urticarial rash and mutations of the gene NLRP. Systemic-onset juvenile idiopathic arthritis (sJIA) is classified as a multifactorial autoinflammatory disease. We report two cases of systemic autoinflammatory disease with homozygous E148Q mutation in the FMF gene. They had unusual features, such as urticarial rash, non-erysipeloid erythema, lymphadenopathy, and hepatosplenomegaly, and neurological findings in one. These patients met the "definition" criteria for FMF with two mutations in the MEFV gene. They fit the "description" criteria for CAPS with their fever, urticaria, and other clinical features. They also met the "classification" criteria for sJIA, with the fever, rash, arthritis, and accompanying systemic features.

PMID: 24217079 [Indexed for MEDLINE]

2220. Int J Pediatr Otorhinolaryngol. 2013 Dec;77(12):2040-3. doi: 10.1016/j.ijporl.2013.10.003. Epub 2013 Oct 24.

Determination of hearing levels in patients with Familial Mediterranean Fever.

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**OBJECTIVE:** Familial Mediterranean Fever is the most common congenital, periodic fever condition that affects over 100,000 people worldwide. In the literature, there is limited number of studies about hearing levels in children with Familial Mediterranean Fever. In the present study, we aimed to investigate hearing levels and cochlear functions by using Distortion product Otoacoustic Emission and High Frequency Audiometry (250-20,000 Hz) in pediatric patients with Familial Mediterranean Fever.

**METHODS:** The study included 62 children with Familial Mediterranean Fever and 27 healthy children with similar age and gender. After otoscopic examination, both groups underwent audiological evaluation including High Frequency Audiometry (250-20,000 Hz) and Distortion product Otoacoustic Emissions. The results obtained were assessed among groups. In addition, these results were compared regarding colchicine use, age at the onset of disease and duration of the diseases in the Familial Mediterranean Fever group.

**RESULTS:** Of the Familial Mediterranean Fever patients, 93.5% were on colchicine therapy and mean duration of colchicine use was  $19.9 \pm 13.9$  months. The mean age at diagnosis was  $6.57 \pm 2.86$  years (min-max: 2-14) and mean duration of disease was  $23 \pm 17$  months (min-max: 6-84). Pure tone audiometry values, and hearing levels between 9000 and 20,000 Hz were similar and within normal range in both groups. The Distortion product Otoacoustic Emissions responses at the frequencies of 1020, 2040, 3000, 4080 and 5040 Hz were similar for both groups.

**CONCLUSION:** To the best of our knowledge, this is the first study evaluating hearing levels at the frequencies of 18k Hz and 20k Hz in children with Familial Mediterranean Fever in the literature. In children with Familial Mediterranean Fever, Pure tone audiometry values, hearing values obtained at all frequencies from 250 to 20,000 Hz, and Distortion product Otoacoustic Emissions levels were within normal range. Furthermore, hearing levels were found to be similar to those in healthy children.

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DOI: 10.1016/j.ijporl.2013.10.003

PMID: 24210292 [Indexed for MEDLINE]

Monogenic diseases associated with intestinal inflammation: implications for the understanding of inflammatory bowel disease.

Uhlig HH.

Comment in

Gut. 2014 Aug;63(8):1367-8.

Gut. 2014 Nov;63(11):1831-2.

Gut. 2014 Jun;63(6):1031-2.

Inflammatory bowel disease (IBD), encompassing Crohn's disease and ulcerative colitis, has multifactorial aetiology with complex interactions between genetic and environmental factors. Over 150 genetic loci are associated with IBD. The genetic contribution of the majority of those loci towards explained heritability is low. Recent studies have reported an increasing spectrum of human monogenic diseases that can present with IBD-like intestinal inflammation. A substantial proportion of patients with those genetic defects present with very early onset of intestinal inflammation. The 40 monogenic defects with IBD-like pathology selected in this review can be grouped into defects in intestinal epithelial barrier and stress response, immunodeficiencies affecting granulocyte and phagocyte activity, hyper- and autoinflammatory disorders as well as defects with disturbed T and B lymphocyte selection and activation. In addition, there are defects in immune regulation affecting regulatory T cell activity and interleukin (IL)-10 signalling. Related to the variable penetrance of the IBD-like phenotype, there is a likely role for modifier genes and gene-environment interactions. Treatment options in this heterogeneous group of disorders range from anti-inflammatory and immunosuppressive therapy to blockade of tumour necrosis factor  $\alpha$  and IL-1 $\beta$ , surgery, haematopoietic stem cell transplantation or gene therapy. Understanding of prototypic monogenic 'orphan' diseases cannot only provide treatment options for the affected patients but also inform on immunological mechanisms and complement the functional understanding of the pathogenesis of IBD.

DOI: 10.1136/gutjnl-2012-303956

PMID: 24203055 [Indexed for MEDLINE]

2222. Front Immunol. 2013 Oct 31;4:351. doi: 10.3389/fimmu.2013.00351.

# The Central Role of Anti-IL-1 Blockade in the Treatment of Monogenic and Multi-Factorial Autoinflammatory Diseases.

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Inherited autoinflammatory diseases are secondary to mutations of proteins playing a pivotal role in the regulation of the innate immunity leading to seemingly unprovoked episodes of inflammation. The understanding of the molecular pathways involved in these disorders has shed new lights on the pattern of activation and maintenance of the inflammatory response and disclosed new molecular therapeutic targets. Cryopyrin-associated periodic syndrome (CAPS) represents the prototype of an autoinflammatory disease. The study of the pathophysiological consequence of mutations in the cryopyrin gene (NLRP3) allowed the identification of intracellular pathways responsible for the activation and secretion of the potent inflammatory cytokine interleukin-1 $\beta$  (IL-1 $\beta$ ). It became clear that several multi-factorial inflammatory conditions display a number of pathogenic and clinical similarities with inherited autoinflammatory diseases. The dramatic effect of interleukin-1 (IL-1) blockade in CAPS opened new perspectives for the treatment of other inherited and multi-factorial autoinflammatory disorders. Several IL-1 blockers are now available on the market. In this review we outline the more recent novelties in the treatment with different IL-1 blockers in inherited and multi-factorial autoinflammatory diseases.

DOI: 10.3389/fimmu.2013.00351

PMCID: PMC3814084

PMID: 24198817

2223. J Pharmacol Exp Ther. 2014 Jan;348(1):202-15. doi: 10.1124/jpet.113.205443. Epub 2013 Nov 5.

Detailed mechanistic analysis of gevokizumab, an allosteric anti-IL-1 $\beta$  antibody with differential receptor-modulating properties.

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Interleukin-1 $\beta$  (IL-1 $\beta$ ) is a proinflammatory cytokine that is implicated in many autoinflammatory disorders, but is also important in defense against pathogens. Thus, there is a need to safely and effectively modulate IL-1 $\beta$  activity to reduce pathology while maintaining function. Gevokizumab is a potent anti-IL-1 $\beta$  antibody being developed as a treatment for diseases in which IL-1 $\beta$  has been associated with pathogenesis. Previous data indicated that gevokizumab negatively modulates IL-1 $\beta$  signaling through an allosteric mechanism. Because IL-1 $\beta$  signaling is a complex, dynamic process involving multiple components, it is important to understand the kinetics of IL-1 $\beta$  signaling and the impact of gevokizumab on this process. In the present study, we measured the impact of gevokizumab on the IL-1 $\beta$  system using Schild analysis and surface plasmon resonance studies, both of which demonstrated that gevokizumab decreases the binding affinity of IL-1 $\beta$  for the IL-1 receptor type I (IL-1RI) signaling receptor, but not the IL-1 counter-regulatory decoy receptor (IL-1 receptor type II). Gevokizumab inhibits both the binding of IL-1 $\beta$  to IL-1RI and the subsequent recruitment of IL-1 accessory protein primarily by reducing the association rates of these interactions. Based on this information and recently published structural data, we propose that gevokizumab decreases the association rate for binding of IL-1 $\beta$  to its receptor by altering the electrostatic surface potential of IL-1 $\beta$ , thus reducing the contribution of electrostatic steering to the rapid association rate. These data indicate, therefore, that gevokizumab is a unique inhibitor of IL-1 $\beta$  signaling that may offer an alternative to current therapies for IL-1 $\beta$ -associated autoinflammatory diseases.

DOI: 10.1124/jpet.113.205443

PMCID: PMC6067399

PMID: 24194526 [Indexed for MEDLINE]

2224. ScientificWorldJournal. 2013 Sep 26;2013:745239. doi: 10.1155/2013/745239. eCollection 2013.

Targeting the B-cell pathway in lupus nephritis: current evidence and future perspectives.

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Nephritis represents a frequent, severe complication of systemic lupus erythematosus. Autoantibodies appear to be fundamental in the pathogenesis of lupus nephritis. Several hypotheses are currently experimentally tested to further elucidate the direct induction of inflammation through interaction of the pathological autoantibodies with intrinsic glomerular components and the triggering of a complement-driven autoinflammatory cascade. B-cells have, in the last decade, emerged as a promising new therapeutic target, as biological treatments successfully attempting B-cell depletion, inhibition of B-cell proliferation and differentiation, or modulation of B-cell function have become bioengineered. Clinical trials have so far proved controversial regarding the efficacy of these new agents. Thus, despite the short and long-term side effects associated with immunosuppressive treatment alternative emerging treatments are still regarded "rescue" regimens in refractory patients. In an effort to accurately evaluate the potential of these therapies in lupus nephritis, several issues have been raised mainly in terms of patient selection criteria and trial duration. This review aims to expand on the proposed pathophysiologic mechanisms implicating the B-cell pathway in the pathogenesis of lupus nephritis and summarize current knowledge obtained from clinical trials introducing these biologics in its treatment. Finally, it will elaborate on potential applications of currently available biologic agents and forthcoming treatment options.

DOI: 10.1155/2013/745239

PMCID: PMC3804405

PMID: 24191142 [Indexed for MEDLINE]

2225. Rheum Dis Clin North Am. 2013 Nov;39(4):735-49. doi: 10.1016/j.rdc.2013.05.002. Epub 2013 Aug 17.

Autoinflammatory bone diseases.

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Autoinflammatory bone disease is a new branch of autoinflammatory diseases caused by seemingly unprovoked activation of the innate immune system leading to an osseous inflammatory process. The inflammatory bone lesions in these disorders are characterized by chronic inflammation that is typically culture negative with no demonstrable organism on histopathology. The most common autoinflammatory bone diseases in childhood include chronic nonbacterial osteomyelitis (CNO), synovitis, acne, pustulosis, hyperostosis, osteitis syndrome, Majeed syndrome, deficiency of interleukin-1 receptor antagonist, and cherubism. In this article, the authors focus on CNO and summarize the distinct genetic autoinflammatory bone syndromes.

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DOI: 10.1016/j.rdc.2013.05.002

PMCID: PMC3823499

PMID: 24182852 [Indexed for MEDLINE]

2226. Rheum Dis Clin North Am. 2013 Nov;39(4):701-34. doi: 10.1016/j.rdc.2013.08.001. Epub 2013 Sep 21.

Monogenic autoinflammatory diseases: disorders of amplified danger sensing and cytokine dysregulation.

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The pathogenesis of monogenic autoinflammatory diseases converges on the presence of exaggerated immune responses that are triggered through activation of altered pattern recognition receptor (PRR) pathways and result in cytokine/chemokine

amplification loops and the inflammatory clinical phenotype seen in autoinflammatory patients. The PRR response can be triggered by accumulation of metabolites, by mutations in sensors leading to their constitutive overactivation, or by mutations in mediator cytokine pathways that lead to amplification and/or inability to downregulate an inflammatory response in hematopoietic and/or nonhematopoietic cells. The study of the pathogenesis of sterile inflammation in patients with autoinflammatory syndromes continues to uncover novel inflammatory pathways.

Published by Elsevier Inc.

DOI: 10.1016/j.rdc.2013.08.001

PMCID: PMC3888876

PMID: 24182851 [Indexed for MEDLINE]

2227. Genet Test Mol Biomarkers. 2014 Feb;18(2):73-6. doi: 10.1089/gtmb.2013.0293. Epub 2013 Nov 1.

Relationship between response to colchicine treatment and MDR1 polymorphism in familial Mediterranean fever patients.

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AIM: Investigate the relationship between MDR1 C3435T polymorphism and colchicine response in Familial Mediterranean fever (FMF) patients.

MATERIALS AND METHODS: Patients (n=50) who received colchicine regularly, were willing to participate in the study, and attended control visits were included in the study. MDR1 C3435T genotype was defined by the real-time polymerase chain reaction method. Patients were divided into three groups. Patients, who recovered from episodes with standard colchicine treatment, and had no attack in the last 1 year were accepted as complete; patients whose episode number and intensity were decreased with the ongoing standard treatment as partial; and patients whose episodes were not decreased despite the standard treatment as nonresponders.

RESULTS: MDR1 C and T allele frequencies of FMF patients with colchicine

responses of complete, partial, and nonresponders were C=0.75 and T=0.25; C=0.56 and T=0.44; and C=0.50 and T=0.50, respectively. When complete responding patients were compared with the partial responding patients, subjects with CT genotype had 6.18 times more increased risk than with CC genotype (OR=6.18; p=0.015). Poor response risk of subjects with the T allele was increased 2.45 times more when compared with the C allele (p=0.03).

CONCLUSION: MDR1 gene C3435T polymorphism enacts an important role on colchicine response in FMF; good response to colchicine treatment was related to the C allele, whereas poor response was related to the T allele in FMF.

DOI: 10.1089/gtmb.2013.0293

PMID: 24180297 [Indexed for MEDLINE]

2228. Clin Exp Rheumatol. 2013 May-Jun;31(3 Suppl 77):155-6. Epub 2013 Sep 9.

Rare NLRP12 variants associated with the NLRP12-autoinflammatory disorder phenotype: an Italian case series.

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Comment in

Clin Exp Rheumatol. 2014 Nov-Dec;32(6):994.

Clin Exp Rheumatol. 2014 Nov-Dec;32(6):993-4.

PMID: 24064030 [Indexed for MEDLINE]

2229. Clin Exp Rheumatol. 2013 May-Jun;31(3 Suppl 77):150-1. Epub 2013 Sep 9.

Interleukin-6 targeting therapy in familial Mediterranean fever.

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PMID: 24064027 [Indexed for MEDLINE]

2230. Clin Exp Rheumatol. 2013 May-Jun;31(3 Suppl 77):127-32. Epub 2013 Sep 9.

Is recurrent aseptic meningitis a manifestation of familial Mediterranean fever?  
A systematic review.

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**OBJECTIVES:** Familial Mediterranean fever (FMF) causes recurrent episodes of fever and painful serositis. It has been suggested that FMF can cause recurrent aseptic meningitis (RAM). Due to the rarity of both diseases, this claim cannot be assessed with epidemiological methods. We therefore decided to perform a systematic review of the literature to assess the number and validity of published case reports.

**METHODS:** Medline, Embase, Pascal, Web of Science and the proceedings of relevant conferences were searched. Two independent investigators selected reports asserting RAM in FMF patients, abstracted data and rated the strength of evidence with a custom tool designed to assess: (a) the diagnosis of FMF; (b) the diagnosis of RAM; and (c) the link between FMF and RAM. A causal link was supported by (i) evidence of inflammation and/or clinical FMF features during episodes of RAM; (ii) effectiveness of colchicine to prevent further bouts of meningitis; and (iii) the exclusion of other causes of RAM.

**RESULTS:** Among 944 retrieved references, 917 were rejected by title and abstract screening and 15 after full text review. The strength of evidence of 12 alleged cases of RAM due to FMF was assessed. FMF was unsupported in 4 cases and RAM in 3 further cases. Four of the 5 remaining cases did not provide adequate evidence to support a causal relationship between FMF and RAM.

CONCLUSIONS: The possibility of RAM due to FMF is poorly supported by a single fairly documented case report that does not, however, meet current diagnostic standards.

PMID: 24064026 [Indexed for MEDLINE]

2231. Clin Exp Rheumatol. 2013 May-Jun;31(3 Suppl 77):118-26. Epub 2013 Sep 9.

Inherited autoinflammatory diseases: a critical digest of the recent literature.

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In this paper we provide a critical digest of the recent literature on inherited autoinflammatory diseases. We reviewed all the articles published during the last 24 months on monogenic autoinflammatory diseases and selected the most relevant studies regarding the pathogenesis, clinical aspects and management of these conditions. In particular, we focused the attention on the more frequent conditions, familial Mediterranean fever (FMF), cryopyrin-associated periodic syndrome (CAPS) and TNF-receptor associated periodic syndrome (TRAPS).

PMID: 24064025 [Indexed for MEDLINE]

2232. Clin Exp Rheumatol. 2013 May-Jun;31(3 Suppl 77):103-7. Epub 2013 Sep 9.

Familial Mediterranean fever: a critical digest of the 2012-2013 literature.

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The year 2012-2013 has been a fertile one in the area of FMF inquiry. Recent studies have led to further insight into the possible mechanisms whereby pyrin mutations might cause the auto-inflammatory phenotype that is characteristic of FMF. Evidence-based guidelines for diagnosis of FMF, including the role of genetic testing, have become available. Risks for colchicine resistance have been partially defined, and a randomised, controlled trial showing efficacy of an interleukin-1 antagonist for treatment of colchicine-resistant or intolerant FMF patients was reported. In this review, we summarise these and other salient findings from the recent FMF literature, and discuss their significance for the clinician.

PMID: 24064023 [Indexed for MEDLINE]

2233. Clin Exp Rheumatol. 2013 May-Jun;31(3 Suppl 77):3-5. Epub 2013 Sep 9.

Taxonomy of auto-inflammatory diseases: time to consider changing some names.

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PMID: 24064011 [Indexed for MEDLINE]

2234. Mol Pharmacol. 2014 Jan;85(1):187-97. doi: 10.1124/mol.113.089573. Epub 2013 Oct 29.

Polarization of the innate immune response by prostaglandin E2: a puzzle of receptors and signals.

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Eicosanoids tailor the innate immune response by supporting local inflammation and exhibiting immunomodulatory properties. Prostaglandin (PG) E<sub>2</sub> is the most abundant eicosanoid in the inflammatory milieu due to the robust production elicited by pathogen-associated molecular patterns on cells of the innate immune system. The different functions and cell distribution of E prostanoid receptors explain the difficulty encountered thus far to delineate the actual role of PGE<sub>2</sub> in the immune response. The biosynthesis of eicosanoids includes as the first step the Ca<sup>2+</sup>- and kinase-dependent activation of the cytosolic phospholipase A<sub>2</sub>, which releases arachidonic acid from membrane phospholipids, and later events depending on the transcriptional regulation of the enzymes of the cyclooxygenase routes, where PGE<sub>2</sub> is the most relevant product. Acting in an autocrine/paracrine manner in macrophages, PGE<sub>2</sub> induces a regulatory phenotype including the expression of interleukin (IL)-10, sphingosine kinase 1, and the tumor necrosis factor family molecule LIGHT. PGE<sub>2</sub> also stabilizes the suppressive function of myeloid-derived suppressor cells, inhibits the release of IL-12 p70 by macrophages and dendritic cells, and may enhance the production of IL-23. PGE<sub>2</sub> is a central component of the inflammasome-dependent induction of the eicosanoid storm that leads to massive loss of intravascular fluid, increases the mortality rate associated with coinfection by *Candida* spp. and bacteria, and inhibits fungal phagocytosis. These effects have important consequences for the outcome of infections and the polarization of the immune response into the T helper cell types 2 and 17 and can be a clue to develop pharmacological tools to address infectious, autoimmune, and autoinflammatory diseases.

DOI: 10.1124/mol.113.089573

PMID: 24170779 [Indexed for MEDLINE]

2235. Ren Fail. 2014 Mar;36(2):306-8. doi: 10.3109/0886022X.2013.846863. Epub 2013 Oct 29.

Pregnancy outcome of five patients with renal amyloidosis regarding familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease affecting mainly patients of the Mediterranean basin and its major complication is the development of renal AA amyloidosis. On the other hand pregnancy with amyloidosis is not common; nevertheless, amyloidosis will complicate pregnancies also with the underlying disease and may cause terrible perinatal morbidities and mortalities. We report here the cases of five pregnant women and their pregnancy outcomes, who have been diagnosed with FMF complicated by renal amyloidosis. In the five cases, we observed that increased pregnancy complication such as small for gestational age, intrauterine growth restriction, preeclampsia and preterm birth.

DOI: 10.3109/0886022X.2013.846863

PMID: 24168456 [Indexed for MEDLINE]

2236. Curr Med Chem. 2014;21(3):261-9.

An update on autoinflammatory diseases.

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Autoinflammatory diseases are a group of clinical conditions other than autoimmune diseases, characterized by recurrent inflammatory episodes. From a pathogenetic point of view they are determined by a dysregulation of innate immunity, without involvement of specific immunity (auto reactive T cells and auto antibodies). Recently, the increased knowledge in the field of auto inflammation highlighted shared immune mechanisms in the pathogenesis of both classical monogenetic and multifactorial auto inflammatory diseases and a broad spectrum of chronic

age-related inflammatory pathologies. The current increase in the prevalence of chronic inflammatory diseases makes this subject of topical interest. In the light of these considerations, we propose an update of auto inflammatory diseases and a new interpretation of auto inflammation with both theoretical and clinical implications.

PMCID: PMC3905709

PMID: 24164192 [Indexed for MEDLINE]

2237. Pak J Biol Sci. 2012 Nov 1;15(21):1045-7.

Behçet's syndrome in Iranian Azari people.

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Behçet's Syndrome (BS) is a chronic recurrent multisystemic inflammatory disorder characterized by oral and genital ulcers, ocular inflammation. Behçet's syndrome has a complex genetic etiology. However, epidemiological studies recommend that genetic factors have a significant influence to its pathogenesis, alike to other autoinflammatory disorders. Epidemiological statistics, clinical records and HLA typing were studied in Iranian Azari patients with Behçet's syndrome. This investigation considered HLA associations with BS and HLA with certain clinical characteristics, age and sex in the (Tabriz) Iran which has an ethnically homogeneous population. HLA-A and HLA-B typing was performed in 290 BS patients, conforming to International Study Group criteria and in 300 blood donors, as controls. Patient records were retrospectively reviewed and patients reassessed clinically. HLA-B5, HLA-B35, HLA-51, HLA-B52 and HLA-CW4 presented significantly high frequencies in all patients. No other HLA type was associated. There was a significant HLA link with male sex in BS patients and Mean age (34 +/- 1.1) was determined. We present the frequency and correlation between Iranian Azari patients with Behçet's syndrome and particular HLA antigens. Ninety nine percent had mouth ulceration, 64% genital ulceration, 72% skin lesions and 52% ocular involvement. This study supports HLA-B5, HLA-B35, HLA-51, HLA-B52 and HLA-CW4 immunogenetic predisposition in an ethnically homogeneous (Iranian Azari)

population.

PMID: 24163948 [Indexed for MEDLINE]

2238. Klin Padiatr. 2013 Nov;225(6):325-30. doi: 10.1055/s-0033-1355372. Epub 2013 Oct 24.

Genotype-phenotype and genotype-origin correlations in children with mediterranean fever in Germany - an AID-net study.

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Familial Mediterranean fever (FMF) is the most inherited common autoinflammatory disease (AID) with mutations in the MEFV (MEditerraneanFeVer) gene. The Mor- and Pras-Score modified for children and C-reactive protein (CRP) were used to assess FMF disease severity in Germany. We evaluate the applicability of the 2 severity scores and the correlations between ethnic origin, phenotype, and genotype. Among 242 children (median 5 age at diagnosis), we detected 431 pyrin mutations and 22 different sequence variants, including one new mutation (p.Gly488Asp). The 5 most -frequent alterations were p.Met694Val (55.2%), p.Met680Ile (11.8%), p.Val726Ala (10%), p.Glu148Gln (7.9%) and p.Met694Ile (2.3%). The prevailing ancestries of 223 cases were Turkish (82.5%) and Lebanese (8.1%). Homozygous p.Met694Val substitution (30.2%) was associated with a more severe disease activity by Mor-Score, as well as with a higher mean CRP (74 mg/l) compared to patients with other mutations. Indeed, Mor- and Pras-Score were inconsistent with each other. A typical distribution of mutations in different ethnic populations was obvious, but not statistically verifiable due to the low number of cases. The homozygous p.Met694Val substitution was associated with a more severe disease activity in our German cohort. The common severity scores were inconsistent in -children.

DOI: 10.1055/s-0033-1355372

PMID: 24158885 [Indexed for MEDLINE]

2239. Case Rep Med. 2013;2013:740837. doi: 10.1155/2013/740837. Epub 2013 Jun 23.

Behçet's Disease, Associated Large Vessel Thrombosis, and Coexistent Thrombophilia: A Distinct Nosological Entity?

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Behçet's disease (BD) represents a multisystemic disorder that combines features of immune-mediated diseases and autoinflammatory disorders. Even though it is recognized that every type or size of vessel can be affected in this disease, there is an inability to describe a coherent model that sufficiently explains the predilection of certain patients with BD for manifesting severe large vessel thrombosis. The inconsistent epidemiologic data and the complex genetic background of BD, along with the controversy of multiple international studies regarding the coexistence of thrombophilia in patients with BD and large vessel thrombosis, make us think that a percentage of these patients may actually suffer from a distinct clinical entity. The stimulus for this concept arose from the clinical observation of three male patients who were admitted to our clinic due to extended vena cava thrombosis. On the occasion of those clinically and laboratory resembling cases, we performed a literature review concerning the epidemiology of BD, associated thrombosis, and coexistent thrombophilic factors, in order to present some evidence, which sustains our hypothesis that certain patients with large vessel thrombosis, who share features of BD and coexistent thrombophilia, should actually be further investigated for the possibility of suffering from a distinct nosological entity.

DOI: 10.1155/2013/740837

PMCID: PMC3789308

PMID: 24151511



2240. Clin Exp Rheumatol. 2014 Jan-Feb;32(1):123-5. Epub 2013 Oct 11.

A novel mutation in the CIAS1/NLRP3 gene associated with an unexpected phenotype of cryopyrin-associated periodic syndromes.

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**OBJECTIVES:** Cryopyrin-associated periodic syndromes (CAPS) comprise a spectrum of distinct, rare, autosomal dominant autoinflammatory disorders of increasing severity caused by NLRP3 gene mutations.

**METHODS:** We describe a 13-year-old female who presented, in the initial phase of the disease, recurrent episodes of high fever, pericarditis, arthralgia, arthritis of the knees, abdominal pain and marked increase in inflammatory markers. In the subsequent months she developed recurrent episodes of chest pain, skin rash and swelling of the subcutaneous tissue, without fever, and with spontaneous resolution.

**RESULTS:** Molecular analysis of the CIAS1 gene revealed the presence of the Q703K variant and also a c.1105C>A mutation in the heterozygous state, that predicts a L369M amino acid substitution. The latter variant has never been reported. The L369M mutation was predicted to significantly affect protein structure (scoring as 'dangerous' and 'deleterious') by the Variant Effect Predictor tool. Therapy with anakinra was started with rapid disappearance of clinical symptoms and normalization of CRP levels in 24 hours.

**CONCLUSIONS:** The rapid response to IL-1 inhibition suggests that the disease of this patient is driven by IL-1 and supports the conclusion that this novel mutation is pathogenic and may be associated with a new CAPS phenotype. The role played by the concomitant presence of the mutation Q703K remains to be clarified.

PMID: 24144430 [Indexed for MEDLINE]

2241. Clin Exp Rheumatol. 2013 May-Jun;31(3 Suppl 77):99-102. Epub 2013 Sep 9.

Macrophage activation syndrome as the initial manifestation of tumour necrosis factor receptor 1-associated periodic syndrome (TRAPS).

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An 11-year-old Turkish girl from a non-consanguineous family was suffering from joint pain, fever, hepatosplenomegaly, and respiratory insufficiency. Laboratory abnormalities were thrombocytopenia, elevated levels of serum transaminases, lactate dehydrogenase, and C-reactive protein (up to 193 mg / l), a hyperferritinaemia of 8030 ng/ml, and an increased sCD25. The tentative diagnosis of macrophage activation syndrome (MAS) was confirmed by the detection of a histiocytosis with haemophagocytosis in the bone marrow. Treatment with dexamethasone, cyclosporine A, and VP16 was successful. However, the diagnosis of MAS on the background of a systemic juvenile idiopathic arthritis was questionable because of recurrent, spontaneously remitting fever phases of 5 to 7 days duration without an obvious infectious aetiology. A positive family history of febrile episodes in three consecutive generations raised the suspicion of a dominantly inherited disease. Genetic studies revealed a likely pathogenetically relevant E56D/p.Glu85Asp mutation in exon 3 of the TNFRSF1A gene. Alterations of the MEFV gene, in contrast, were not found. To our knowledge, this is the first case of a macrophage activation syndrome as the initial manifestation of TRAPS. Similar case reports in patients with the far more common familial Mediterranean fever (FMF) have been published already.

PMID: 24064022 [Indexed for MEDLINE]

2242. Clin Exp Rheumatol. 2013 May-Jun;31(3 Suppl 77):68-70. Epub 2013 Sep 9.

The prevalence of atopy in patients with familial Mediterranean fever and Behçet's disease.

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**OBJECTIVES:** The purpose of this study is to investigate the prevalence of atopy in patients with Behçet's disease (BD) and familial Mediterranean fever (FMF).

**METHODS:** In this study, 42 BD patients, 40 FMF patients and 49 healthy subjects were included. The skin test was applied to the whole group. If one or more allergen response was equal or greater than histamine response, it was accepted as atopy. At the same time, total serum IgE and peripheral blood eosinophil levels were also determined.

**RESULTS:** The frequency of atopy was found to be 2.4% (1/42 patients) in BD patients and 5% (2/40 patients) in FMF patients and 16.3% (8/49 individuals) in healthy controls. In the BD patients, positivity to skin prick test was significantly lower than the control group ( $p=0.035$ ). The mean serum total IgE level and eosinophil counts did not differ between the three groups. In 33.3% of BD patients, 39.8% of FMF patients and 20.8% of controls levels of IgE lower than 20 kU/L were found (both groups  $p<0.05$ ).

**CONCLUSIONS:** The related conditions with Th-2 cell response such as atopy seem to be low frequency in BD and FMF patients.

PMID: 24064018 [Indexed for MEDLINE]

2243. Clin Exp Rheumatol. 2013 May-Jun;31(3 Suppl 77):64-7. Epub 2013 Sep 9.

Fever in Behçet's syndrome.

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**OBJECTIVES:** Fever is taken to be rare in Behçet's syndrome (BS) and when present it is usually considered to be associated with vascular disease. The aim of this study was to formally investigate the presence of fever as a clinical feature in BS patients and suitable controls.

**METHODS:** The study consisted of 2 parts. In the first part, 500 patients with BS, 94 with familial Mediterranean fever (FMF), 100 with ankylosing spondylitis (AS), and 72 with systemic lupus erythematosus (SLE) along with 100 healthy controls (HC) were surveyed with the help of a questionnaire for the history of periodic fever episodes. In the second part, body temperature was measured in 98 newly diagnosed BS patients having at least one active BS lesion and 61 HC. Temperature was measured 3 times and the highest reading was used in the analyses.

**RESULTS:** First part: history of fever episodes was present in 22% patients with BS, 87% with FMF, 33% with SLE and 8% with AS. None of the HC recalled a fever episode. Patients with BS who reported fever episodes were more likely to have major organ involvement such as vascular, neurological or joint involvement. Second part: The mean body temperature reading was similar (albeit statistically different) among patients with BS ( $36.72 \pm 0.42^{\circ}\text{C}$ ) compared to that of the HC ( $36.56 \pm 0.27^{\circ}\text{C}$ ) ( $p=0.004$ ).

**CONCLUSIONS:** In this study, 22% of patients with BS reported a history of fever episodes. As previously reported, fever attacks seemed to be associated strongly with vascular, neurological or joint involvement. The increase in temperature accompanying active BS lesions was modest even when the highest values were considered.

PMID: 24064017 [Indexed for MEDLINE]

2244. Clin Exp Rheumatol. 2013 May-Jun;31(3 Suppl 77):60-3. Epub 2013 Sep 9.

MEFV gene mutations and their clinical significance in Korean patients with adult-onset Still's disease.

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**OBJECTIVES:** Adult-onset Still's disease (AOSD) and periodic fever syndrome share clinical features in some aspects. Familial Mediterranean fever (MEFV) is a typical periodic fever syndrome and MEFV gene mutations may contribute to the

clinical features of certain rheumatic diseases. The purpose of this study is to research the incidence and clinical utility of MEFV gene mutations in Korean AOSD patients.

**METHODS:** The study included 96 AOSD patients and 165 healthy controls. In both groups, genomic DNA was isolated and genotyped using restriction fragment length polymorphism for 5 MEFV gene mutations (E148Q, P369S, M680I, V726A and M694V). In the AOSD patients, the clinical significance of MEFV mutation was assessed by the laboratory and clinical features.

**RESULTS:** M680I, V726A and M694V were not found in both groups. P369S was detected in 7 (7.3%) AOSD patients and 10 (6.1%) healthy controls. E148Q mutation was found in 77 (46.7%) among healthy controls with 6 QQ and 44 (45.8%) of AOSD patients with 5 QQ, respectively. The allele frequency of E148Q was 0.25 in AOSD patients, and that of P369S was 0.04. However, there was no significant difference in most clinical manifestations and laboratory findings by the presence and absence of E148Q mutation.

**CONCLUSIONS:** MEFV mutations including E148Q mutation were not associated with the development of AOSD patients in Korea. Although high incidence of E148Q mutation was found, E148Q mutation did not show major effect on the clinical features of AOSD. But we need to look for association with clinical response to certain treatments and long-term prognosis.

PMID: 24064016 [Indexed for MEDLINE]

2245. Clin Exp Rheumatol. 2013 May-Jun;31(3 Suppl 77):57-9. Epub 2013 Sep 9.

Vitamin B12 levels in familial Mediterranean fever patients treated with colchicine.

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**OBJECTIVES:** Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disease characterised by paroxysmal attacks of serosal inflammation. Colchicine is highly effective in preventing these attacks but it

may also disrupt the intestinal absorption of vitamin B12. We hypothesised that patients treated with colchicine for a prolonged period could develop deficiency of the vitamin.

**METHODS:** Ninety-five adult FMF patients on regular colchicine treatment for at least 2 years and age and sex-matched 90 healthy controls were enrolled and complete blood count with platelets, vitamin B12 and folic acid were measured in each person. We also investigated 15 adult FMF patients who were not yet on colchicine.

**RESULTS:** The mean vitamin B12 values were not significantly different between the groups (352.12 (SD=171.62) pg/mL vs. 360.96 (SD=146.53) pg/mL,  $p=0.71$ ), but there were significantly more vitamin B12 deficient cases among FMF patients (12 vs. 3;  $p=0.021$ ) and 3 out of these 12 had megaloblastic anaemia. None of the vitamin B12 deficient controls had anaemia. We could not identify any disorder which might have causative effect for the deficiency among this subgroup. The mean vitamin B12 value of 15 colchicine-naïve cases was not significantly different from patients on colchicine ( $p=0.356$ ).

**CONCLUSIONS:** We did not observe significant vitamin B12 deficiency among colchicine-treated FMF patients but some cases may be more prone to developing this potentially serious disorder.

PMID: 24064015 [Indexed for MEDLINE]

2246. Clin Exp Rheumatol. 2013 May-Jun;31(3 Suppl 77):41-6. Epub 2013 Sep 9.

Current trends in colchicine treatment in familial Mediterranean fever.

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**OBJECTIVES:** Since the publication of the first reports on the efficiency of colchicine in familial Mediterranean fever (FMF), very few randomised studies have investigated issues related to its long-term use. Thus, different approaches taken by physicians involved in FMF care, are exclusively empiric, emulative, and based on case-reports or case-series. Problems such as colchicine intolerance and

colchicine resistance have not been solved yet. This paper aims to evaluate trends in colchicine therapy among physicians taking care of FMF patients around the world.

**METHODS:** We conducted a survey by sending questionnaires to FMF research and treatment centres in Europe and Asia. Many issues (such as dosages, schedules, side effects, interactions, efficacy and toxicity monitoring, definition of colchicine intolerance, colchicine resistance and responsiveness, etc) have been investigated. When more than 70% of physicians responded giving similar answers to an item, the response was considered as a 'trend'. A comparison between answers of physicians from FMF-prevalent and non-prevalent countries was also made.

**RESULTS:** Thirty-five physicians from 11 countries filled the questionnaires, taking care of a total of more than 15000 FMF patients (pts). Different approaches were evident among the various physicians. Statistically significant different approaches between physicians from FMF-prevalent countries with respect to those from non-prevalent countries were found in items like colchicine during pregnancy, severity score and blood tests for disease monitoring. No consensus was found regarding the definition of colchicine resistance.

**CONCLUSIONS:** The current study demonstrated significant variations in the strategy of colchicine therapy for FMF around the world and re-emphasised the need for standardised definitions of colchicine resistance and colchicine intolerance.

PMID: 24064013 [Indexed for MEDLINE]

2247. Nat Struct Mol Biol. 2013 Nov;20(11):1304-9. doi: 10.1038/nsmb.2692. Epub 2013 Oct 20.

Mechanism of allosteric activation of SAMHD1 by dGTP.

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SAMHD1, a dNTP triphosphohydrolase (dNTPase), has a key role in human innate immunity. It inhibits infection of blood cells by retroviruses, including HIV, and prevents the development of the autoinflammatory Aicardi-Goutières syndrome (AGS). The inactive apo-SAMHD1 interconverts between monomers and dimers, and in the presence of dGTP the protein assembles into catalytically active tetramers. Here, we present the crystal structure of the human tetrameric SAMHD1-dGTP complex. The structure reveals an elegant allosteric mechanism of activation through dGTP-induced tetramerization of two inactive dimers. Binding of dGTP to four allosteric sites promotes tetramerization and induces a conformational change in the substrate-binding pocket to yield the catalytically active enzyme. Structure-based biochemical and cell-based biological assays confirmed the proposed mechanism. The SAMHD1 tetramer structure provides the basis for a mechanistic understanding of its function in HIV restriction and the pathogenesis of AGS.

DOI: 10.1038/nsmb.2692

PMCID: PMC3833828

PMID: 24141705 [Indexed for MEDLINE]

2248. Braz J Med Biol Res. 2013 Oct;46(10):904-8. doi: 10.1590/1414-431X20133178. Epub 2013 Sep 18.

Relationship between genetic mutation variations and acute-phase reactants in the attack-free period of children diagnosed with familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is a periodic autoinflammatory disease characterized by chronic inflammation. This study investigated the relationship between acute-phase reactants and gene mutations in attack-free periods of childhood FMF. Patients diagnosed with FMF were divided into four groups based on genetic features: no mutation, homozygous, heterozygous, and compound heterozygous. These groups were monitored for 2 years, and blood samples were collected every 6 months during attack-free periods. Erythrocyte sedimentation



rate, C-reactive protein, fibrinogen, and white blood cell count were measured. A disease severity score was determined for each patient. Mean values for erythrocyte sedimentation rate and fibrinogen were significantly different in the homozygous group. White blood cell count and C-reactive protein were similar between the groups. Disease severity score was higher in patients with the M694V mutation than in individuals without the mutation, as well as in those with other mutation groups. Periodic follow-up of patients with FMF MEFV mutations in subjects with acute-phase reactants may be useful in the prevention of morbidity.

DOI: 10.1590/1414-431X20133178

PMCID: PMC3854308

PMID: 24141617 [Indexed for MEDLINE]

2249. BMC Med Genet. 2013 Sep 3;14:88. doi: 10.1186/1471-2350-14-88.

Incidence of hereditary amyloidosis and autoinflammatory diseases in Sweden: endemic and imported diseases.

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**BACKGROUND:** Amyloidoses are a heterogeneous group of progressive diseases caused by tissue deposition of misfolded proteins. According to the International Classification of Diseases, hereditary amyloidosis is divided into neuropathic and non-neuropathic forms. In Sweden, neuropathic hereditary amyloidosis has been identified as familial amyloidotic polyneuropathy (FAP), a fatal disease that is treated by liver transplantation. The non-neuropathic form includes familial autoinflammatory diseases. As no incidence data on these hereditary diseases are available and as even diagnostic data on non-neuropathic forms are lacking we determined the incidence of these diseases and characterized non-neuropathic conditions.

**METHODS:** Patients were identified using data from the Swedish Hospital Discharge Register and from the Outpatient Register for 2001 through 2008. All patients discharged with hereditary amyloidosis diagnoses were included and standardized incidence rates were calculated.

**RESULTS:** Non-neuropathic disease was diagnosed in 210 patients, with an incidence of 2.83 per million. FAP was diagnosed in 221 patients, with an incidence of 2.02 per million. Two northern provinces that are home to 5% of the Swedish population accounted for 77% of FAP cases; the incidence in one of them, West Bothnia, was

100 times that in the rest of Sweden. Approximately 98% of non-neuropathic disease patients were immigrants, most of whom were from the Eastern Mediterranean area. Young Syrian descendants had the highest incidence rate, which was over 500-fold higher than that in individuals with Swedish parents. Even the early onset of these conditions identified them as familial autoinflammatory diseases.

CONCLUSIONS: FAP cases were highly concentrated in the two northernmost provinces. Non-neuropathic familial autoinflammatory diseases were of early-onset and immigrant origin most likely related to periodic fever syndromes.

Paradoxically, FAP has remained endemic, in spite of population movements within the country, while familial autoinflammatory diseases, with an incidence exceeding that of FAP, were brought into the country as a result of immigration mainly from the Eastern Mediterranean area.

DOI: 10.1186/1471-2350-14-88

PMCID: PMC3766062

PMID: 24138840 [Indexed for MEDLINE]

2250. *Pediatr Rheumatol Online J.* 2013 Oct 17;11(1):38. doi: 10.1186/1546-0096-11-38.

Elevated levels of CXCL10 in the Periodic Fever, Aphthous stomatitis, Pharyngitis and cervical Adenitis syndrome (PFAPA) during and between febrile episodes; an indication of a persistent activation of the innate immune system.

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BACKGROUND: The Periodic Fever, Aphthous stomatitis, Pharyngitis and cervical Adenitis syndrome (PFAPA) is the most common periodic fever syndrome in childhood. Clinically, PFAPA may resemble autoinflammatory diseases, but the etiology is not fully understood.

METHODS: We measured inflammatory proteins in plasma and hematologic parameters in children with PFAPA during and between febrile episodes, and in a control group with suspected bacterial pneumonia. In children with PFAPA, a first blood sample was taken within 24 hours of a febrile episode and a second sample between

episodes. In children with pneumonia, the first sample was taken shortly after admission and a second sample after full recovery.

**RESULTS:** A total of 22 children with PFAPA and 14 children with pneumonia were included. In children with PFAPA, levels of interleukin (IL) 6, CXCL10 and CCL4 were significantly increased during febrile episodes. The levels of IL-6 and CXCL10 were higher in children with PFAPA during febrile episodes than in children with pneumonia. The levels of CXCL10 remained higher in children with PFAPA between febrile episodes compared to children with pneumonia after recovery. Children with PFAPA had a relative eosinopenia and lymphocytopenia with reduced numbers of both CD4+ and CD8+ T cells during febrile episodes. This pattern was not observed in the children with pneumonia.

**CONCLUSIONS:** The results indicate an innate immune response as the initial step in PFAPA, and a subsequent adaptive response with activation and redistribution of T cells. Moreover, an activation of the innate immune system involving CXCL10 may persist between febrile episodes. CXCL10 may be a possibly clinical marker in children with PFAPA.

DOI: 10.1186/1546-0096-11-38

PMCID: PMC3852891

PMID: 24134207

2251. Orphanet J Rare Dis. 2013 Oct 16;8:162. doi: 10.1186/1750-1172-8-162.

The expanding spectrum of rare monogenic autoinflammatory diseases.

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Monogenic autoinflammatory diseases are a group of hereditary disorders characterized by a clinical and biological inflammatory syndrome in which there is little or no evidence of autoimmunity. The discovery of the first causative gene in 1997 was rapidly followed by the identification of many others from the same group. The mutated proteins can be directly or indirectly involved in the regulation of inflammation. The available literature includes numerous reviews,

which address the principle diseases, but we wanted to focus on the most recent rare syndromes. A comprehensive review is thus provided, including taxonomic, genetic, and epidemiological data, along with characteristics defining positive and differential diagnoses and treatment. We believe that this update will assist physicians in correctly naming their patient's illness. This is an essential step for the effective and targeted management of an orphan disease.

DOI: 10.1186/1750-1172-8-162

PMCID: PMC4016572

PMID: 24131530 [Indexed for MEDLINE]

2252. PLoS One. 2013 Oct 9;8(10):e75242. doi: 10.1371/journal.pone.0075242. eCollection 2013.

Thorough investigation of a canine autoinflammatory disease (AID) confirms one main risk locus and suggests a modifier locus for amyloidosis.

Olsson M(1), Tintle L, Kierczak M, Perloski M, Tonomura N, Lundquist A, Murén E, Fels M, Tengvall K, Pielberg G, Dufaure de Citres C, Dorso L, Abadie J, Hanson J, Thomas A, Leegwater P, Hedhammar Å, Lindblad-Toh K, Meadows JR.

Author information:

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Autoinflammatory disease (AID) manifests from the dysregulation of the innate immune system and is characterised by systemic and persistent inflammation. Clinical heterogeneity leads to patients presenting with one or a spectrum of phenotypic signs, leading to difficult diagnoses in the absence of a clear genetic cause. We used separate genome-wide SNP analyses to investigate five signs of AID (recurrent fever, arthritis, breed specific secondary dermatitis, otitis and systemic reactive amyloidosis) in a canine comparative model, the pure bred Chinese Shar-Pei. Analysis of 255 DNA samples revealed a shared locus on chromosome 13 spanning two peaks of association. A three-marker haplotype based on the most significant SNP ( $p < 2.6 \times 10^{-8}$ ) from each analysis showed that one haplotypic pair (H13-11) was present in the majority of AID individuals, implicating this as a shared risk factor for all phenotypes. We also noted that a genetic signature (F ST) distinguishing the phenotypic extremes of the breed

specific Chinese Shar-Pei thick and wrinkled skin, flanked the chromosome 13 AID locus; suggesting that breed development and differentiation has played a parallel role in the genetics of breed fitness. Intriguingly, a potential modifier locus for amyloidosis was revealed on chromosome 14, and an investigation of candidate genes from both this and the chromosome 13 regions revealed significant ( $p<0.05$ ) renal differential expression in four genes previously implicated in kidney or immune health (AOAH, ELMO1, HAS2 and IL6). These results illustrate that phenotypic heterogeneity need not be a reflection of genetic heterogeneity, and that genetic modifiers of disease could be masked if syndromes were not first considered as individual clinical signs and then as a sum of their component parts.

DOI: 10.1371/journal.pone.0075242

PMCID: PMC3793984

PMID: 24130694 [Indexed for MEDLINE]

2253. J Rheumatol. 2013 Dec;40(12):2083-7. doi: 10.3899/jrheum.130520. Epub 2013 Oct 15.

Familial Mediterranean fever (FMF) with proteinuria: clinical features, histology, predictors, and prognosis in a cohort of 25 patients.

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Comment in

J Rheumatol. 2013 Dec;40(12):1948-50.

OBJECTIVE: Reactive (AA) amyloidosis may complicate familial Mediterranean fever

(FMF), the prototype of autoinflammatory diseases. Thus, proteinuria in FMF is commonly viewed as resulting from amyloidosis, and kidney biopsy is deemed superfluous. However, nephropathy other than amyloidosis has been described in FMF, but its rate and distinctive characteristics are unknown. Our aim was to determine the rate and underlying pathology of FMF-related nonamyloidotic proteinuria and compare its clinical course, demographic, and genetic features to those of FMF-amyloid nephropathy.

**METHODS:** This study is a retrospective analysis of data from patients with FMF undergoing kidney biopsy for proteinuria above 0.5 g/24 h, over 10 years (2001-2011). Clinical, laboratory, genetic, and pathology data were abstracted from patient files. Biopsies were viewed by an experienced pathologist, as necessary.

**RESULTS:** Of the 25 patients referred for kidney biopsy, only 15 (60%) were diagnosed with amyloid kidney disease (AKD), and 10 were diagnosed with another nephropathy. The AKD and nonamyloid kidney disease (NAKD) groups were comparable on most variables, but showed distinct characteristics with regard to the degree of proteinuria ( $6.45 \pm 4.3$  g vs  $2.14 \pm 1.6$  g,  $p = 0.006$ ), rate of severe FMF (14 vs 5 patients,  $p = 0.022$ ), and rate of development of end stage renal disease (73.3% vs 20%,  $p = 0.015$ ), respectively.

**CONCLUSION:** NAKD is common in FMF and, compared to amyloidosis, it is featured with milder course and better prognosis. Contrary to common practice, it is highly recommended to obtain a kidney biopsy from patients with FMF and proteinuria more than 0.5 g/24 h.

DOI: 10.3899/jrheum.130520

PMID: 24128782 [Indexed for MEDLINE]

2254. Arthritis Care Res (Hoboken). 2014 May;66(5):765-72. doi: 10.1002/acr.22206.

Challenges in diagnosing Muckle-Wells syndrome: identifying two distinct phenotypes.

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**OBJECTIVE:** The diagnosis of Muckle-Wells syndrome (MWS) remains challenging due to the clinical heterogeneity and lack of diagnostic criteria. The aims of this study were to describe key elements of the diagnostic evaluation process in MWS and compare identified variables between patients diagnosed in childhood and adulthood.

**METHODS:** A cohort study of consecutive patients with a clinical and genetic diagnosis of MWS was conducted at 2 reference centers for autoinflammatory diseases. Demographic information, clinical presentation, access to care, and preclinical evaluation variables were captured. Presenting symptoms were compared between groups of patients diagnosed in childhood and adulthood. Prediction analysis explored variables associated with late diagnosis. Correspondence analysis identified clinical phenotypes.

**RESULTS:** A total of 34 MWS patients were included (16 males, 18 females) and median age at diagnosis was 31.5 years (range 0.5-75 years). Patients diagnosed during childhood reported musculoskeletal symptoms (62%), rash (62%), fever (54%), and abdominal pain (31%). Those diagnosed as adults described musculoskeletal symptoms (86%), rash (67%), hearing loss (52%), and fatigue (29%). Hearing loss was associated with late diagnosis, while access-to-care variables were not predictive. Correspondence analysis identified distinct clinical phenotypes as follows: an "inflammatory phenotype" (most commonly seen in patients diagnosed in childhood and characterized by relapsing fever and abdominal pain), an intermediate phenotype, and an "organ-disease" phenotype in patients diagnosed during adulthood and characterized by fatigue and hearing loss.

**CONCLUSION:** Distinct clinical phenotypes were identified in patients with MWS. These are closely related to age at diagnosis. The presence of these phenotypes has to be considered when developing diagnostic criteria for MWS.

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DOI: 10.1002/acr.22206

PMID: 24127202 [Indexed for MEDLINE]

2255. J Clin Immunol. 2013 Nov;33(8):1289-92.

Exome sequencing reveals RAG1 mutations in a child with autoimmunity and sterile chronic multifocal osteomyelitis evolving into disseminated granulomatous disease.

Reiff A, Bassuk AG, Church JA, Campbell E, Bing X, Ferguson PJ.

We describe a boy who developed autoinflammatory (chronic sterile multifocal osteomyelitis) and autoimmune (autoimmune cytopenias; vitiligo) phenotypes who subsequently developed disseminated granulomatous disease. Whole exome sequencing revealed homozygous RAG1 mutations thus expanding the spectrum of combined immunodeficiency with autoimmunity and granuloma that can occur with RAG deficiency.

DOI: 10.1007/s10875-013-9953-7

PMCID: PMC3873094

PMID: 24122031 [Indexed for MEDLINE]

2256. J Infect. 2014 Jan;68 Suppl 1:S83-93. doi: 10.1016/j.jinf.2013.09.017. Epub 2013 Oct 10.

Prolonged and recurrent fevers in children.

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Some children referred for prolonged fever are actually not having elevated temperatures; the approach here requires dissection of the history and correction of health misperceptions. Others have well-documented fevers associated with clinical, laboratory, or epidemiologic findings that should point to a specific diagnosis. "Fever-of-Unknown-Origin" (FUO) is the clinical scenario of daily fever for  $\geq 14$  days that defies explanation after a careful history, physical examination, and basic laboratory tests. The diagnostic approach requires a meticulous fever diary, serial clinical and laboratory evaluations, vigilance for the appearance of new signs and symptoms, and targeted investigations; the pace of the work-up is determined by the severity of the illness. Approximately half of children with FUO will have a self-limited illness and will never have a specific diagnosis made; the other half will ultimately be found to have, in order, infectious, inflammatory, or neoplastic conditions. Irregular,



intermittent, recurrent fevers in the well-appearing child are likely to be sequential viral illnesses. Monogenic autoinflammatory diseases should be considered in those who do not fit the picture of recurrent infections and who do not have hallmarks of immune deficiency. Stereotypical febrile illnesses that recur with clockwork periodicity should raise the possibilities of cyclic neutropenia, if the cycle is approximately 21 days, or periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome, the most common periodic fever in childhood.

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DOI: 10.1016/j.jinf.2013.09.017

PMID: 24120354 [Indexed for MEDLINE]

2257. Br J Dermatol. 2014 Jan;170(1):59-65. doi: 10.1111/bjd.12631.

Bimodal immune activation in psoriasis.

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Comment in

Br J Dermatol. 2014 Jan;170(1):7-8.

Psoriasis is an immune-regulated skin disease with various clinical subtypes and disease activities. The majority of patients present with predominantly stable plaques. At the onset of new lesions, plaque-type psoriasis frequently demonstrates pin-sized and highly inflammatory papules sometimes with an inflammatory border. The histopathology of initial psoriasis differs from stable plaque-type psoriasis. Early lesions demonstrate innate immune cells with neutrophils, degranulating mast cells and macrophages. These are followed by interleukin (IL)-1-dependent T helper (Th)17 cells, finally resulting in the Th1-dominated immunopathology of stable plaque-type psoriasis, where mononuclear cells predominate with interspersed neutrophilic (Munro) microabscesses. These features suggest a bimodal immune pathway where alternate activation of either

innate (autoinflammatory) or adaptive (autoimmune) immunity predominates. Neutrophilic infiltrations appear during early psoriasis with Munro abscesses. They are time limited and occur periodically, clinically best seen in linear nail pitting. These features strongly suggest a critical role for an IL-1-Th17-dominated autoinflammation in the initiation of psoriasis, followed by a Th1-dominated late-phase reaction. The concept of bimodal immune activation helps to explain results from therapeutic interventions that are variable and previously only partly understood.

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DOI: 10.1111/bjd.12631

PMID: 24117368 [Indexed for MEDLINE]

2258. Eur J Clin Invest. 2013 Dec;43(12):1314-27. doi: 10.1111/eci.12170. Epub 2013 Oct 14.

Familial mediterranean fever: a fascinating model of inherited autoinflammatory disorder.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is a rare inherited autosomal recessive autoinflammatory disorder characterized by recurrent and self-limited episodes of fever and painful serositis, lasting 1-3 days. FMF occurs almost exclusively among ethnic groups of the Mediterranean basin, although cases have also been found in Japan and Korean populations. Diagnosis is based on clinical features, response to colchicine and genetic analysis. Novel drugs are emerging, allowing better management of colchicine-resistant/colchicine-intolerant patients. This review aims to attract the attention of the readers on differential diagnosis and management of patients with FMF.

**METHODS:** The current state-of-the-art on FMF is outlined, with respect to epidemiological, genetic, pathophysiological and therapeutic characteristics, based on critical analysis of solid scientific literature.

RESULTS: FMF is more frequent than it was thought before. The phenotypic expression of M694V is more severe than that of V726A. Patients with M694V/M694V homozygosity are exposed to a higher risk of developing renal amyloidosis, arthritis, dermatologic and oral lesions, higher fever and more frequent painful attacks. Life-long therapy with colchicine (1·0-2·4 mg/day) is effective and safe to prevent recurrent attacks and renal amyloidosis and to reverse proteinuria. In nonresponder patients, alternative novel approaches include interleukin-1 receptor antagonist anakinra and the interleukin-1 decoy receptor rilonacept.

CONCLUSIONS: The prognosis of FMF is normal if AA amyloidosis is prevented. Colchicine remains the first-line therapy to treat pain and prevent amyloidosis. A follow-up should include clinical evaluation, therapeutic adjustments, measurement of serum amyloid A and proteinuria.

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Published by John Wiley & Sons Ltd.

DOI: 10.1111/eci.12170

PMID: 24117178 [Indexed for MEDLINE]

2259. *Pediatr Int.* 2013 Dec;55(6):671-4. doi: 10.1111/ped.12224.

Primary immunodeficiency in Japan; epidemiology, diagnosis, and pathogenesis.

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Primary immunodeficiency (PID) constitutes a large group of diseases, including almost 180 hereditary disorders. The patients show susceptibility to various infections due to congenital defects of the immune system. It is also known that PID patients suffer from non-infectious complications, including autoimmune diseases and malignant disorders. During the last 20 years the number of known PID has increased considerably. New PID conferring a specific predisposition to infections with one or a few pathogens have been described. Disorders of innate immunity and various autoinflammatory disorders were included in new categories. In contrast, the incidence, clinical manifestations, and genetic factors of PID

seem to be different among countries or races. The clinical manifestations can differ depending on the hygiene conditions, health-care environment, and vaccination policy, and so on. A nationwide survey on PID patients in Japan provided a lot of information regarding these issues, and it uncovered a previously unknown complication of PID, endocrine disorders. In this review, the data concerning epidemiology and clinical characteristics of PID in Japan obtained in the nationwide questionnaire survey, and the results of studies on the clinical and genetic characteristics of Japanese patients with Mendelian susceptibility to mycobacterial disease and interleukin-1 receptor-associated kinase 4 deficiency are presented in the light of their pathogenesis and pathophysiology.

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DOI: 10.1111/ped.12224

PMID: 24112462 [Indexed for MEDLINE]

2260. Int J Rheumatol. 2013;2013:498581. doi: 10.1155/2013/498581. Epub 2013 Sep 9.

Anti-CCP Antibodies Are Not Associated with Familial Mediterranean Fever in Childhood.

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**Objective.** Anticyclic citrullinated peptide antibodies (anti-CCP) testing is useful in the diagnosis of rheumatoid arthritis (RA) with high specificity. Arthritis is a very common clinical manifestation in children with familial Mediterranean fever (FMF). The aim of the study was to show the presence of anti-CCP antibodies in child individuals diagnosed with FMF. **Material and Methods.** The study groups comprised one hundred and twenty-six patients (126) diagnosed with FMF (female/male (n): 66/60) and 50 healthy controls (female/male (n): 25/25). Clinical and laboratory assessments of the FMF patients were performed during attack-free periods. Erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP), fibrinogen, and anti-CCP antibody levels were measured.

Results. Anti-CCP was negative in healthy controls and also in all FMF patients. There was not a significant difference in anti-CCP between the patient and the control groups. Our study has shown that anti-CCP was correlated moderately with age ( $r_s = 0.271$ ;  $P = 0.0020$ ), duration of illness ( $r_s = 0.331$ ;  $P < 0.0001$ ), and colchicine therapy ( $r_s = 0.259$ ;  $P = 0.004$ ). Conclusion. Our data show that anti-CCP antibodies are not associated with FMF. Anti-CCP does not have a priority for identifying FMF arthritis from the other inflammatory arthritis.

DOI: 10.1155/2013/498581

PMCID: PMC3782833

PMID: 24106502

2261. Inflamm Bowel Dis. 2014 Jan;20(1):213-27. doi: 10.1097/01.MIB.0000436959.62286.f9.

Cutaneous manifestations in patients with inflammatory bowel diseases: pathophysiology, clinical features, and therapy.

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The skin is one of the most common extraintestinal organ system affected in patients with inflammatory bowel disease (IBD), including both Crohn's disease and ulcerative colitis. The skin manifestations associated with IBD are polymorphic and can be classified into 4 categories according to their pathophysiology: (1) specific, (2) reactive, (3) associated, and (4) induced by IBD treatment. Cutaneous manifestations are regarded as specific if they share with IBD the same granulomatous histopathological pattern: perianal or metastatic

Crohn's disease (commonly presenting with abscesses, fistulas or hidradenitis suppurativa-like features) is the prototype of this setting. Reactive cutaneous manifestations are different from IBD in the histopathology but have close physiopathological links: pyoderma gangrenosum, a neutrophil-mediated autoinflammatory skin disease typically manifesting as painful ulcers, is the paradigm of this group. Among the cutaneous diseases associated with IBD, the most commonly seen are erythema nodosum, a form of panniculitis most commonly involving bilateral pretibial areas, and psoriasis, a T helper 1/T helper 17-mediated erythematous squamous inflammatory disease. Finally, the number of cutaneous adverse reactions because of IBD therapies is progressively increasing. The most frequent drug-induced cutaneous manifestations are psoriasis-like, eczema-like, and lichenoid eruptions, as well as cutaneous lupus erythematosus for biologics, and nonmelanoma skin cancer, mainly basal cell and squamous cell carcinomas for thiopurines.

DOI: 10.1097/01.MIB.0000436959.62286.f9

PMID: 24105394 [Indexed for MEDLINE]

2262. Can J Vet Res. 2013 Jul;77(3):183-90.

Program of vaccination and antibiotic treatment to control polyserositis caused by *Haemophilus parasuis* under field conditions.

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The present study investigated the effects of vaccinating sows and piglets or piglets alone against *Haemophilus parasuis* on the prevalence of *H. parasuis* in nasal swabs, on the humoral and cellular immune responses, and on the production parameters of piglets at 3 Korean farms with a clinical history of polyserositis caused by *H. parasuis*. Piglets born to vaccinated or non-vaccinated sows were subdivided into 3 groups: vaccinated sows and vaccinated pigs (VS-VP), non-vaccinated sows and vaccinated pigs (NVS-VP), and non-vaccinated sows and non-vaccinated pigs (NVS-NVP). The proportion of piglets with positive nasal swabs was significantly lower ( $P < 0.05$ ) in the vaccinated animals (VS-VP and

NVS-VP groups) than in the non-vaccinated animals (NVS-NVP group) at 35 and 60 d of age at the 3 farms. The overall growth performance (from 7 to 60 d of age) of the vaccinated piglets was significantly better ( $P < 0.05$ ) than that of the non-vaccinated piglets at the 3 farms. Piglets in the VS-VP group had significantly higher levels ( $P < 0.05$ ) of *H. parasuis*-specific IgG antibodies, lymphocyte proliferation, and interferon- $\gamma$ -secreting cells than piglets in the NVS-VP and NVS-NVP groups on days 1, 7, 21, 35, and 60 after birth at the 3 farms.

Publisher: Ce projet visait à étudier les effets de la vaccination contre *Haemophilus parasuis* des truies et des porcelets ou des porcelets uniquement sur la prévalence d'*H. parasuis* dans des écouvillons nasaux, sur les réponses immunitaires humorale et cellulaire, et sur les paramètres de production des porcelets dans trois fermes coréennes avec une histoire de cas cliniques de polysérosites causés par *H. parasuis*. Les porcelets nés de truies vaccinées et non-vaccinées ont été répartis en trois groupes : truies vaccinées et porcelets vaccinés (VS-VP), truies non-vaccinées et porcelets vaccinés (NVS-VP), et truies non-vaccinées et porcelets non-vaccinés (NVS-NVP). La proportion de porcelets positifs pour *H. parasuis* à partir de l'écouvillon nasal était significativement plus faible ( $P < 0,05$ ) chez les animaux vaccinés (groupes VS-VP et NVS-VP) que chez les animaux non-vaccinés (groupe NVS-NVP) à 35 et 60 jours d'âge sur les trois fermes. Sur les 3 fermes, les performances de croissance globales (de 7 à 60 jours d'âge) des porcelets vaccinés étaient significativement meilleures ( $P < 0,05$ ) que celles des porcelets non-vaccinés. Sur les trois fermes, les porcelets du groupe VS-VP avaient des niveaux significativement plus élevés ( $P < 0,05$ ) d'anticorps IgG spécifiques contre *H. parasuis*, de prolifération lymphocytaire, et de cellules sécrétant de l'interféron- $\gamma$  que les porcelets dans les groupes NVS-VP et NVS-NVP aux jours 1, 7, 21, 35, et 60 après la naissance. (Traduit par Docteur Serge Messier).

PMCID: PMC3700443

PMID: 24101794 [Indexed for MEDLINE]

2263. J Immunol. 2013 Nov 15;191(10):5036-43. doi: 10.4049/jimmunol.1301132. Epub 2013 Oct 7.

SOCS3 deletion in T lymphocytes suppresses development of chronic ocular inflammation via upregulation of CTLA-4 and expansion of regulatory T cells.

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Suppressors of cytokine signaling (SOCS) proteins are negative-feedback regulators of the JAK/STAT pathway, and SOCS3 contributes to host immunity by regulating the intensity and duration of cytokine signals and inflammatory responses. Mice with *Socs3* deletion in myeloid cells exhibit enhanced STAT3 signaling, expansion of Th1 and Th17 cells, and develop severe experimental autoimmune encephalomyelitis. Interestingly, development of the unique IL-17/IFN- $\gamma$  double-producing (Th17/IFN- $\gamma$  and Tc17/IFN- $\gamma$ ) subsets that exhibit strong cytotoxic activities and are associated with pathogenesis of several autoimmune diseases has recently been shown to depend on epigenetic suppression of SOCS3 expression, further suggesting involvement of SOCS3 in autoimmunity and tumor immunity. In this study, we generated mice with *Socs3* deletion in the CD4 T cell compartment (CD4-SOCS3 knockout [KO]) to determine in vivo effects of the loss of *Socs3* in the T cell-mediated autoimmune disease, experimental autoimmune uveitis (EAU). In contrast to the exacerbation of experimental autoimmune encephalomyelitis in myeloid-specific SOCS3-deleted mice, CD4-SOCS3KO mice were protected from acute and chronic uveitis. Protection from EAU correlated with enhanced expression of CTLA-4 and expansion of IL-10-producing regulatory T cells with augmented suppressive activities. We further show that SOCS3 interacts with CTLA-4 and negatively regulates CTLA-4 levels in T cells, providing a mechanistic explanation for the expansion of regulatory T cells in CD4-SOCS3 during EAU. Contrary to in vitro epigenetic studies, Th17/IFN- $\gamma$  and Tc17/IFN- $\gamma$  populations were markedly reduced in CD4-SOCS3KO, suggesting that SOCS3 promotes expansion of the Th17/IFN- $\gamma$  subset associated with development of severe uveitis. Thus, SOCS3 is a potential therapeutic target in uveitis and other autoinflammatory diseases.

DOI: 10.4049/jimmunol.1301132

PMCID: PMC4041279

PMID: 24101549 [Indexed for MEDLINE]



## Colchicine: New Insights to an Old Drug.

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Colchicine is an ancient drug that is used for symptomatic relief in a wide range of inflammatory diseases including gout, Behçet syndrome, and familial Mediterranean fever. Recognition of its antiinflammatory properties and of its unpleasant gastrointestinal side effects date back thousands of years. Despite this, uncertainty remains concerning its mechanism of action and very few randomized controlled trials have been carried out to examine its safety and efficacy to date. Although it is an effective drug, its use is hindered by a very narrow therapeutic index. This review attempts to summarize recent developments concerning the use of colchicine in the treatment of gout with particular focus on its mechanism of action and toxicity.

DOI: 10.1097/01.mjt.0000433937.07244.e1

PMID: 24100258 [Indexed for MEDLINE]

2265. J Child Neurol. 2014 Nov;29(11):1473-8. doi: 10.1177/0883073813503990. Epub 2013 Oct 4.

Peripheral facial palsy in children.

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The aim of this study is to evaluate the types and clinical characteristics of peripheral facial palsy in children. The hospital charts of children diagnosed with peripheral facial palsy were reviewed retrospectively. A total of 81

children (42 female and 39 male) with a mean age of  $9.2 \pm 4.3$  years were included in the study. Causes of facial palsy were 65 (80.2%) idiopathic (Bell palsy) facial palsy, 9 (11.1%) otitis media/mastoiditis, and tumor, trauma, congenital facial palsy, chickenpox, Melkersson-Rosenthal syndrome, enlarged lymph nodes, and familial Mediterranean fever (each 1; 1.2%). Five (6.1%) patients had recurrent attacks. In patients with Bell palsy, female/male and right/left ratios were 36/29 and 35/30, respectively. Of them, 31 (47.7%) had a history of preceding infection. The overall rate of complete recovery was 98.4%. A wide variety of disorders can present with peripheral facial palsy in children. Therefore, careful investigation and differential diagnosis is essential.

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DOI: 10.1177/0883073813503990

PMID: 24097851 [Indexed for MEDLINE]

2266. J Rheumatol. 2013 Oct;40(10):1768-9. doi: 10.3899/jrheum.130332.

Ocular myositis occurring with NOD2-associated autoinflammatory disease.

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DOI: 10.3899/jrheum.130332

PMID: 24085756 [Indexed for MEDLINE]

2267. Pediatr Neurol. 2013 Dec;49(6):417-9. doi: 10.1016/j.pediatrneurol.2013.07.010. Epub 2013 Sep 29.

Colchicine treatment in children with familial Mediterranean fever: is it a risk factor for neuromyopathy?

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**BACKGROUND:** We cared for a 17-year-old adolescent with familial Mediterranean fever under colchicine treatment. Because of the increased creatinine kinase level (3937 U/L) observed in this individual, we planned to assess all pediatric patients with familial Mediterranean fever under colchicine treatment to detect any resultant neuromyopathy.

**METHODS:** The study included 88 children with familial Mediterranean fever who were receiving colchicine. The patient with myopathy was not included in the study. Serum creatinine kinase levels were measured and nerve conduction studies were carried out in all patients.

**RESULTS:** The study included 88 patients (47 female, 53.4%) with an average age of  $10.1 \pm 3.35$  years. The average period of colchicine use was  $28.25 \pm 17.66$  months. Side effects of colchicine were detected in 10 patients (11%)--as diarrhea in eight patients, leukopenia in one patient, and hair loss in one patient. Nerve conduction studies determined incidental carpal tunnel syndrome in only one patient.

**CONCLUSIONS:** Our study did not suggest an elevated risk of neuromyopathy associated with the use of colchicine for familial Mediterranean fever.

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DOI: 10.1016/j.pediatrneurol.2013.07.010

PMID: 24084143 [Indexed for MEDLINE]

2268. Rheumatol Int. 2014 Feb;34(2):207-12. doi: 10.1007/s00296-013-2858-1. Epub 2013 Sep 26.

The MEFV mutations and their clinical correlations in children with familial Mediterranean fever in southeast Turkey.

Ece A(1), Çakmak E, Uluca Ü, Kelekçi S, Yolbaş İ, Güneş A, Yel S, Tan İ, Şen V.

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The aim of this study was to determine the Mediterranean fever (MEFV) gene mutations and their clinical correlations in children with familial Mediterranean fever (FMF) in southeast Turkey. Clinical and laboratory characteristics of 147 (65 males, 82 females) consecutive children with FMF having a positive MEFV gene mutation were prospectively investigated. Patients with negative MEFV gene mutations or atypical FMF presentations and those from other regions of the country were excluded. Clinical manifestations and disease severity scores were recorded. The six most frequent MEFV mutations including M694V, V726A, R726H, P369S, E148Q and P369S were investigated by a reverse hybridization test method. The median age of study group was 9.0 years, median age at diagnosis was 7.8 years, median age at disease onset was 5.0 years, and median follow-up duration was 4.0 years. A positive family history of FMF and parent-to-offspring transmission was found in 58.5 and 42.2 % of families, respectively. The frequencies of independent alleles, with decreasing order, were E148Q (30.7 %), M694V (26.0 %), R761H (13.5 %), V726A (13.0 %), P369S (10.5 %) and M680I (6.3 %) in FMF patients. The M694V subgroup had higher mean disease severity score and longer attack duration compared with E148Q and other mutations subgroups ( $p < 0.05$ ). Two patients with amyloidosis had the M694V homozygote genotype. In conclusion contrast to other regions and many other ethnicities of the world, the most frequent MEFV gene mutation was E148Q in southeast Turkey. The M694V mutation frequency was lower, and disease severity was relatively mild in FMF children of this region.

DOI: 10.1007/s00296-013-2858-1

PMID: 24071932 [Indexed for MEDLINE]

2269. Clin Transl Allergy. 2013 Sep 26;3(1):32. doi: 10.1186/2045-7022-3-32.

Gene hunting in autoinflammation.

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Steady progress in our understanding of the genetic basis of autoinflammatory

diseases has been made over the past 16 years. Since the discovery of the familial Mediterranean fever gene MEFV (also known as marenostin) in 1997, 18 other genes responsible for monogenic autoinflammatory diseases have been identified to date. The discovery of these genes was made through the utilisation of many genetic mapping techniques, including next generation sequencing platforms. This review article clearly describes the gene hunting approaches, methods of data analysis and the technological platforms used, which has relevance to all those working within the field of gene discovery for Mendelian disorders.

DOI: 10.1186/2045-7022-3-32

PMCID: PMC3849995

PMID: 24070009

2270. Front Immunol. 2013 Sep 23;4:295. doi: 10.3389/fimmu.2013.00295.

A role for NADPH oxidase in antigen presentation.

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The nicotinamide adenine dinucleotide phosphate (NADPH) oxidase expressed in phagocytes is a multi-subunit enzyme complex that generates superoxide ( $O_2^{\cdot-}$ ). This radical is an important precursor of hydrogen peroxide ( $H_2O_2$ ) and other reactive oxygen species needed for microbicidal activity during innate immune responses. Inherited defects in NADPH oxidase give rise to chronic granulomatous disease (CGD), a primary immunodeficiency characterized by recurrent infections and granulomatous inflammation. Interestingly, CGD, CGD carrier status, and oxidase gene polymorphisms have all been associated with autoinflammatory and autoimmune disorders, suggesting a potential role for NADPH oxidase in regulating adaptive immune responses. Here, NADPH oxidase function in antigen processing and presentation is reviewed. NADPH oxidase influences dendritic cell (DC) crosspresentation by major histocompatibility complex class I molecules through regulation of the phagosomal microenvironment, while in B lymphocytes, NADPH oxidase alters epitope selection by major histocompatibility complex class II

molecules.

DOI: 10.3389/fimmu.2013.00295

PMCID: PMC3779930

PMID: 24069023

2271. PLoS One. 2013 Sep 16;8(9):e73443. doi: 10.1371/journal.pone.0073443. eCollection 2013.

First report of circulating microRNAs in tumour necrosis factor receptor-associated periodic syndrome (TRAPS).

Lucherini OM(1), Obici L, Ferracin M, Fulci V, McDermott MF, Merlini G, Muscari I, Magnotti F, Dickie LJ, Galeazzi M, Negrini M, Baldari CT, Cimaz R, Cantarini L.

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Tumor necrosis factor-receptor associated periodic syndrome (TRAPS) is a rare autosomal dominant autoinflammatory disorder characterized by recurrent episodes of long-lasting fever and inflammation in different regions of the body, such as the musculo-skeletal system, skin, gastrointestinal tract, serosal membranes and eye. Our aims were to evaluate circulating microRNAs (miRNAs) levels in patients with TRAPS, in comparison to controls without inflammatory diseases, and to correlate their levels with parameters of disease activity and/or disease severity. Expression levels of circulating miRNAs were measured by Agilent microarrays in 29 serum samples from 15 TRAPS patients carrying mutations known to be associated with high disease penetrance and from 8 controls without inflammatory diseases. Differentially expressed and clinically relevant miRNAs were detected using GeneSpring GX software. We identified a 6 miRNAs signature able to discriminate TRAPS from controls. Moreover, 4 miRNAs were differentially expressed between patients treated with the interleukin (IL)-1 receptor antagonist, anakinra, and untreated patients. Of these, miR-92a-3p and miR-150-3p expression was found to be significantly reduced in untreated patients, while their expression levels were similar to controls in samples obtained during anakinra treatment. MiR-92b levels were inversely correlated with the number of

fever attacks/year during the 1(st) year from the index attack of TRAPS, while miR-377-5p levels were positively correlated with serum amyloid A (SAA) circulating levels. Our data suggest that serum miRNA levels show a baseline pattern in TRAPS, and may serve as potential markers of response to therapeutic intervention.

DOI: 10.1371/journal.pone.0073443

PMCID: PMC3774691

PMID: 24066048 [Indexed for MEDLINE]

2272. Anadolu Kardiyol Derg. 2013 Sep;13(6):608-9. doi: 10.5152/akd.2013.205. Epub 2013 Sep 10.

Increased mean platelet volume in patients with familial Mediterranean fever may not be a marker of atherosclerosis risk.

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Comment in

Anadolu Kardiyol Derg. 2013 Sep;13(6):609.

Comment on

Anadolu Kardiyol Derg. 2013 Jun;13(4):357-62.

DOI: 10.5152/akd.2013.205

PMID: 24064087 [Indexed for MEDLINE]

2273. J Lipid Res. 2013 Dec;54(12):3430-7. doi: 10.1194/jlr.M042549. Epub 2013 Sep 23.

Sufficient production of geranylgeraniol is required to maintain endotoxin tolerance in macrophages.

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Endotoxin tolerance allows macrophages to produce large quantities of proinflammatory cytokines immediately after their contact with lipopolysaccharides (LPSs), but prevents their further production after repeated exposure to LPSs. While this response is known to prevent overproduction of proinflammatory cytokines, the mechanism through which endotoxin tolerance is established has not been identified. In the current study, we demonstrate that sufficient production of geranylgeraniol (GGOH) in macrophages is required to maintain endotoxin tolerance. We show that increased synthesis of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR) protein following LPS treatment is required to produce enough GGOH to inhibit expression of Malt1, a protein known to stimulate expression of proinflammatory cytokines, in macrophages repeatedly exposed to LPSs. Depletion of GGOH caused by inhibition of HMGCR led to increased Malt1 expression in macrophages subjected to repeated exposure to LPSs. Consequently, endotoxin tolerance was impaired, and production of interleukin 1- $\beta$  and other proinflammatory cytokines was markedly elevated in these cells. These results suggest that insufficient production of GGOH in macrophages may cause autoinflammatory diseases.

DOI: 10.1194/jlr.M042549

PMCID: PMC3826689

PMID: 24062519 [Indexed for MEDLINE]

2274. Curr Opin Immunol. 2013 Oct;25(5):598-605. doi: 10.1016/j.coi.2013.08.005. Epub 2013 Sep 18.

Systems approaches to human autoimmune diseases.

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Systemic autoimmune diseases result from interactions between genes and environmental triggers that lead to dysregulation of both innate and adaptive immunity. Systems biology approaches enable the global characterization of complex systems at the DNA, RNA and protein levels. Recent technological breakthroughs such as deep sequencing or high-throughput proteomics are revealing novel inflammatory pathways involved in autoimmunity. Herein, we review recent developments, challenges and promising avenues in the use of systems approaches to understand human systemic autoimmune and autoinflammatory diseases.

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DOI: 10.1016/j.coi.2013.08.005

PMCID: PMC3924714

PMID: 24055331 [Indexed for MEDLINE]

2275. J Immunol. 2013 Oct 15;191(8):4317-25. doi: 10.4049/jimmunol.1301465. Epub 2013 Sep 16.

IL-33 markedly activates murine eosinophils by an NF- $\kappa$ B-dependent mechanism differentially dependent upon an IL-4-driven autoinflammatory loop.

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Eosinophils are major effector cells in type 2 inflammatory responses and become activated in response to IL-4 and IL-33, yet the molecular mechanisms and cooperative interaction between these cytokines remain unclear. Our objective was to investigate the molecular mechanism and cooperation of IL-4 and IL-33 in eosinophil activation. Eosinophils derived from bone marrow or isolated from IL5-transgenic mice were activated in the presence of IL-4 or IL-33 for 1 or 4 h, and the transcriptome was analyzed by RNA sequencing. The candidate genes were validated by quantitative PCR and ELISA. We demonstrated that murine-cultured eosinophils respond to IL-4 and IL-33 by phosphorylation of STAT-6 and NF- $\kappa$ B, respectively. RNA sequence analysis of murine-cultured eosinophils indicated that

IL-33 induced 519 genes, whereas IL-4 induced only 28 genes, including 19 IL-33-regulated genes. Interestingly, IL-33 induced eosinophil activation via two distinct mechanisms, IL-4 independent and IL-4 secretion/autostimulation dependent. Anti-IL-4 or anti-IL-4R $\alpha$  Ab-treated cultured and mature eosinophils, as well as IL4- or Stat6-deficient cultured eosinophils, had attenuated protein secretion of a subset of IL-33-induced genes, including Retnla and Ccl17. Additionally, IL-33 induced the rapid release of preformed IL-4 protein from eosinophils by a NF- $\kappa$ B-dependent mechanism. However, the induction of most IL-33-regulated transcripts (e.g., Il6 and Il13) was IL-4 independent and blocked by NF- $\kappa$ B inhibition. In conclusion, we have identified a novel activation pathway in murine eosinophils that is induced by IL-33 and differentially dependent upon an IL-4 auto-amplification loop.

DOI: 10.4049/jimmunol.1301465

PMCID: PMC3807853

PMID: 24043894 [Indexed for MEDLINE]

2276. J Am Coll Cardiol. 2013 Nov 12;62(20):1817-25. doi: 10.1016/j.jacc.2013.08.726. Epub 2013 Sep 11.

Colchicine and the heart: pushing the envelope.

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Colchicine, a natural and ancient drug still used today, is traditionally considered the staple therapy for gout and a second-line treatment for pericarditis, as well as a basic part of familial Mediterranean fever and Behcet's disease management. It is commonly classified as an anti-inflammatory agent, although its mechanism of action does not involve the arachidonic acid pathway affected by non-steroid anti-inflammatory drugs and glucocorticoids. Colchicine inhibits microtubule polymerization by binding to tubulin, thus affecting any process that requires cytoskeletal changes, including cell mitosis

and neutrophil motility. Recent studies suggest that colchicine may prove to be useful in a much wider spectrum of cardiovascular diseases than previously suspected, rekindling the interest in this old drug. In this review we briefly present the biochemical characteristics, mechanism of action and side-effects of colchicine, as well as examine what is currently known about the promising role of colchicine in cardiovascular medicine beyond pericardial disease.

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DOI: 10.1016/j.jacc.2013.08.726

PMID: 24036026 [Indexed for MEDLINE]

2277. Saudi J Kidney Dis Transpl. 2013 Sep;24(5):950-8.

Incidence and clinical outcome of renal amyloidosis: a retrospective study.

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The kidneys are affected in almost all patients with amyloid A in secondary amyloidosis (AA) amyloidosis but less frequently in immunoglobulin light chains in primary systemic amyloidosis (AL) amyloidosis. In this study, we present the incidence, etiology, clinical manifestations, biochemical features and clinical course of renal amyloidosis. We conducted a retrospective study on a group of 40 cases with renal biopsy-proven amyloidosis. They constituted 2.5% of the total cases of renal biopsies performed in the Theodor Bilharz Research Institute, Cairo, Egypt, during the period from February 2003 to May 2009. The mean age (30 males, ten females) was  $36.51 \pm 10.32$  years. Thirty-two of the cases had secondary AA amyloidosis and eight cases had primary AL amyloidosis. The causes of secondary amyloidosis were as follows: 12 (30%) familial Mediterranean fever (FMF), eight (20%) pulmonary tuberculosis, four (10%) chronic osteomyelitis, four (10%) bronchiectasis, three (7%) rheumatoid arthritis and one (2%) rheumatic heart disease. The eight cases of primary AL amyloidosis comprised of five cases that were associated with myeloma (13%) and three (8%) cases that were idiopathic.

Among the 23 patients with AA amyloidosis, after six months of treatment with colchicine, the proteinuria improved, serum albumin level increased and edema disappeared in 13 patients. In four cases of AA amyloidosis who were clinically and biochemically normal after colchicine therapy, a second renal biopsy disclosed decreased amyloid deposition compared with the first biopsy. In the three renal transplanted patients who had amyloidosis secondary to FMF and were treated with colchicines, AA amyloidosis did not recur in the transplanted kidney. It might be possible that in AL amyloidosis, treatment with methotrexate, melphalan and prednisolone may improve survival. The incidence of renal amyloidosis is increasing and colchicine can be used in secondary amyloidosis as it may have an effect on reducing the production of the amyloid precursor proteins and in reducing proteinuria.

PMID: 24029260 [Indexed for MEDLINE]

2278. Ann Rheum Dis. 2014 Dec;73(12):2168-73. doi: 10.1136/annrheumdis-2013-203666. Epub 2013 Sep 11.

Validation of the auto-inflammatory diseases activity index (AIDAI) for hereditary recurrent fever syndromes.

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**OBJECTIVES:** To validate the Auto-Inflammatory Diseases Activity Index (AIDAI) in the four major hereditary recurrent fever syndromes (HRFs): familial Mediterranean fever (FMF), mevalonate kinase deficiency (MKD), tumour necrosis factor receptor-associated periodic syndrome (TRAPS) and cryopyrin-associated periodic syndromes (CAPS).

**METHODS:** In 2010, an international collaboration established the content of a disease activity tool for HRFs. Patients completed a 1-month prospective diary with 12 yes/no items before a clinical appointment during which their physician assessed their disease activity by a questionnaire. Eight international experts in auto-inflammatory diseases evaluated the patient's disease activity by a blinded web evaluation and a nominal group technique consensus conference, with their consensus judgement considered the gold standard.

Sensitivity/specificity/accuracy measures and the ability of the score to discriminate active from inactive patients via the best cut-off score were calculated by a receiver operating characteristic analysis.

**RESULTS:** Consensus was achieved for 98/106 (92%) cases (39 FMF, 35 CAPS, 14 TRAPS and 10 MKD), with 26 patients declared as having inactive disease and 72 as having active disease. The median total AIDAI score was 14 (range=0-175). An AIDAI cut-off score  $\geq 9$  discriminated active from inactive patients, with sensitivity/specificity/accuracy of 89%/92%/90%, respectively, and an area under the curve of 98% (95% CI 96% to 100%).

**CONCLUSIONS:** The AIDAI score is a valid and simple tool for assessing disease activity in FMF/MKD/TRAPS/CAPS. This tool is easy to use in clinical practice and has the potential to be used as the standard efficacy measure in future clinical trials.

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DOI: 10.1136/annrheumdis-2013-203666

PMCID: PMC4251184

PMID: 24026675 [Indexed for MEDLINE]

2279. Pediatrics. 2013 Oct;132(4):e1043-7. doi: 10.1542/peds.2012-3935. Epub 2013 Sep 9.

First clinical description of an infant with interleukin-36-receptor antagonist deficiency successfully treated with anakinra.

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Comment in

Br J Dermatol. 2014 May;170(5):1198-9.

YM is the first son of Tunisian consanguineous parents who developed, at 2 weeks of life, an erythematous and scaly eruption, with subsequent rapid evolution toward generalized pustular psoriasis. Afterward, cutaneous flares of diffuse erythematous rash and pustules involving the whole body appeared, with a once weekly periodicity. Intense irritability was present during flares without fever. Moreover, since 1 month of age the infant presented with diarrhea, dysphagia, and reduced feeding rate, with failure to thrive. Laboratory tests during acute flares showed marked leukocytosis, thrombocytosis, and anemia without C-reactive protein elevation. Skin biopsy and clinical presentation were consistent with pustular psoriasis; nevertheless, the patient did not respond to high-potency topical corticosteroids and retinoid acid. As the patient presented with repeated skin flares early after birth, as well as serious constitutional distress with failure to thrive, an autoinflammatory syndrome like interleukine-1-receptor

antagonist deficiency or interleukin-36-receptor antagonist deficiency (DITRA) was considered. The hypothesis was reinforced by parental consanguinity, and absence of skin lesion improvement under standard topical treatment. Genetic analyses showed a homozygous mutation in the IL36RN gene (L27P), which represents the same mutation recently described in DITRA patients. At age 6 months we started treatment with the recombinant interleukin-1 receptor antagonist anakinra with efficacy both on constitutional symptoms and skin involvement. DITRA is a recently described autoinflammatory disease characterized by repeated flares of generalized pustular psoriasis, high fever, asthenia, and systemic inflammation. We report herein the first exhaustive clinical description of an infant with DITRA who was successfully treated with anakinra.

DOI: 10.1542/peds.2012-3935

PMID: 24019411 [Indexed for MEDLINE]

2280. Orphanet J Rare Dis. 2013 Sep 10;8:139. doi: 10.1186/1750-1172-8-139.

Methodological challenges in monitoring new treatments for rare diseases: lessons from the cryopyrin-associated periodic syndrome registry.

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**BACKGROUND:** The Cryopyrin-Associated Periodic Syndromes (CAPS) are a group of rare hereditary autoinflammatory diseases and encompass Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS), and Neonatal Onset Multisystem Inflammatory Disease (NOMID). Canakinumab is a monoclonal antibody directed against IL-1 beta and approved for CAPS patients but requires post-approval monitoring due to low and short exposures during the licensing process. Creative approaches to observational methodology are needed, harnessing novel registry strategies to ensure Health Care Provider reporting and patient monitoring.

**METHODS:** A web-based registry was set up to collect information on long-term safety and effectiveness of canakinumab for CAPS.

**RESULTS:** Starting in November 2009, this registry enrolled 241 patients in 43

centers and 13 countries by December 31, 2012. One-third of the enrolled population was aged < 18; the overall population is evenly divided by gender. Enrolment is ongoing for children.

CONCLUSIONS: Innovative therapies in orphan diseases require post-approval structures to enable in depth understanding of safety and natural history of disease. The rarity and distribution of such diseases and unpredictability of treatment require innovative methods for enrolment and follow-up. Broad international practice-based recruitment and web-based data collection are practical.

DOI: 10.1186/1750-1172-8-139

PMCID: PMC3848430

PMID: 24016338 [Indexed for MEDLINE]

2281. Cell Metab. 2013 Sep 3;18(3):403-15. doi: 10.1016/j.cmet.2013.08.011.

DNA damage triggers a chronic autoinflammatory response, leading to fat depletion in NER progeria.

Karakasilioti I(1), Kamileri I, Chatzinikolaou G, Kosteas T, Vergadi E, Robinson AR, Tsamardinos I, Rozgaja TA, Siakouli S, Tsatsanis C, Niedernhofer LJ, Garinis GA.

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Lipodystrophies represent a group of heterogeneous disorders characterized by loss of fat tissue. However, the underlying mechanisms remain poorly understood. Using mice carrying an ERCC1-XPF DNA repair defect systematically or in adipocytes, we show that DNA damage signaling triggers a chronic autoinflammatory response leading to fat depletion. Ercc1<sup>-/-</sup> and aP2-Ercc1F<sup>-/-</sup> fat depots show extensive gene expression similarities to lipodystrophic Pparγ(Δi/+ ) animals, focal areas of ruptured basement membrane, the reappearance of primary cilia, necrosis, fibrosis, and a marked decrease in adiposity. We find that persistent DNA damage in aP2-Ercc1F<sup>-/-</sup> fat depots and in adipocytes ex vivo triggers the induction of proinflammatory factors by promoting transcriptionally active



histone marks and the dissociation of nuclear receptor corepressor complexes from promoters; the response is cell autonomous and requires ataxia telangiectasia mutated (ATM). Thus, persistent DNA damage-driven autoinflammation plays a causative role in adipose tissue degeneration, with important ramifications for progressive lipodystrophies and natural aging.

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DOI: 10.1016/j.cmet.2013.08.011

PMCID: PMC4116679

PMID: 24011075 [Indexed for MEDLINE]

2282. Semin Ophthalmol. 2013 Sep-Nov;28(5-6):327-32. doi: 10.3109/08820538.2013.825285. Epub 2013 Sep 6.

Blau syndrome-associated uveitis and the NOD2 gene.

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Blau syndrome (BS), a rare autosomal dominant autoinflammatory syndrome, is an example of a monogenic disease. It was first described as a classic triad of uveitis, arthritis, and exanthema, typically seen in patients less than four years of age. Since that time, the phenotype has been expanded to include fever, cranial neuropathies, cardiovascular abnormalities, and granulomas of the liver and kidney. The ocular inflammation is often a panuveitis that occurs later in the disease course and typically carries the greatest morbidity in BS. BS has been mapped to the chromosomal region 16q12-21, also known as the NOD2 gene (formerly CARD15/NOD2). The disease is secondary to a single amino acid mutation NOD2 that leads to peptidoglycan-independent activity of nuclear factor (NF)- $\kappa$ B. Clinical and genetic aspects of BS will be discussed, as well as recent advances in treatment protocols.

DOI: 10.3109/08820538.2013.825285

PMID: 24010719 [Indexed for MEDLINE]

2283. Korean J Intern Med. 2013 Sep;28(5):594-8. doi: 10.3904/kjim.2013.28.5.594. Epub 2013 Aug 14.

The presence of MEFV gene mutations in patients with primary osteoarthritis who require surgery.

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**BACKGROUND/AIMS:** Chronic arthritis of familial Mediterranean fever (FMF) involves weight-bearing joints and can occur in patients without a history of acute attack. Our aim was to investigate a possible causal relationship between FMF and osteoarthritis in a population in which FMF is quite common.

**METHODS:** Patients with late stage primary osteoarthritis were enrolled, and five MEFV gene mutations were investigated. The frequency of MEFV gene mutations was compared among patients with osteoarthritis and a previous healthy group from our center.

**RESULTS:** One hundred patients with primary osteoarthritis and 100 healthy controls were studied. The frequency of MEFV gene mutations was significantly lower in the osteoarthritis group (9% vs. 19%). M694V was the most frequent mutation (5%) in the osteoarthritis group, whereas in the control group, E148Q was the most common (16%). In subgroup analyses, the mutation frequency of patients with hip osteoarthritis was not different from that of patients with knee osteoarthritis and controls (7.1%, 9.7%, and 19%, respectively). There were no differences among the three groups with respect to MEFV gene mutations other than E148Q (8.1% vs. 3.6%). E148Q was significantly lower in the osteoarthritis group than in the controls (16% vs. 1%), although the mutations did not differ between patients with knee osteoarthritis and controls.

**CONCLUSIONS:** In a population with a high prevalence of MEFV gene mutations, we did not find an increased mutation rate in patients with primary osteoarthritis. Furthermore, we found that some mutations were significantly less frequent in patients with osteoarthritis. Although the number of patients studied was insufficient to claim that E148Q gene mutation protects against osteoarthritis, the potential of this gene merits further investigation.

DOI: 10.3904/kjim.2013.28.5.594  
PMCID: PMC3759766  
PMID: 24009456 [Indexed for MEDLINE]

2284. Expert Opin Ther Targets. 2013 Nov;17(11):1243-7. doi:  
10.1517/14728222.2013.835399. Epub 2013 Sep 4.

Transient receptor potential melastatin 2: a novel target for treatment of gout.

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Gout is an ancient autoinflammatory disease that affects millions of people worldwide. It is characterized by unbearable recurrent pain due to the massive local inflammation caused by the metabolic product, monosodium urate crystals. Although conventional therapies for gout can reduce the pain in patients, the severe undesirable side effects require the urgent need for novel therapies that can more specifically target gout-associated inflammatory pathways. Recent scientific advance on the mechanistic study of gout-associated inflammation is discussed and the potential of targeting the transient receptor potential melastatin 2 is highlighted as a novel therapeutic approach for the treatment of gout.

DOI: 10.1517/14728222.2013.835399  
PMCID: PMC4106263  
PMID: 24004350 [Indexed for MEDLINE]

2285. J Vet Med Sci. 2014 Jan;76(1):109-12. Epub 2013 Aug 28.

Digoxigenin-labeled in situ hybridization for the detection of *Streptococcus suis* DNA in polyserositis and a comparison with biotinylated in situ hybridization.

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The objective of this study was to develop digoxigenin-labeled in situ hybridization (ISH) for the detection of *Streptococcus suis* in naturally infected pigs with polyserositis and to compare it with biotinylated ISH. Digoxigenin-labeled hybridization signals for *S. suis* were observed in cells that had infiltrated the fibrous polyserositis and microcolonies in the blood vessels. Mock hybridization showed no hybridization signals for endogenous digoxigenin. Biotinylated hybridization signals for *S. suis* were observed in cells that had infiltrated the fibrous polyserositis. However, similar hybridization signals were also observed in the fibrous inflammatory area using mock hybridization for endogenous biotin. The present study demonstrated that digoxigenin-labeled ISH is a valuable diagnostic tool for specific detection of *S. suis* in polyserositic tissues without nonspecific reactions compared with biotinylated ISH.

PMCID: PMC3979959

PMID: 23985415 [Indexed for MEDLINE]

2286. Arthritis Rheum. 2013 Nov;65(11):2971-83. doi: 10.1002/art.38134.

Increased intracellular oxygen radical production in neutrophils during febrile episodes of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome.

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**OBJECTIVE:** Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is an autoinflammatory disease of unknown etiology that primarily affects preschool-aged children. PFAPA syndrome is characterized by

recurrent attacks of fever and symptoms of inflammation consistent with the disease acronym. Since autoinflammatory diseases are, by definition, mediated by cells of the innate immune system, the aim of this study was to evaluate the functional features of neutrophils, the most abundant innate immune cell in the circulation, in children with PFAPA syndrome.

**METHODS:** Blood polymorphonuclear leukocytes (PMNs), obtained from patients with PFAPA syndrome during both febrile and asymptomatic, afebrile phases of the disease, as well as from healthy children (afebrile controls) and children with fever and abdominal pain (febrile controls), were analyzed for 3 key neutrophil characteristics: 1) apoptosis (measured by annexin V/7-aminoactinomycin D staining), 2) production of reactive oxygen species (ROS) (measured by luminol/isoluminol-amplified chemiluminescence), and 3) priming status (measured as responsiveness to galectin-3 and up-regulation of CD11b).

**RESULTS:** Compared to PMNs obtained from patients with PFAPA syndrome during an afebrile interval and those from febrile controls, PMNs obtained from patients during a PFAPA syndrome flare produced elevated levels of intracellular NADPH oxidase-derived ROS, had significantly diminished rates of spontaneous apoptosis, and displayed signatures of priming. In contrast, PMNs from afebrile patients with PFAPA syndrome had a significantly elevated rate of spontaneous apoptosis compared to PMNs from afebrile controls.

**CONCLUSION:** These findings demonstrate that 3 key aspects of neutrophil innate immune function, namely, apoptosis, priming, and generation of an intracellular oxidative burst, are altered, most prominently during febrile attacks, in children with PFAPA syndrome.

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DOI: 10.1002/art.38134

PMID: 23983059 [Indexed for MEDLINE]

2287. Int J Rheum Dis. 2013 Jun;16(3):373-5. doi: 10.1111/1756-185X.12004. Epub 2012 Oct 22.

Two cases of familial Mediterranean fever associated with sarcoidosis (Lofgren's syndrome) and rheumatoid arthritis.

Erten S, Erzurum C, Kosker TA, Doğan HT, Altunoglu A.

DOI: 10.1111/1756-185X.12004

PMID: 23981767 [Indexed for MEDLINE]

2288. Int J Rheum Dis. 2013 Jun;16(3):347-51. doi: 10.1111/1756-185X.12072. Epub 2013 May 23.

MEFV gene mutations in Henoch-Schönlein purpura.

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**AIM:** Coexistence of familial Mediterranean fever (FMF) with various systemic vasculitides, including Henoch-Schönlein purpura (HSP) and other inflammatory disorders has been reported and the MEFV gene has been suggested to play an important role in the pathogenesis of this association. In the present study, the mutation rate of the MEFV gene in HSP and its association with the clinical course of the disease were evaluated.

**METHOD:** The study group comprised 68 children (36 boys and 32 girls) diagnosed as having HSP. The spectrum and degree of organ involvement and the levels of serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were documented for each patient. Allele-specific PCR using oligonucleotide probes which include 12 MEFV mutations (E148Q, P369S, F479L, M680I [G/C], M680I [G/A], I692del, M694V, M694I, K695R, V726A, A744S, R761H) were used for mutation analysis.

**RESULTS:** Of the 68 patients studied, 50 (74%) showed no mutation, while 18 (26%) had MEFV mutation. Mutation analysis of the whole group revealed that 15 (22%) patients were heterozygous for one of the screened MEFV mutations, while three (4.5%) patients were compound heterozygous for two of the studied mutations, and one (1.5%) patient was homozygous for E148Q/E148Q mutations. Gastrointestinal and joint involvement, and edema were more frequently observed in patients with MEFV mutations, while ESR and CRP levels were significantly higher ( $P < 0.05$ ) in patients with MEFV mutations.

**CONCLUSION:** MEFV mutations, especially, E148Q and M694V, mutations might be associated with HSP and may affect clinical presentation and laboratory findings in HSP patients.

DOI: 10.1111/1756-185X.12072

PMID: 23981758 [Indexed for MEDLINE]

2289. Clin Exp Rheumatol. 2013 Sep-Oct;31(5):788-94. Epub 2013 Aug 2.

New insights in the pathogenesis and therapy of idiopathic recurrent pericarditis in children.

Gaspari S(1), Marsili M, Imazio M, Brucato A, Di Blasi Lo Cuccio C, Chiarelli F, Breda L.

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Pericarditis has several different causes, however, in about 70% of paediatric patients, a specific aetiology cannot be detected and the pericarditis is considered idiopathic. Recurrences may occur in up to 15-30% of cases. The pathogenesis of recurrent disease is controversial. Infectious, autoimmune and autoinflammatory pathways have been proposed as mechanisms involved in recurrences. Therapeutic strategies are not standardised, non-steroidal anti-inflammatory drugs at high dosages being the mainstay of therapy with the possible addition of low dose colchicine to prevent recurrences. Biological agents are considered a possible new therapeutic frontiers in the care of idiopathic recurrent pericarditis.

PMID: 23981280 [Indexed for MEDLINE]

2290. J Matern Fetal Neonatal Med. 2014 May;27(7):733-6. doi:  
10.3109/14767058.2013.837446. Epub 2013 Sep 25.

Retrospective evaluation of pregnancy outcomes in women with familial Mediterranean fever.

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**AIM:** Familial Mediterranean fever (FMF) is an autosomal recessive condition characterized by periodic attacks of fever, aseptic serositis and synovitis. In this study, we investigated maternal and neonatal outcomes in pregnant patients with FMF.

**METHODS:** This retrospective study consisted of 46 pregnant patients with FMF who attended the perinatology clinic of Dr Zekai Tahir Burak Research and Training Hospital between January 2008 and December 2012. The following clinical and demographic data were obtained by reviewing the patients' medical records: maternal age, colchicine use during pregnancy, obstetric history, pregnancy outcome and maternal and neonatal complications during the current pregnancy.

**RESULTS:** The patients with FMF had higher rates of premature rupture of membranes (PROM) and Cesarean delivery as well as low birth weight infants; however, rates of stillbirth, gestational diabetes, preeclampsia did not differ between the groups. Preterm delivery rates were higher in the study group, but this difference did not reach statistical significance. Patients with pregnancy complications had significantly more basal proteinuria than did patients without complications. Nine patients did not receive colchicine therapy in the previous or current pregnancies. Within this subgroup, four (44.4%) of the patients had a history of two or more previous miscarriages. However, there were only three cases (8.1%) of two or more miscarriages among 37 patients who received colchicine; this difference was statistically significant

**CONCLUSIONS:** FMF leads to higher rates of PROM, recurrent miscarriage and preterm deliveries. Colchicine treatment is safe in pregnancy and may lead to a decreased miscarriage rate.

DOI: 10.3109/14767058.2013.837446

PMID: 23981183 [Indexed for MEDLINE]

2291. J Eur Acad Dermatol Venereol. 2014 Jun;28(6):679-88. doi: 10.1111/jdv.12252. Epub 2013 Aug 24.



Skin rash and arthritis a simplified appraisal of less common associations.

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Skin and joint manifestations are part of the clinical spectrum of many disorders. Well-known associations include psoriatic arthritis and arthritis associated with autoimmune connective tissue diseases. This review focuses on less common associations where skin lesions can provide easily accessible and valuable diagnostic clues, and directly lead to the specific diagnosis or limit the list of possibilities. This may also affect health care resources as diagnostic tests are often low-specific, highly expensive and poorly available. This group of diseases can be divided into two subsets, based on the presence/absence of fever, and then further classified according to elementary skin lesions (macular, urticarial, maculo-papular, vesico-bullous, pustular, petechial and nodular). In most instances joint involvement occurs as peripheral migrating polyarthritis. Erythematous macular or urticarial rashes occur in most febrile disorders such as monogenic autoinflammatory syndromes, Schnitzler's syndrome, Still's disease and rheumatic fever and afebrile diseases as urticarial vasculitis. Pustular rash may be observed in chronic recurrent multifocal osteomyelitis (CRMO) and pyogenic arthritis with pyoderma gangrenosum and acne (PAPA) syndrome (both febrile) as well as in Behcet's disease and Synovitis, acne, pustulosis, hyperostosis and osteitis syndrome (both non-febrile). Papular lesions are typical of secondary syphilis, sarcoidosis, interstitial granulomatous dermatitis, papular petechial of cutaneous small-vessel vasculitis and nodular lesions of polyarteritis nodosa and multicentric reticulohistiocytosis all of which are afebrile. Differential diagnosis includes infections and drug reactions which may mimic several of these conditions. To biopsy the right skin lesion at the right time it is essential to obtain relevant histological information.

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DOI: 10.1111/jdv.12252

PMID: 23980929 [Indexed for MEDLINE]

2292. PLoS One. 2013 Aug 19;8(8):e72138. doi: 10.1371/journal.pone.0072138. eCollection 2013.

S100A8 and S100A9 induce cytokine expression and regulate the NLRP3 inflammasome via ROS-dependent activation of NF- $\kappa$ B(1.).

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S100A8 and S100A9 are cytoplasmic proteins expressed by phagocytes. High concentrations of these proteins have been correlated with various inflammatory conditions, including autoimmune diseases such as rheumatoid arthritis and Crohn's disease, as well as autoinflammatory diseases. In the present study, we examined the effects of S100A8 and S100A9 on the secretion of cytokines and chemokines from PBMCs. S100A8 and S100A9 induced the secretion of cytokines such as IL-6, IL-8, and IL-1 $\beta$ . This secretion was associated with the activation and translocation of the transcription factor NF- $\kappa$ B. Inhibition studies using antisense RNA and the pharmacological agent BAY-117082 confirmed the involvement of NF- $\kappa$ B in IL-6, IL-8, and IL-1 $\beta$  secretion. S100A8- and S100A9-mediated activation of NF- $\kappa$ B, the NLR family, pyrin domain-containing 3 (NLRP3) protein, and pro-IL-1 $\beta$  expression was dependent on the generation of reactive oxygen species. This effect was synergistically enhanced by ATP, a known inflammasome activator. These results suggest that S100A8 and S100A9 enhance the inflammatory response by inducing cytokine secretion of PBMCs.

DOI: 10.1371/journal.pone.0072138

PMCID: PMC3747084

PMID: 23977231 [Indexed for MEDLINE]

2293. Gene. 2013 Nov 1;530(1):100-3. doi: 10.1016/j.gene.2013.08.026. Epub 2013 Aug 22.

Common MEFV gene mutations in Turkish patients with Behcet's disease.

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Behcet's disease (BD) is a chronic systemic inflammatory disorder whose etiology has not been fully established yet. The Mediterranean Fever (MEFV) gene has been identified as the cause of Familial Mediterranean Fever (FMF). BD shows similarities with FMF, in terms of clinical findings and treatments, as well as their geographical and ethnic co-occurrence. In this study we investigated common MEFV gene mutation frequencies in Turkish patients with BD in an area of Turkey where both diseases are frequently encountered. We screened 207 BD patients who had no symptoms and family history for FMF and 200 healthy subjects for five common MEFV gene mutations (E148Q, M680I, M694V, V726A, P369S) and clinical features. Seventy-five patients were found to carry a single MEFV mutation, and six patients were compound heterozygous. The difference in the frequency of the MEFV mutation between the BD and control groups was statistically significant ( $p < 0.001$ , odds ratio [OR] 2.74, 95% confidence interval [CI] 1.75-4.29). The frequencies of E148Q and M680I mutations were significantly higher in the BD group ( $p = 0.001$ ,  $p = 0.046$ , respectively). The frequency of uveitis was significantly lower in patients with the mutation than in patients without the mutation ( $p = 0.029$ , OR 0.54, 95% CI 0.30-0.98). There was no statistical significance between carriers and non-carriers with respect to gender and other manifestations of BD. The frequency of the MEFV mutation was significantly higher in patients with BD compared to the healthy control group. Based on our results, MEFV mutations appear to have a role in the pathogenesis of BD.

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DOI: 10.1016/j.gene.2013.08.026

PMID: 23973724 [Indexed for MEDLINE]

2294. Biomed Res Int. 2013;2013:485103. doi: 10.1155/2013/485103. Epub 2013 Jul 23.

From the Mediterranean to the sea of Japan: the transcontinental odyssey of autoinflammatory diseases.

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Autoinflammatory diseases are comprehensively caused by aberrant production of proinflammatory cytokines and are revealed by cyclically and spontaneously occurring inflammatory events. Over the last decade, there has been a revolution in the understanding of periodic fever syndromes, cryopyrinopathies, and skin disorders with pyogenic, granulomatous, or dystrophic features, which have been recognized across different countries spanning from the Mediterranean basin to the Japanese archipelago. Many children and adults with autoinflammatory diseases continue to elude diagnosis, and the diagnostic delay of many years puts these patients at risk of long-term severe complications, such as amyloidosis. Any hint of suspicion of autoinflammatory disease thus needs to be highlighted in various medical specialties, and this review examines their frequencies around the world, trying to match them with geographic location, ethnic and genetic data, in an attempt to realize a geoepidemiologic map for most of these conditions.

DOI: 10.1155/2013/485103

PMCID: PMC3736491

PMID: 23971037 [Indexed for MEDLINE]

2295. Mediators Inflamm. 2013;2013:939847. doi: 10.1155/2013/939847. Epub 2013 Jul 21.

Biological treatments: new weapons in the management of monogenic autoinflammatory disorders.

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Treatment of monogenic autoinflammatory disorders, an expanding group of

hereditary diseases characterized by apparently unprovoked recurrent episodes of inflammation, without high-titre autoantibodies or antigen-specific T cells, has been revolutionized by the discovery that several of these conditions are caused by mutations in proteins involved in the mechanisms of innate immune response, including components of the inflammasome, cytokine receptors, receptor antagonists, and oversecretion of a network of proinflammatory molecules. Aim of this review is to synthesize the current experience and the most recent evidences about the therapeutic approach with biologic drugs in pediatric and adult patients with monogenic autoinflammatory disorders.

DOI: 10.1155/2013/939847

PMCID: PMC3736401

PMID: 23970817 [Indexed for MEDLINE]

2296. Rheumatology (Oxford). 2014 Mar;53(3):573-4. doi: 10.1093/rheumatology/ket211. Epub 2013 Aug 22.

Efficacy of tocilizumab for interstitial lung disease in an undifferentiated autoinflammatory disorder partially responsive to anakinra.

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DOI: 10.1093/rheumatology/ket211

PMID: 23970544 [Indexed for MEDLINE]

2297. Clin Ophthalmol. 2013;7:1581-5. doi: 10.2147/OPHTH.S49281. Epub 2013 Aug 6.

Obvious optic disc swelling in a patient with cryopyrin-associated periodic syndrome.

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Cryopyrin-associated periodic syndrome (CAPS) is a group of rare hereditary autoinflammatory diseases caused by mutations of the NLRP3 gene, and leads to excessive production of the proinflammatory cytokine, interleukin-1 $\beta$ . A 35-year-old male presented with recurrent symptoms of urticarial-like rash, periodic fever, arthralgia, headache, and eye redness. His best-corrected visual acuity was 1.0 OD and 0.9 OS. Slit-lamp examination showed conjunctival and episcleral injection in both eyes. Ophthalmoscopy revealed obvious bilateral optic disc swelling and retinal vascular sheathing around the optic discs. Spectral domain optical coherence tomography also showed obvious optic disc swelling. Steroid and nonsteroidal anti-inflammatory drugs did not improve these symptoms. Genetic testing detected a heterozygous mutation of c.907G>A. Thus, the patient was genetically confirmed with CAPS. Visual acuity did not decrease for 3 years, although the optic discs became white in color. CAPS should therefore be distinguished from other disorders when examining optic disc swelling and/or uveitis patients with urticarial-like rash and periodic fever.

DOI: 10.2147/OPTH.S49281

PMCID: PMC3743521

PMID: 23966762

2298. Ann Rheum Dis. 2014 Dec;73(12):2160-7. doi: 10.1136/annrheumdis-2013-204184. Epub 2013 Aug 21.

The phenotype of TNF receptor-associated autoinflammatory syndrome (TRAPS) at presentation: a series of 158 cases from the Eurofever/EUROTRAPS international registry.

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**OBJECTIVE:** To evaluate the genetic findings, demographic features and clinical presentation of tumour necrosis factor receptor-associated autoinflammatory syndrome (TRAPS) in patients from the Eurofever/EUROTRAPS international registry.

**METHODS:** A web-based registry collected retrospective data on patients with TNFRSF1A sequence variants and inflammatory symptoms. Participating hospitals included paediatric rheumatology centres and adult centres with a specific interest in autoinflammatory diseases. Cases were independently validated by experts in the disease.

**RESULTS:** Complete information on 158 validated patients was available. The most common TNFRSF1A variant was R92Q (34% of cases), followed by T50M (10%). Cysteine residues were disrupted in 27% of cases, accounting for 39% of sequence variants. A family history was present in 19% of patients with R92Q and 64% of those with other variants. The median age at which symptoms began was 4.3 years but 9.1% of patients presented after 30 years of age. Attacks were recurrent in 88% and the commonest features associated with the pathogenic variants were fever (88%), limb pain (85%), abdominal pain (74%), rash (63%) and eye manifestations (45%). Disease associated with R92Q presented slightly later at a median of 5.7 years with significantly less rash or eye signs and more headaches. Children were more likely than adults to present with lymphadenopathy, periorbital oedema and abdominal pains. AA amyloidosis has developed in 16 (10%) patients at a median age of 43 years.

**CONCLUSIONS:** In this, the largest reported case series to date, the genetic heterogeneity of TRAPS is accompanied by a variable phenotype at presentation. Patients had a median 70 symptomatic days a year, with fever, limb and abdominal pain and rash the commonest symptoms. Overall, there is little evidence of a significant effect of age or genotype on disease features at presentation.

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DOI: 10.1136/annrheumdis-2013-204184

PMCID: PMC4251160

PMID: 23965844 [Indexed for MEDLINE]



Epub 2013 Aug 20.

Microbial activation of gut dendritic cells and the control of mucosal immunity.

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Current data support a role for gut colonization in maintaining balanced mucosal and systemic immune responses and have suggested aberrant innate immune recognition of enteric bacteria as an initiator of the adaptive immune damage associated with inflammatory bowel disease (Crohn's disease and ulcerative colitis). In fact, data from human studies and experimental mouse models have implicated transformation of the gut microbiota from a beneficial symbiotic state to one of imbalance or "dysbiosis" in the pathogenesis of several autoinflammatory diseases, including allergic skin and respiratory disorders, rheumatoid arthritis, type I diabetes, and colorectal cancer. The host has evolved to co-exist and maintain a mutualistic relationship with the commensal microbes of the gut, and it is the function of the host innate immune system to initiate and maintain this homeostasis, while retaining the ability to respond appropriately to pathogenic organisms. In this review, we discuss the molecular and cellular interactions of the mucosal immune system that decide this delicate balance of mutualism. Furthermore, we will highlight the role of dendritic cells in preserving this precarious balance and how gene products of commensal microbes may play an integral role in re-establishing this balance once it has gone awry.

DOI: 10.1089/jir.2013.0046

PMCID: PMC3814820

PMID: 23962004 [Indexed for MEDLINE]

2300. J Korean Med Sci. 2013 Aug;28(8):1145-53. doi: 10.3346/jkms.2013.28.8.1145. Epub 2013 Jul 31.

Serum level of interleukin-33 and soluble ST2 and their association with disease activity in patients with Behcet's disease.

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Comment in

J Korean Med Sci. 2014 Jan;29(1):153.

J Korean Med Sci. 2014 Jan;29(1):153-4.

Interleukin (IL)-33 is an important mediator of innate immunity. Behcet's disease (BD) is an autoinflammatory disorder characterized by hyperactivity of the innate immune response. We measured serum levels of IL-33 and its receptor soluble ST2 (sST2) in patients with BD to investigate their association with disease activity. Serum levels of both IL-33 and sST2 were higher in patients with BD compared with those in normal controls (IL-33:  $594.48 \pm 175.04$  pg/mL in BD and  $224.23 \pm 56.64$  pg/mL in normal controls [ $P=0.048$ ], sST2:  $99.01 \pm 15.92$  pg/mL in BD and  $23.56 \pm 3.25$  pg/mL in normal controls [ $P<0.001$ ]). IL-33 and sST2 expression in skin tissue, as shown by immunohistochemistry, was higher in patients with BD compared with that in the normal controls. Serum sST2 level correlated significantly with the BD currently active form (BDCAF), Iranian BD dynamic activity measure (IBDDAM), erythrocyte sedimentation rate and C-reactive protein. Multiple linear regression showed that serum sST2 was an independent factor associated with IBDDAM (regression coefficient, 0.374;  $P=0.004$ ), and BDCAF (regression coefficient, 0.236;  $P=0.047$ ). These results demonstrate that IL-33 and sST2 are highly expressed in patients with BD and that serum sST2 is an independent factor associated with IBDDAM and BDCAF, suggesting a potential role for sST2 as a surrogate marker of disease activity in patients with BD.

DOI: 10.3346/jkms.2013.28.8.1145

PMCID: PMC3744701

PMID: 23960440 [Indexed for MEDLINE]

2301. Immunol Rev. 2013 Sep;255(1):13-24. doi: 10.1111/imr.12089.

The expanding role of NLRs in antiviral immunity.

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Nucleotide oligomerization and binding domain (NOD)-like receptors (NLRs) are a major constituent of the cytosolic innate immune-sensing machinery and participate in a wide array of pathways including nuclear factor  $\kappa$ B (NF- $\kappa$ B), mitogen-activated protein kinase (MAPK), inflammasome, and type I interferon (IFN) signaling. NLRs have known roles in autoimmune, autoinflammatory, and infectious diseases. With respect to virus infection, NLRP3 is the most extensively studied NLR, including mechanisms of activation and inhibition. Furthermore, the importance of NLRP3 in both innate and adaptive immunity has been demonstrated. In comparison to NLRP3, the roles of other NLRs during virus infection are only just emerging. NLRC2 is an important activator of innate antiviral signaling and was recently found to mitigate inflammation during virus infection through autophagy. Finally, functions for NLRX1 in immune modulation and reactive oxygen species production require further examination and the importance of NLRC5 as a transactivator of major histocompatibility complex (MHC) class I and antigen presentation is currently developing. In this review, we discuss current knowledge pertaining to viruses and NLRs as well as areas of potential research, which will help advance the study of NLR biology during virus infection.

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DOI: 10.1111/imr.12089

PMCID: PMC3759815

PMID: 23947344 [Indexed for MEDLINE]

2302. Z Rheumatol. 2013 Sep;72(7):634-40, 642. doi: 10.1007/s00393-013-1160-7.

[Secondary immunodeficiency in rheumatological diseases].

[Article in German]

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Immunosuppressive treatment plays a crucial role in the management of autoimmune and autoinflammatory diseases. Knowledge about the ensuing immune deficits resulting from these therapies as well as common infections in immunocompromised patients should be familiar to all doctors involved in the prescription and administration of immunosuppressive drugs. Comprehensive pretreatment screening, regular monitoring both during and following treatment as well common sense preventive measures, such as vaccination can help further minimise the risk of infection.

DOI: 10.1007/s00393-013-1160-7

PMID: 23942561 [Indexed for MEDLINE]

2303. Dermatology. 2013;227(1):26-30. doi: 10.1159/000351323. Epub 2013 Aug 8.

A new infant case of Nakajo-Nishimura syndrome with a genetic mutation in the immunoproteasome subunit: an overlapping entity with JMP and CANDLE syndrome related to PSMB8 mutations.

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Nakajo-Nishimura syndrome (NNS) is a very rare hereditary autoinflammatory disorder that generally has its onset in infancy with pernio-like rashes and gradually develops into partial lipodystrophy. A distinct homozygous PSMB8 mutation encoding an immunoproteasome subunit has recently been identified as its genetic cause. Here, we report a new case of a patient with NNS who developed exudative erythemas on his face and extremities at 2 months of age, along with high fever, elevated serum hepatic aminotransferase levels and hepatosplenomegaly. Massive infiltration of inflammatory cells was observed histologically in the dermis and subcutis without apparent leukocytoclastic vasculitis. These symptoms improved with oral corticosteroids but recurred periodically, and a thin angular face with long clubbed fingers gradually

developed. Identification of the PSMB8 mutation finalized the diagnosis of NNS at 5 years of age. Understanding a variety of clinicopathological features at the developmental stages is necessary to make an early diagnosis of NNS.

DOI: 10.1159/000351323

PMID: 23942189 [Indexed for MEDLINE]

2304. *Pediatr Int.* 2014 Feb;56(1):13-8. doi: 10.1111/ped.12192.

Evaluation of non-surgical causes of cardiac tamponade in children at a cardiac surgery center.

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**BACKGROUND:** The aim of this study was to examine the causes of cardiac tamponade in children undergoing percutaneous pericardiocentesis.

**METHOD:** Patients who presented with other complaints but were diagnosed with cardiac tamponade based on clinical and echocardiographic findings between January 2010 and January 2013 were retrospectively investigated.

Electrocardiography, telecardiography and transthoracic echocardiography were performed. Pericardiocentesis was performed percutaneously under continuous blood pressure and rhythm monitoring with echocardiography and fluoroscopy. Pericardial fluid was analyzed on hemography and biochemistry.

**RESULTS:** Fourteen patients (six boys, eight girls; median age, 7 years) underwent pericardiocentesis for cardiac tamponade. At presentation, 78% had dyspnea, 56% chest pain, and 49% fever. All had cardiomegaly, and their cardiothoracic index was 0.56-0.72. Also, all patients had sinus tachycardia; 78%, low QRS voltage; 70%, ST-T changes; and 50% QRS alternans. On echocardiography the widest diameter of pericardial effusion was between 12 mm and 36 mm depth around the heart. The pericardial fluid was purulent in one, serohemorrhagic in seven, serofibrinous in two, and serous in four cases. Pericardiocentesis was unsuccessful in two patients, who underwent open surgical drainage, with no complications. Based on pericardial fluid characteristics and additional tests, cardiac tamponade was caused by an infection in five patients, hypothyroidism in two, familial

Mediterranean fever in two, malignancy in one, acute rheumatic fever in one, collagen tissue disease (systemic lupus erythematosus) in one, catheter placement-associated damage in one, and idiopathic pulmonary arterial hypertension in one patient.

CONCLUSION: Pericardial effusion and cardiac tamponade in children have varied causes, and early treatment is life saving.

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DOI: 10.1111/ped.12192

PMID: 23937542 [Indexed for MEDLINE]

2305. Joint Bone Spine. 2013 Dec;80(6):645-9. doi: 10.1016/j.jbspin.2013.03.004. Epub 2013 Aug 6.

Myositis in a patient with familial Mediterranean fever and spondyloarthritis successfully treated with anakinra.

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Familial Mediterranean fever is an autosomal-recessive autoinflammatory disorder more commonly observed in Mediterranean populations and characterized by recurrent episodes of fever, serositis, myalgia and arthritis. There is rarely any association with spondyloarthritis. The most important long-term complication is progressive systemic type AA amyloidosis. Treatment with colchicine is effective in reducing the frequency of attacks and prevents the development of amyloidosis. However, 5% of cases are considered resistant to colchicine. We here describe the case of a 39-year-old man, with a history of arthritis, arthralgias, and sacroiliitis in the course of a familial Mediterranean fever. He is homozygous for the M694I mutation in the MEFV gene. He subsequently developed myositis of the right quadriceps muscle confirmed by magnetic resonance imaging, electromyography and histology. He had frequent and severe arthralgias, despite colchicine, then etanercept and adalimumab, impairing his quality of life. The

patient was successfully treated with the IL-1 receptor antagonist anakinra with a dramatic improvement of muscular and articular symptoms. To our knowledge, our patient is the first patient with coexisting FMF, spondyloarthritis and myositis responding to anakinra treatment. Moreover this is the second case in the literature of myositis associated with familial Mediterranean fever.

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DOI: 10.1016/j.jbspin.2013.03.004

PMID: 23928237 [Indexed for MEDLINE]

2306. Dig Dis Sci. 2013 Nov;58(11):3212-7. doi: 10.1007/s10620-013-2814-7. Epub 2013 Aug 8.

Can serum fetuin-A be regarded as an inflammatory marker among patients with familial Mediterranean fever?

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**BACKGROUND/AIM:** Familial Mediterranean fever (FMF), the most frequent periodic fever syndrome, is an autosomal recessive inherited disease that predominantly affects eastern Mediterranean populations. Fetuin-A is a well known negative acute-phase protein. Studies of this glycoprotein as a marker of inflammation in FMF are limited. We have investigated the relationship between serum levels of fetuin-A and inflammatory markers in patients with FMF before, during, and after FMF attacks.

**METHODS:** Sixty-seven patients with FMF were enrolled in this study. Serum fetuin-A, seruloplasmin, fibrinogen, C reactive protein (CRP), white blood cell count (WBC), calcium, and erythrocyte sedimentation rate (ESR) were measured three times: during the attack-free period, 12 h after FMF attacks, and 7 days after FMF attacks. Plasma fetuin-A concentration was measured by use of an enzyme-linked immunoassay (ELISA) kit. Correlations and differentiation between

the serum fetuin-A and other inflammatory markers in patients with FMF were investigated by use of the paired-samples T test and the Pearson correlation test ( $p < 0.01$ ).

**RESULTS:** Serum fetuin-A levels of all FMF patients in the attack period were significantly lower than in the attack-free period ( $p < 0.001$ ). In contrast, serum seruloplasmin ( $p < 0.05$ ), fibrinogen ( $p < 0.001$ ), CRP ( $p < 0.05$ ), WBC ( $p < 0.05$ ), and ESR ( $p < 0.05$ ) were all significantly higher than in the attack-free period. Plasma fetuin-A is significantly and inversely highly correlated with the other inflammatory markers.

**CONCLUSION:** Fetuin-A might be a novel indicator of disease activity in patients with FMF and could be used as an adjunctive marker for differentiation of FMF attacks. The negative correlation between serum fetuin-A and other inflammatory markers may also be indicative of inflammation-dependent downregulation of fetuin-A expression in FMF patients.

DOI: 10.1007/s10620-013-2814-7

PMID: 23925820 [Indexed for MEDLINE]

2307. Ren Fail. 2013 Oct;35(9):1304. doi: 10.3109/0886022X.2013.824382. Epub 2013 Aug 7.

Rapidly progressive glomerulonephritis in a patient with familial Mediterranean fever and renal amyloidosis.

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DOI: 10.3109/0886022X.2013.824382

PMID: 23924034 [Indexed for MEDLINE]

2308. Curr Opin Rheumatol. 2013 Sep;25(5):658-64. doi: 10.1097/BOR.0b013e328363eb08.

Autoinflammatory bone disorders: update on immunologic abnormalities and clues about possible triggers.



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**PURPOSE OF REVIEW:** To provide an update on the genetics and immunologic basis of autoinflammatory bone disorders including chronic recurrent multifocal osteomyelitis including the monogenic forms of the disease.

**RECENT FINDINGS:** Ongoing research in murine, canine and human models of sterile bone inflammation has solidified the hypothesis that sterile bone inflammation can be genetically driven. Mutations in *Pstpip2*, *LPIN2* and *IL1RN* have been identified in monogenic autoinflammatory bone disorders that have allowed more detailed dissection of the immunologic defects that can produce sterile osteomyelitis. Recent studies in murine chronic multifocal osteomyelitis, deficiency of the interleukin-1 receptor antagonist (DIRA), Majeed syndrome and SAPHO syndrome reveal abnormalities in innate immune system function. IL-1 pathway dysregulation is present in several of these disorders and blocking IL-1 therapeutically has resulted in control of disease in DIRA, Majeed syndrome and in some cases of SAPHO and CRMO. Basic research demonstrates the importance of the innate immune system in disease pathogenesis and offers clues about potential disease triggers.

**SUMMARY:** Research and clinical data produced over the last several years support the important role of innate immunity in sterile osteomyelitis. Based on what has been learned in the monogenic autoinflammatory bone disorders, IL-1 is emerging as an important pathway in the development of sterile bone inflammation.

DOI: 10.1097/BOR.0b013e328363eb08

PMCID: PMC4912130

PMID: 23917160 [Indexed for MEDLINE]

2309. Eur J Obstet Gynecol Reprod Biol. 2013 Oct;170(2):449-51. doi: 10.1016/j.ejogrb.2013.07.023. Epub 2013 Jul 31.

Assessment of ovarian reserve based on hormonal parameters, ovarian volume, and antral follicle count in women with familial Mediterranean fever.

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**OBJECTIVE:** To evaluate ovarian reserve in women with familial Mediterranean fever (FMF).

**STUDY DESIGN:** Thirty women with FMF (20-29 years) and thirty healthy controls (20-29 years) were admitted to this study. Basal serum levels of follicle-stimulating hormone (FSH), oestradiol (E2), luteinizing hormone (LH) and inhibin B were measured on cycle day 3. All participants underwent transvaginal ultrasonographic examination on the third day of their menstrual cycle for the determination of ovarian volume (OV) and total antral follicle count (AFC).

**RESULTS:** Women with FMF had significantly higher concentrations of FSH, LH and E2 than healthy controls. Total AFC was significantly lower in women with FMF than in healthy controls. OV was also lower in the FMF group but there was no statistically significant difference in OV between the groups. Age was negatively associated with FSH and LH. Inhibin B was found to be negatively correlated with LH and OV.

**CONCLUSIONS:** In this preliminary study, the first in FMF patients, we found that ovarian reserve was reduced in women with FMF compared with healthy controls. FMF may affect the ovarian reserve but the mechanism of this effect is unclear.

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DOI: 10.1016/j.ejogrb.2013.07.023

PMID: 23915763 [Indexed for MEDLINE]

2310. BMC Pharmacol Toxicol. 2013 Aug 5;14:40. doi: 10.1186/2050-6511-14-40.

Anakinra pharmacokinetics in children and adolescents with systemic-onset juvenile idiopathic arthritis and autoinflammatory syndromes.

Urien S, Bardin C, Bader-Meunier B, Mouy R, Compeyrot-Lacassagne S, Foissac F, Florkin B, Wouters C, Neven B, Treluyer JM, Quartier P.

**BACKGROUND:** Anakinra pharmacokinetics and pharmacodynamics were investigated in

children and adolescents treated for systemic-onset juvenile idiopathic arthritis (SJIA) and autoinflammatory syndromes.

**METHODS:** Anakinra was given subcutaneously at doses between 2 and 10 mg/kg (maximum 100 mg) per day. Anakinra concentrations were recorded in patients, as well as C-reactive protein (CRP) levels, on different occasions. The data were fitted to a pharmacokinetic-pharmacodynamic model via a population approach using Monolix.

**RESULTS:** A total of 87 children and adolescents, 8 months to 21 years old, were available for pharmacokinetic evaluation. A one compartment model with linear absorption and elimination described the pharmacokinetics. Taking into account bodyweight to explain variations in apparent clearance (CL/F) and distribution volume (V/F) significantly reduced the associated between-subject and between-occasion variabilities. The final estimates were 6.24 L/h/70 kg and 65.2 L/70 kg for CL/F and V/F respectively. A mixture pharmacodynamic model described the CRP level change during anakinra treatment for the SJIA patients with 2 subpopulations, patients with high baseline and large CRP decrease and patients with low baseline and small CRP decrease followed by a re-increase in CRP levels. There was no significant effect of the combined anti-inflammatory treatment. The proportion of patients for which the development of a resistance to treatment was significant was 62% and the corresponding time was approximately 60 days.

**CONCLUSIONS:** Based on effects in SJIA, a prospective dosage adjustment was proposed based on a 0.4 mg/L C<sub>ss</sub> target in order to obtain a CRP decrease to 10 mg/L or below.

DOI: 10.1186/2050-6511-14-40

PMCID: PMC3750485

PMID: 23915458 [Indexed for MEDLINE]

2311. Genet Med. 2014 Mar;16(3):258-63. doi: 10.1038/gim.2013.112. Epub 2013 Aug 1.

Patient management and the association of less common familial Mediterranean fever symptoms with other disorders.

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**PURPOSE:** In this study, we present clinical data from 16,000 familial Mediterranean fever patients. We also discuss the clinical manifestation of a subset of these patients and their potential symptom associations with other disorders.

**METHODS:** Familial Mediterranean fever patients were confirmed using Tel-Hashomer criteria and were tested for the 12 most common mutations using the familial Mediterranean fever StripAssay. A total of 100 samples were selected, and their MEFV gene exons and intron junctions were completely sequenced.

**RESULTS:** We observed that in children severe phenotypes with polyserositis, erysipelas-like erythema, splenomegaly, and vasculitis are associated with high penetrance of exon 10 mutations, particularly M694V. Several forms of arthritis were associated with familial Mediterranean fever, including acute mono/oligoarthritis in the lower extremities, destructive arthritis, ankylosing spondylitis, sacroiliitis, arthritis of the hip joint, and juvenile chronic arthritis. Severe life-threatening complications, such as adhesive intestinal obstruction, renal amyloidosis, and uncommon/rare symptoms were sometimes the only form of familial Mediterranean fever manifestation.

**CONCLUSION:** We suggest performing familial Mediterranean fever genetic testing for patients presenting with rare/uncommon symptoms also common in other disorders, to prevent misdiagnosis or delayed diagnosis. In our experience, the most effective patient management for familial Mediterranean fever was its rapid diagnosis through genetic testing, initiation of colchicine therapy, and promotion of attack prevention through counseling.

DOI: 10.1038/gim.2013.112

PMID: 23907647 [Indexed for MEDLINE]

2312. J Leukoc Biol. 2013 Nov;94(5):1091-6. doi: 10.1189/jlb.1012510. Epub 2013 Jul 30.

Technical advance: Inhibition of neutrophil chemotaxis by colchicine is modulated through viscoelastic properties of subcellular compartments.

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Colchicine is an efficient drug for the management of inflammatory diseases, such as gouty arthritis and familial Mediterranean fever. It affects neutrophil activity by interfering with the formation of microtubules. To test the hypothesis that therapeutic concentrations of colchicine modulate the mechanical properties of these cells, we applied a combination of biophysical techniques (optical stretching and microrheology) to analyze cellular deformability. The contribution of the subcellular compartments to the regulation of cell mechanics was determined by fitting a multicomponent model of cellular viscoelasticity to time-dependent deformation curves. Neutrophils were found to be less deformable in response to 10 ng/ml colchicine. The model-based analysis of cellular deformation revealed a decrease in cytoplasmatic elasticity and a substantial increase in both elasticity and viscosity of the cell membrane compartment in response to colchicine. These results correlate with a reduced number of cytoplasmatic microtubules and an increase in subcortical actin filaments. The latter finding was confirmed by microrheology and fluorescence microscopy. Neutrophil migration through small pores requiring substantial cellular deformations, but not through large pores, was significantly impaired by colchicine. These data demonstrate that colchicine determines mechanics of neutrophils and, thereby, motility in confined spaces, which is crucial during extravasation of neutrophils in response to inflammatory stimuli.

DOI: 10.1189/jlb.1012510

PMID: 23901122 [Indexed for MEDLINE]

2313. Clin Exp Rheumatol. 2013 May-Jun;31(3 Suppl 77):141-9. Epub 2013 Jul 24.

The most recent advances in pathophysiology and management of tumour necrosis factor receptor-associated periodic syndrome (TRAPS): personal experience and literature review.

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Tumour necrosis factor-receptor associated periodic syndrome (TRAPS) is a rare autosomal dominant autoinflammatory disorder characterised by recurrent episodes of long-lasting fever and inflammation in different regions of the body, as musculo-skeletal system, skin, gastrointestinal tube, serosal membranes and eye. Inflammatory attacks usually start in the pediatric age with initial corticosteroid-responsiveness. Most reported cases of TRAPS involve patients of European ancestry and diagnosis can be formulated by the combination of genetic analysis and a compatible phenotype. Its prognosis is strictly dependent on the appearance of amyloidosis, secondary to uncontrolled relapsing inflammation. Thanks to a better understanding of its pathogenesis, the disease is now managed with anti-interleukin (IL)-1 antagonists, rather than corticosteroids or tumour necrosis factor (TNF) inhibitors. The aim of this review is to describe the current understanding and advances of TRAPS genetic basis, pathogenesis and management options by integrating the most recent data in the medical literature.

PMID: 23899820 [Indexed for MEDLINE]

2314. Rev Clin Esp. 2013 Aug-Sep;213(6):319-20. doi: 10.1016/j.rce.2013.05.003. Epub 2013 Jul 5.

Autoinflammatory diseases, more frequent than it seems?

[Article in English, Spanish]

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DOI: 10.1016/j.rce.2013.05.003

PMID: 26530945

2315. Gut Liver. 2013 Jul;7(4):497-9. doi: 10.5009/gnl.2013.7.4.497. Epub 2013 Jul 11.

Bloody Diarrhea as a Presentation Manifestation of Familial Mediterranean Fever in a Patient with Compound Heterozygote Mutations of the MEFV Gene.

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Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease characterized by episodic fever and inflammatory polyserositis, which could lead to a variety of manifestations, including recurrent abdominal pain. Herein, a 12-year-old boy who has suffered from fever and bloody diarrhea since early childhood is described. All structural and underlying disorders leading to bleeding were excluded. Genetic studies indicated compound heterozygote mutations of M680I/R761H in the MEFV gene, which confirmed the diagnosis of FMF. Therefore, treatment with colchicine was started, which led to symptom relief. As gastrointestinal manifestations appear to be the main features of FMF, bloody diarrhea could also be considered an initial symptom of FMF.

DOI: 10.5009/gnl.2013.7.4.497

PMCID: PMC3724042

PMID: 23898394

2316. Swiss Med Wkly. 2013 Jul 29;143:w13816. doi: 10.4414/smw.2013.13816. eCollection 2013.

Acute coronary syndrome in patients younger than 30 years--aetiologies, baseline characteristics and long-term clinical outcome.

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**BACKGROUND:** Coronary atherosclerosis begins early in life, but acute coronary syndromes in adults aged <30 years are exceptional. We aimed to investigate the rate of occurrence, clinical and angiographic characteristics, and long-term clinical outcome of acute coronary syndrome (ACS) in young patients who were referred to two Swiss hospitals.

**METHODS:** From 1994 to 2010, data on all patients with ACS aged <30 years were retrospectively retrieved from our database and the patients were contacted by phone or physician's visit. Baseline, lesion and procedural characteristics, and clinical outcome were compared between patients in whom an underlying atypical aetiology was found (non-ATS group; ATS: atherosclerosis) and patients in whom no such aetiology was detected (ATS group). The clinical endpoint was freedom from any major adverse cardiac event (MACE) during follow-up.

**RESULTS:** A total of 27 young patients with ACS aged <30 years were admitted during the study period. They accounted for 0.05% of all coronary angiograms performed. Mean patient age was  $26.8 \pm 3.5$  years and 22 patients (81%) were men. Current smoking (81%) and dyslipidaemia (59%) were the most frequent risk factors. Typical chest pain ( $n = 23$ ; 85%) and ST-segment elevation myocardial infarction (STEMI;  $n = 18$  [67%]) were most often found. The ATS group consisted of 17 patients (63%) and the non-ATS group of 10 patients (37%). Hereditary thrombophilia was the most frequently encountered atypical aetiology ( $n = 4$ ; 15%). At 5 years, mortality and MACE rate were 7% and 19%, respectively.

**CONCLUSION:** ACS in young patients is an uncommon condition with a variety of possible aetiologies and distinct risk factors. In-hospital and 5-year clinical outcome is satisfactory.

DOI: 10.4414/smw.2013.13816

PMID: 23896944 [Indexed for MEDLINE]

2317. PLoS One. 2013 Jul 24;8(7):e69757. doi: 10.1371/journal.pone.0069757. Print 2013.

Involvement of the same TNFR1 residue in mendelian and multifactorial inflammatory disorders.



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**OBJECTIVES:** TNFRSF1A is involved in an autosomal dominant autoinflammatory disorder called TNFR-associated periodic syndrome (TRAPS). Most TNFRSF1A mutations are missense changes and, apart from those affecting conserved cysteines, their deleterious effect remains often questionable. This is especially true for the frequent R92Q mutation, which might not be responsible for TRAPS per se but represents a susceptibility factor to multifactorial inflammatory disorders. This study investigates TRAPS pathophysiology in a family exceptional by its size (13 members) and compares the consequences of several mutations affecting arginine 92.

**METHODS:** TNFRSF1A screening was performed by PCR-sequencing. Comparison of the 3-dimensional structure and electrostatic properties of wild-type and mutated TNFR1 proteins was performed by in silico homology modeling. TNFR1 expression was assessed by FACS analysis, western blotting and ELISA in lysates and supernatants of HEK293T cells transiently expressing wild-type and mutated TNFR1.

**RESULTS:** A TNFRSF1A heterozygous missense mutation, R92W (c.361C>T), was shown to perfectly segregate with typical TRAPS manifestations within the family investigated ( $p < 5.10(-4)$ ). It was associated with very high disease penetrance (0.9). Prediction of its impact on the protein structure revealed local conformational changes and alterations of the receptor electrostatic properties. R92W also impairs the TNFR1 expression at the cell surface and the levels of soluble receptor. Similar results were obtained with R92P, another mutation previously identified in a very small familial form with incomplete penetrance and variable expressivity. In contrast, TNFR1-R92Q behaves like the wild-type receptor.

**CONCLUSIONS:** These data demonstrate the pathogenicity of a mutation affecting arginine 92, a residue whose involvement in inflammatory disorders is deeply debated. Combined with previous reports on arginine 92 mutations, this study discloses an unusual situation in which different amino acid substitutions at the same position in the protein are associated with a clinical spectrum bridging Mendelian to multifactorial conditions.

DOI: 10.1371/journal.pone.0069757  
PMCID: PMC3722142  
PMID: 23894535 [Indexed for MEDLINE]

2318. Actas Dermosifiliogr. 2013 Sep;104(7):617-22. doi: 10.1016/j.adengl.2012.11.020. Epub 2013 Jul 23.

Advances in the diagnosis and treatment of tumor necrosis factor receptor-associated periodic syndrome.

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Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is a rare autosomal dominant disease included in the group of autoinflammatory syndromes. It is characterized by recurrent episodes of fever and inflammation in different regions of the body. The main clinical manifestations are myalgia, migratory erythematous rash, periorbital edema, and abdominal pain. The diagnosis is reached using gene analysis and prognosis depends on the appearance of amyloidosis secondary to the recurrent episodes of inflammation. Tumor necrosis factor inhibitors and corticosteroids are the most widely used treatments. In recent years, significant advances have been made in the diagnosis and treatment of TRAPS, thanks to a better understanding of its pathogenesis. Dermatologists must be aware that the skin manifestations of TRAPS are particularly important, as they are often diagnostic.

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DOI: 10.1016/j.adengl.2012.11.020  
PMID: 23891452 [Indexed for MEDLINE]

2319. Reumatismo. 2013 Jun 12;65(2):55-62. doi: 10.4081/reumatismo.2013.55.

Childhood versus adulthood-onset autoinflammatory disorders: myths and truths

intertwined.

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Autoinflammatory disorders are characterized by spontaneous episodes of systemic inflammation deriving from inherited defects of the innate immune system. Childhood is usually the lifetime involved in most inherited autoinflammatory disorders, but a moderate number of patients may experience disease onset during adulthood. Herein we report our experience in the clinical and genetic approach to the diagnosis of autoinflammatory disorders in regard of the first 500 pediatric and adult patients evaluated during the period 2007-2012 in our Center, due to histories of periodically-recurring inflammatory attacks, giving emphasis to the differences observed according to patients' age and to the most relevant data differentiating child and adult-onset autoinflammatory disorders in the medical literature.

DOI: 10.4081/reumatismo.2013.55

PMID: 23877409 [Indexed for MEDLINE]

2320. J Clin Rheumatol. 2013 Aug;19(5):246-51. doi: 10.1097/RHU.0b013e31829ce005.

Disease severity in adult patients of Turkish ancestry with familial mediterranean fever living in Germany or Turkey. Does the country of residence affect the course of the disease?

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BACKGROUND: The environment may affect the course of familial Mediterranean fever

(FMF).

**OBJECTIVE:** The objective of this study was to compare disease severity between adult FMF patients in Turkey (TR) and Germany (G).

**METHODS:** Adult FMF patients of Turkish ancestry on colchicine living in Turkey (n = 40) or G (n = 35) were compared. Disease severity, C-reactive protein (CRP), and erythrocyte sedimentation rate were assessed.

**RESULTS:** Groups differed significantly in the following aspects: age at onset of disease (TR: 15.6, G: 10.8 years;  $P = 0.02$ ), delay between onset and initiation of colchicine treatment (TR: 6.8 years, G: 14.9 years;  $P < 0.001$ ), female gender (TR: 80%, G: 57.1%;  $P = 0.04$ ), and duration of disease (TR: 14.4 years, G: 23.4 years;  $P < 0.001$ ). There was no significant difference in colchicine treatment concerning average dosing and duration of therapy. No significant difference could be found between the 2 groups in CRP and disease severity as assessed by the score of Pras et al. (Am J Med Genet. 1998;75:216-219) even after adjusting for potential confounding variables. Mean erythrocyte sedimentation rate was significantly higher among patients living in G (TR: 13.2 mm/first hour, G: 26.3 mm/first hour;  $P < 0.001$ ). Among patients living in Germany, there was a significant difference in age at FMF onset depending on their country of birth (born in TR: 14.9 years, born in G: 6.9 years;  $P = 0.0001$ ).

**CONCLUSIONS:** In adult FMF patients living in Turkey or Germany, no difference in disease activity or CRP could be found. German patients were younger at onset of disease and had a longer delay between onset and initiation of colchicine treatment.

DOI: 10.1097/RHU.0b013e31829ce005

PMID: 23872541 [Indexed for MEDLINE]

2321. Clin Pharmacol Ther. 2014 Jan;95(1):89-97. doi: 10.1038/clpt.2013.148. Epub 2013 Jul 18.

Novel therapeutics for the treatment of familial Mediterranean fever: from colchicine to biologics.

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Erratum in

Clin Pharmacol Ther. 2014 Jan;95(1):110.

Familial Mediterranean fever (FMF), an inherited autosomal recessive disorder, is characterized by sporadic, paroxysmal attacks of fever and serosal inflammation, lasting 1-3 days. Patients may develop renal amyloidosis, arthritis, serositis, and skin and oral lesions. Diagnosis is based on clinical features, response to treatment with colchicine, and genetic analysis. Colchicine prevents attacks and renal amyloidosis, in addition to reversing proteinuria. Nonresponders may receive novel therapy, including interleukin (IL)-1 receptor antagonists and IL-1 decoy receptor. Recently, new options have been considered.

DOI: 10.1038/clpt.2013.148

PMID: 23867542 [Indexed for MEDLINE]

2322. Biomed Res Int. 2013;2013:185317. doi: 10.1155/2013/185317. Epub 2013 Jun 20.

Is neutrophil/lymphocyte ratio associated with subclinical inflammation and amyloidosis in patients with familial Mediterranean fever?

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**BACKGROUND:** The purpose of the present study is to determine the association between neutrophil/lymphocyte ratio and both subclinical inflammation and amyloidosis in familial Mediterranean fever.

**METHODS:** Ninety-four patients with familial Mediterranean fever and 60 healthy volunteers were included in the study. Of the patients, 12 had familial Mediterranean fever related amyloidosis. The neutrophil/lymphocyte ratio of the patients was obtained from the hematology laboratory archive.

**RESULTS:** The neutrophil/lymphocyte ratio was significantly higher among persons with familial Mediterranean fever compared to healthy individuals ( $P < 0.0001$ ).

Also, neutrophil/lymphocyte ratio was significantly higher in patients with amyloidosis than in amyloidosis-free patients ( $P < 0.0001$ ). Since NLR was evaluated in nonamyloid and amyloid stages of the same patient population (type 1 phenotype), we obtained significant statistical differences ( $1.95 \pm 0.30$  versus  $2.64 \pm 0.48$ ,  $P < 0.05$ , resp.). With the cutoff value of neutrophil/lymphocyte ratio  $>2.21$  and AUC = 0.734 ( $P = 0.009$ ), it was a reliable marker in predicting the development of amyloidosis.

**CONCLUSION:** The neutrophil/lymphocyte ratio, an emerging marker of inflammation, is higher in patients with familial Mediterranean fever in attack-free periods. The neutrophil/lymphocyte ratio may be a useful marker in predicting the development of amyloidosis.

DOI: 10.1155/2013/185317

PMCID: PMC3705820

PMID: 23865042 [Indexed for MEDLINE]

2323. Cell J. 2013 Summer;15(2):152-9. Epub 2013 Jul 2.

Mediterranean Fever gene analysis in the azeri turk population with familial mediterranean Fever: evidence for new mutations associated with disease.

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**OBJECTIVE:** Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent febrile attacks accompanied by serosal and synovial membrane inflammation. FMF is caused by mutations in the MEFV gene and are found usually among Mediterranean populations, Armenians, Turks, Arabs and Jews. The aim of this study was to determine the frequency of MEFV gene mutations among FMF

patients in the Azeri Turk population in North-West of Iran.

**MATERIALS AND METHODS:** In this descriptive study, 130 FMF patients with Azeri Turk origin were screened for mutations in four exons (2, 3, 5 and 10) of MEFV gene. Genomic DNA was extracted from whole blood and entered in ARMS-PCR and PCR-RFLP reactions. When cases were negative in ARMS-PCR and PCR-RFLP, the exons were amplified and subjected to direct sequencing.

**RESULTS:** Our results showed that the most common mutations in this study population was M694V (40.19%) followed by E148Q (17.64%), V726A (13.72%), M680I (12.74%) and M694I (2.94%) mutations. Four new mutations including K618N, K716M, S614F and G136E were identified in our study.

**CONCLUSION:** The prevalence of five common mutations in our study was highly similar to previous studies analysing the Mediterranean basin populations. Investigation by sequencing also revealed four new variants in the study population. The main genotype-phenotype correlation finding was the presence of M694V mutation in homozygote or compound heterozygote state in the patients with renal manifestations.

PMCID: PMC3712776

PMID: 23862117

2324. Am J Case Rep. 2013 Jul 10;14:241-4. doi: 10.12659/AJCR.889260. Print 2013.

Posterior reversible encephalopathy syndrome in a renal transplanted patient.

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**PATIENT:** Male, 28 **FINAL DIAGNOSIS:** Posterior reversible encephalopathy syndrome

**Symptoms:** Headache • pain around umbilical region • seizures • visual disturbances

**MEDICATION:** Mycophenolate mofetil **Clinical Procedure:** Treatment of parasitosis •

antiepileptic treatment • control of hypertension • changing mycophenolate

mofetil to everolimus **Specialty:** Transplantology.

**OBJECTIVE:** Unusual or unexpected effect of treatment.

**BACKGROUND:** Posterior reversible encephalopathy syndrome (PRES) is characterized by reversible neurological findings with clinical hallmarks such as headache,

confusion, seizures, cortical visual disturbances, and other focal neurological signs.

CASE REPORT: A 28-year-old male patient was hospitalized secondary to diarrhea and abdominal pain. He had renal transplantation due to renal amyloidosis secondary to familial Mediterranean fever (FMF). In his clinical follow-up, he had seizures, hemiparesis, blurred vision, and vomited an *Ascaris lumbricoides*. MRI results led to diagnosis of PRES. Mycophenolate mofetil was changed to everolimus, his systolic blood pressure kept below 140 mm hg, and his intestinal parasitosis was treated. During follow-up, he had no pain and no diarrhea. His neurological symptoms turned to normal within 48 hours and neuroradiological findings returned to normal within 2 weeks.

CONCLUSIONS: PRES is a rare disorder of unknown incidence in renal transplantation patients. Early diagnosis is very important to prevent irreversible neurological sequelae. PRES is totally reversible with cessation of the offending agent, rapid control of hypertension, and treatment of the underlying disease. For early diagnosis and to reduce morbidity and mortality, stool sample examination should be made in patients taking immunosuppressive drugs.

DOI: 10.12659/AJCR.889260

PMCID: PMC3711906

PMID: 23861991

2325. Lupus. 2013 Sep;22(10):1056-9. doi: 10.1177/0961203313497117. Epub 2013 Jul 16.

A Japanese pediatric patient with coexisting systemic lupus erythematosus and familial Mediterranean fever.

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This case report describes a Japanese girl with systemic lupus erythematosus who had recurrent fevers and erythema nodosum. She was later found to carry the complex allele E148Q/R202Q/P369S/R408Q of MEFV, the gene responsible for familial



Mediterranean fever.

DOI: 10.1177/0961203313497117

PMID: 23861027 [Indexed for MEDLINE]

2326. Eur Rev Med Pharmacol Sci. 2013 Jul;17(13):1820-3.

First and second trimester biochemical markers in familial mediterranean fever.

Turkcapar F(1), Engin-Üstün Y, Simsek OY, Deveer R, Danisman N, Dilmen U, Mollamahmutoglu L.

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**OBJECTIVES:** Our aim was to investigate whether the maternal serum concentrations of first and second trimester serum analytes are altered in familial Mediterranean fever (FMF) pregnancies.

**MATERIALS AND METHODS:** The screening tests were compared in a series of 16 serum samples from FMF pregnancies and in a cohort of 48 pregnant women with normal pregnancy. Serum samples were obtained between 11 and 13 weeks; 16 and 18 weeks gestation.

**RESULTS:** Serum pregnancy-associated plasma protein-A (PAPP-A) levels, expressed as multiples of the median ( $0.9 \pm 0.45$  MoM) in the control group, were significantly higher than FMF patients ( $0.6 \pm 0.3$  MoM) ( $p = 0.027$ ). Analyses of alpha-fetoprotein, human chorionic gonadotropin and oestriol levels showed no significant differences between FMF and normal pregnancies.

**CONCLUSIONS:** Our study revealed that low levels of PAPP-A are associated with FMF.

PMID: 23852910 [Indexed for MEDLINE]

2327. Methods Mol Biol. 2013;1040:117-35. doi: 10.1007/978-1-62703-523-1\_10.

Inflammasome activation and inhibition in primary murine bone marrow-derived

cells, and assays for IL-1 $\alpha$ , IL-1 $\beta$ , and caspase-1.

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Through its ability to control the proteolytic maturation and secretion of interleukin-1 family cytokines, the inflammasome occupies a central role in the activation of inflammation and also influences the shaping of adaptive immunity. Since it affects a multitude of different immune responses from autoinflammatory diseases to host defense, vaccine efficacy, and even cancer, it has become of interest to many researchers. Here, we describe a straightforward method for inflammasome assays in primary murine bone marrow--derived myeloid cells. The protocol encompasses cell handling, inflammasome activation and inhibition, as well as the detection of IL-1 $\beta$ , caspase-1, and IL-1 $\alpha$  by ELISA and Western blot.

DOI: 10.1007/978-1-62703-523-1\_10

PMID: 23852601 [Indexed for MEDLINE]

2328. Open Rheumatol J. 2013 Apr 19;7:22-5. doi: 10.2174/1874312901307010022. Print 2013.

MEFV Variants in Patients with PFAPA Syndrome in Japan.

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**BACKGROUND:** The pathogenesis of PFAPA (periodic fever, aphthous stomatitis, pharyngitis, adenitis) syndrome is unknown as yet. In order to understand whether genes implicated in other auto-inflammatory diseases might be involved in the pathogenesis of PFAPA, all variants in the genes causing familial Mediterranean fever (FMF), tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), and Hyper IgD syndrome were analyzed in children with PFAPA.

**PATIENTS AND METHODS:** All variants in MEFV, TNFRSF1A, and MVK were analyzed in 20

patients with PFAPA. PFAPA were diagnosed by previous published criteria. The findings of all analyses in PFAPA patients were compared with those of unaffected normal subjects (n=62).

**RESULTS:** In the 13 children of 20 with PFAPA, the heterozygous variants of MEFV (5 patients: E148Q-L110P, 2 patients: E148Q, 1 patient: E148Q-L110P/E148Q, 1 patient: E148Q-P369S-R408Q-E84K, 1 patient: E148Q-L110P-P369S-A408G, 1 patient: R202Q, 1 patient: P115R) were found. No variants belonging to TNFRSF1A or MVK were detected in children with PFAPA. The frequency of the E148Q-L110P variants in children with PFAPA was significantly higher than that observed in unaffected normal subjects (7/20 versus 8/62). The duration of the episodes of illness in PFAPA children with MEFV variants was shorter than that of patients without variants.

**CONCLUSION:** Genes involved in the development and progression of MEFV may affect the incidence and the phenotype of PFAPA in children.

DOI: 10.2174/1874312901307010022

PMCID: PMC3681033

PMID: 23847694

2329. PLoS One. 2013 Jul 3;8(7):e68431. doi: 10.1371/journal.pone.0068431. Print 2013.

The risk of familial Mediterranean fever in MEFV heterozygotes: a statistical approach.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disorder due to MEFV mutations and one of the most frequent Mediterranean genetic diseases. The observation of many heterozygous patients in whom a second mutated allele was excluded led to the proposal that heterozygosity could be causal. However, heterozygosity might be coincidental in many patients due to the very high rate of mutations in Mediterranean populations.

**OBJECTIVE:** To better delineate the pathogenicity of heterozygosity in order to

improve genetic counselling and disease management.

**METHODS:** Complementary statistical approaches were used: estimation of FMF prevalence at population levels, genotype comparison in siblings from 63 familial forms, and genotype study in 557 patients from four Mediterranean populations.

**RESULTS:** At the population level, we did not observe any contribution of heterozygosity to disease prevalence. In affected siblings of patients carrying two MEFV mutations, 92% carry two mutated alleles, whereas 4% are heterozygous with typical FMF diagnosis. We demonstrated statistically that patients are more likely to be heterozygous than healthy individuals, as shown by the higher ratio heterozygous carriers/non carriers in patients ( $p < 10^{-7}$ ) ( $p < 0.003$ ). The risk for heterozygotes to develop FMF was estimated between  $2.1 \times 10^{-3}$  and  $5.8 \times 10^{-3}$  and the relative risk, as compared to non carriers, between 6.3 and 8.1.

**CONCLUSIONS:** This is the first statistical demonstration that heterozygosity is not responsible for classical Mendelian FMF per se, but constitutes a susceptibility factor for clinically-similar multifactorial forms of the disease. We also provide a first estimate of the risk for heterozygotes to develop FMF.

DOI: 10.1371/journal.pone.0068431

PMCID: PMC3700951

PMID: 23844200 [Indexed for MEDLINE]

2330. Ren Fail. 2013 Sep;35(8):1071-4. doi: 10.3109/0886022X.2013.811345. Epub 2013 Jul 10.

Is colchicine therapy effective in all patients with secondary amyloidosis?

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**OBJECTIVE:** Although colchicine is effective on prevention and regression of amyloidosis in many cases, rate of unresponsiveness to colchicine therapy is not too low. However, there is no sufficient data about which factors effect to response of colchicine therapy on regression of amyloidosis.

**MATERIALS AND METHODS:** 24 patients with renal amyloidosis were enrolled into the

study. The patients were divided in two groups according to urinary protein excretions: non-nephrotic stage (14/24) and nephrotic stage (10/24). The patients were also categorized according to the etiology of amyloidosis; familial Mediterranean fever (FMF)-associated amyloidosis (15/24) versus rheumatoid disorders (RD)-associated amyloidosis (9/24). The changes of amount of proteinuria and estimated glomerular filtration rates were investigated after colchicine treatment started in these groups.

RESULTS: The mean follow-up period was  $27.7 \pm 19.2$  months. After initiating colchicine therapy, the degree of proteinuria was decreased higher than 50% in 11/14 (78%) of non-nephrotic patients and elevated only in three (22%) patients.

In nephrotic group, proteinuria was increased in 5/10 (50%) of patients.

Glomerular filtration rates were stable in nephrotic and non-nephrotic groups.

Presenting with nephrotic syndrome was higher in RD-associated amyloidosis (RD\_A) group (5/9) than FMF-associated amyloidosis (FMF\_A) group (5/15) without statistical significance ( $p > 0.05$ ). After colchicine treatment, proteinuria was decreased in 12/15 patients in FMF\_A group, however, the significant decreasing of proteinuria was not observed in RD\_A group ( $p = 0.05$  vs.  $p > 0.05$ ).

CONCLUSION: Colchicine therapy was found more effective in low proteinuric stage of amyloidosis. The beneficial effect of colchicine therapy was not observed in patients with RD- associated amyloidosis.

DOI: 10.3109/0886022X.2013.811345

PMID: 23841746 [Indexed for MEDLINE]

2331. Nat Rev Rheumatol. 2013 Oct;9(10):624-9. doi: 10.1038/nrrheum.2013.101. Epub 2013 Jul 9.

How should we approach classification of autoinflammatory diseases?

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The notion of 'autoinflammatory' disease was introduced at the end of the 1990s, and, since then, this concept has rapidly evolved. As a result, multiple

definitions of autoinflammatory disease, and classifications of conditions encompassed by these definitions, have been proposed; this succession highlights advances that have been made in understanding of the innate immune system, and especially the roles of IL-1 $\beta$  and the inflammasome in autoinflammatory conditions. However, the definitions and classifications that have been suggested to date face a number of structure and content issues. We therefore propose another, more clinically-oriented, definition: autoinflammatory diseases are diseases with clinical signs of inflammation, associated with elevated levels of acute-phase reactants, which are attributable to dysfunction of the innate immune system, genetically-determined or triggered by an endogenous factor. From this foundation, we propose a clinically-based classification of autoinflammatory diseases, and go on to discuss how immunological diseases as a whole, including autoimmune diseases, can be appropriately located within a continuum only if the classification process is multidimensional. For this purpose, we appeal to the philosophical concepts of family resemblance and signature.

DOI: 10.1038/nrrheum.2013.101

PMID: 23838615 [Indexed for MEDLINE]

2332. *Pediatr Neurol.* 2013 Oct;49(4):289-91. doi: 10.1016/j.pediatrneurol.2013.05.003. Epub 2013 Jul 6.

Recurrent peripheral facial palsy in a child with familial Mediterranean fever.

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**BACKGROUND:** Recurrent peripheral facial palsy is uncommon in children. It mostly occurs as an idiopathic disorder and to a lesser extent in the setting of some infectious, genetic, or systemic disorders. However, its association with familial Mediterranean fever has not been reported before.

**PATIENT:** We present a 14-year-old girl who experienced three episodes of right-sided peripheral facial palsy during a 9-month interval. She had a diagnosis of familial Mediterranean fever (homozygous with M694V mutation) and she had been receiving colchicine for 8 years. Recurrent peripheral facial palsy

could be a neurological manifestation of vasculitis in familial Mediterranean fever.

CONCLUSION: Recurrent peripheral facial palsy may be a manifestation of familial Mediterranean fever in children.

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DOI: 10.1016/j.pediatrneurol.2013.05.003

PMID: 23838413 [Indexed for MEDLINE]

2333. J Dermatol. 2013 Sep;40(9):749-51. doi: 10.1111/1346-8138.12227. Epub 2013 Jul 9.

Novel IL36RN mutation in a Japanese case of early onset generalized pustular psoriasis.

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Generalized pustular psoriasis is a distinct type of psoriasis characterized by recurrent febrile attacks with disseminated subcorneal pustules on generalized skin rashes. Recently, homozygous and compound heterozygous mutations of the IL36RN gene, which encodes the anti-inflammatory cytokine interleukin (IL)-36 receptor antagonist, were identified in familial and sporadic cases of various ethnicities with generalized pustular psoriasis. Here we report a 39-year-old Japanese male patient who had suffered from repeated attacks of generalized pustular psoriasis since infancy with intervals of several years. At presentation, erythematous lesions with a few pustules were found only on some parts of the body and controlled with topical corticosteroids. An analysis of the IL36RN gene revealed compound heterozygous mutations of c.28C>T and c.368C>T. While the former mutation causing the premature termination p.Arg10X is recurrent in Japanese cases, the latter missense mutation causing p.Thr123Met substitution is novel, but another mutation in the same position has been reported in one Japanese case. Our report further supports the presence of the Japanese-specific hot spots in the IL36RN gene, 28C and 368C, and suggests the functional significance of Thr123. This special type of generalized pustular psoriasis caused by IL36RN mutations has been designated as deficiency for IL-36 receptor

antagonist, a new hereditary autoinflammatory disease, and its phenotypes have emerged to include other related pustular disorders, palmoplantar pustulosis, acrodermatitis continua of Hallopeau, and acute generalized exanthematous pustulosis. The genetic analysis of the cases with these diseases would be important for establishment and application of the specific treatments targeting the IL-36 signaling.

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DOI: 10.1111/1346-8138.12227

PMID: 23834760 [Indexed for MEDLINE]

2334. BMJ Case Rep. 2013 Jul 4;2013. pii: bcr2012008395. doi: 10.1136/bcr-2012-008395.

Familial Mediterranean fever without fever as a cause of monoarthritis.

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Familial Mediterranean fever (FMF) is an autosomal recessive hereditary disease. FMF-related arthritis affects large joints, especially in the lower extremities. It starts with acute pain and swelling and affects one joint at a time. Fever is the most common symptom in FMF. Monoarthritis as the sole symptom is relatively rare and thus delayed diagnosis of the disease in a patient who had been suffering from monoarthritis for several years. Genetic analysis showing typical mutations in the patient eventually resulted in correct diagnosis, although classical clinical diagnostic criteria were not met. The patient received appropriate therapy with colchicine, which led to remission of the symptoms.

DOI: 10.1136/bcr-2012-008395

PMCID: PMC3736377

PMID: 23832993 [Indexed for MEDLINE]

2335. J Biol Regul Homeost Agents. 2013 Apr-Jun;27(2):329-36.



Colchicine modulates expression of pro-inflammatory genes in neutrophils from patients with familial Mediterranean fever and healthy subjects.

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Colchicine (Col) is a microtubule depolymerizing drug, widely used for treatment of familial Mediterranean fever (FMF). Mechanisms by which Col exerts its beneficial effects are not yet completely understood, especially with respect to gene expression in polymorphonuclear neutrophils (PMNs), the main effector cells in acute inflammatory attacks of FMF. This study was, therefore, designed to elucidate possible modulatory effect of Col on expression of inflammation-related genes in circulating PMNs from 16 FMF patients in the remission period and 11 healthy subjects. In vitro effect of Col exposure (1 microg/ml) on expression of 8 selected genes was examined using quantitative real-time RT-PCR. Col up-regulated expression of IL-8 and IL-1beta genes in FMF (13-fold and 2.7-fold, p less than 0.05, respectively) and healthy (3-fold and 6.5-fold, p less than 0.05, respectively) PMNs, and down-regulated caspase-1 in FMF neutrophils (3-fold, p less than 0.05). In FMF PMNs treated with Col mRNAs of IL-8 (51-fold, p less than 0.01) and c-FOS (7-fold, p less than 0.05) transcripts were elevated compared to those from healthy subjects. By contrast, caspase-1 mRNA was decreased in FMF neutrophils compared to healthy cells (1.6-fold, p less than 0.05). Hereby, we provide evidence that, at least in vitro, Col displays pro-inflammatory potential in respect to IL-1beta and IL-8 genes. At the same time, our findings implicate suppression of caspase-1 expression by Col as a potential mechanism for its effects in FMF treatment.

PMID: 23830384 [Indexed for MEDLINE]

2336. Eur J Clin Microbiol Infect Dis. 2013 Dec;32(12):1605-10. doi: 10.1007/s10096-013-1919-4. Epub 2013 Jul 5.

Circulating galectin-3 in infections and non-infectious inflammatory diseases.

ten Oever J(1), Giamarellos-Bourboulis EJ, van de Veerdonk FL, Stelma FF, Simon A, Janssen M, Johnson M, Pachot A, Kullberg BJ, Joosten LA, Netea MG.

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Recent studies point to a dual role for galectin-3 as both a circulating damage-associated molecular pattern and a cell membrane-associated pattern recognition receptor. The aim of this study was to assess the potential of circulating galectin-3 for discriminating between infections and non-infectious inflammatory disorders on the one hand, and between fungal and bacterial infections on the other. Galectin-3 and C-reactive protein (CRP) were measured in the plasma of 127 patients with either non-infectious inflammatory disorders (gout, autoinflammatory syndrome or pancreatitis) or an infection (viral lower respiratory tract infection, bacterial sepsis or candidaemia). Circulating galectin-3 concentrations were increased in patients with infections when compared with healthy volunteers or patients with non-infectious inflammatory diseases. At cut-off values with a specificity of 95%, the sensitivity of galectin-3 ( $>20.6$  ng/ml) to discriminate between an infection and non-infectious inflammation was higher than that of CRP ( $>156$  mg/l): 43% [95% confidence interval (CI) 33-53%] versus 27% (95% CI 19-37%),  $p = 0.03$ . After exclusion of patients with CRP  $<156$  mg/l, galectin-3 concentration  $>20.6$  ng/ml could identify 41 % (95% CI 29-53%) of the patients with an infection at the cost of one false-positive with non-infectious inflammation. Using this sequential approach, 57% of the patients with an infection could be selected. Galectin-3 concentrations were similar in patients with bacterial and Candida sepsis, while being lower in viral respiratory infections. Although galectin-3 does not discriminate between bacterial and Candida sepsis, the sequential use of CRP and galectin-3 in distinguishing infectious diseases from non-infectious inflammation may be superior to CRP alone.

DOI: 10.1007/s10096-013-1919-4

PMID: 23828453 [Indexed for MEDLINE]

Autoinflammatory diseases and syndromes in dermatology. Preface.

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DOI: 10.1016/j.det.2013.05.002

PMID: 23827254 [Indexed for MEDLINE]

2338. Dermatol Clin. 2013 Jul;31(3):507-11. doi: 10.1016/j.det.2013.04.007. Epub 2013 Jun 14.

Controlling inflammation: contemporary treatments for autoinflammatory diseases and syndromes.

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The continuous advance in the search for the cause and pathogenesis of the autoinflammatory syndromes, as well as reports of the efficacy of specific inflammation-mediator suppressors, has changed the way these syndromes are approached and treated; both the acute and long-term treatment of these diseases has improved significantly. Etiologic and pathophysiologic manipulation is and will be the future for controlling, even curing, this new and rare set of diseases.

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DOI: 10.1016/j.det.2013.04.007

PMID: 23827252 [Indexed for MEDLINE]

2339. *Dermatol Clin.* 2013 Jul;31(3):495-506. doi: 10.1016/j.det.2013.04.006. Epub 2013 May 25.

Type 2 diabetes mellitus: a metabolic autoinflammatory disease.

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The recent molecular, biologic, and genetic understanding of the inflammasome has revolutionized the diagnosis of and therapy for the phenotypically heterogeneous group of rare oligogenic disorders, now recognized to have autoinflammatory origin. This article reviews the importance of inflammasome activation in the central and peripheral mechanisms underlying a common, multifactorial, lifestyle-related, and polygenetic disease (type 2 diabetes mellitus), and conceptualizes the notion that this health challenge should now be recognized to have an autoinflammatory cause. It is hoped that targeting these mechanisms will enable the introduction of novel therapies that attack the basic pathogenetic mechanisms of type 2 diabetes mellitus rather than the epiphenomena that are its consequences.

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DOI: 10.1016/j.det.2013.04.006

PMID: 23827251 [Indexed for MEDLINE]

2340. *Dermatol Clin.* 2013 Jul;31(3):481-94. doi: 10.1016/j.det.2013.04.003. Epub 2013 Jun 2.

Autoinflammatory diseases in pediatrics.

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Autoinflammatory diseases (AIDs) are characterized by recurrent episodes of systemic and organ-specific inflammation. Many of these diseases share fever as a common presenting feature. Physicians need to consider AIDs in children with recurrent, unexplained fevers, when infectious and malignant causes have been discarded. This article discusses the differential diagnosis of recurrent fever in children, with a focus on AIDs. It discusses pharyngitis, and cervical adenitis and the monogenic autoinflammatory diseases that cause recurrent fevers including familial Mediterranean fever, hyper-immunoglobulin (Ig) D and periodic fever syndrome, tumor necrosis factor receptor-associated periodic syndrome, cryopyrin associated periodic syndromes, deficiency of interleukin-36 receptor antagonist, Majeed syndrome, chronic atypical neutrophilic dermatosis with lipodystrophy and increased temperature syndrome, and deficiency of the interleukin-1 receptor antagonist. In addition, the granulomatous disorders, pyogenic sterile arthritis, pyoderma gangrenosum, and acne and Blau syndrome, will be discussed.

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DOI: 10.1016/j.det.2013.04.003

PMID: 23827250 [Indexed for MEDLINE]

2341. *Dermatol Clin.* 2013 Jul;31(3):471-80. doi: 10.1016/j.det.2013.05.001.

Autoinflammatory syndromes.

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Autoinflammatory syndromes comprise a diagnostically challenging group of systemic inflammatory disorders uniquely related by (1) dysregulation of innate immunity, (2) inflammasome activation, (3) dramatic clinical features (high fevers, neutrophilic rashes, and bone or synovial involvement), (4) impressive

acute phase responses, and (5) effective treatment with cytokine inhibitors. This review details some of the more common autoinflammatory disorders, their distinguishing features and dermatologic manifestations, and how an accurate diagnosis can be established in patients presenting with periodic or intermittent febrile disorders.

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DOI: 10.1016/j.det.2013.05.001

PMCID: PMC4489412

PMID: 23827249 [Indexed for MEDLINE]

2342. *Dermatol Clin.* 2013 Jul;31(3):461-70. doi: 10.1016/j.det.2013.04.002. Epub 2013 May 14.

Autoinflammatory disorders, pain, and neural regulation of inflammation.

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Autoinflammatory disorders are disorders of the innate immune system that are distinct from autoimmune disorders. Dysregulation of the innate immune system, specifically an increase in interleukin-1 beta (IL-1 $\beta$ ), gives rise to a spectrum of symptoms marked by inflammation and pain. Identification of causative gene mutations led to the discovery of the inflammasome. Many autoinflammatory disorders also have a strong pain component. The contribution of IL-1 $\beta$  to pain and neural involvement is underappreciated. This article provides an overview of the current autoinflammatory disorders and highlights the contribution IL-1 $\beta$  makes to pain in these disorders.

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DOI: 10.1016/j.det.2013.04.002

PMID: 23827248 [Indexed for MEDLINE]

2343. *Dermatol Clin*. 2013 Jul;31(3):445-60. doi: 10.1016/j.det.2013.04.009. Epub 2013 Jun 14.

Psoriasis as autoinflammatory disease.

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This article presents a summary of the evidence for a link between autoinflammatory diseases and psoriasis. The main concepts regarding the disease state of psoriasis are discussed and these lead to a change in the perspective on the clinical and pathophysiologic nature of psoriasis as a chronic, recurrent disease with important genetically defined features, and an associated or concomitant systemic inflammatory state that involves a multifactorial cellular and molecular network, transforming the old perception of psoriasis as a localized autoimmune skin disease, to one of psoriasis as a systemic inflammatory disease with autoinflammatory features and severe associated comorbid conditions.

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DOI: 10.1016/j.det.2013.04.009

PMID: 23827247 [Indexed for MEDLINE]

2344. *Dermatol Clin*. 2013 Jul;31(3):427-35. doi: 10.1016/j.det.2013.04.004. Epub 2013 May 10.

What do autoinflammatory syndromes teach about common cutaneous diseases such as pyoderma gangrenosum? A commentary.

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Pyoderma gangrenosum (PG) is a neutrophilic dermatosis characterized by ulcerating skin lesions with rapid onset and recalcitrant treatment course. PG treatment targets an array of inflammatory pathways with variable success. One of the hallmark features of PG is its association with a broad spectrum of systemic disorders. The authors hypothesize that there are common inflammatory pathways linking these systemic disorders to neutrophilic dermatoses. Rare autoinflammatory diseases offer insights into the understanding of inflammatory skin conditions. This article explores observations of the natural history of PG that illuminate aspects of PG pathogenesis, highlighting the role of autoinflammatory mediators.

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DOI: 10.1016/j.det.2013.04.004

PMID: 23827245 [Indexed for MEDLINE]

2345. *Dermatol Clin*. 2013 Jul;31(3):405-25. doi: 10.1016/j.det.2013.04.001. Epub 2013 Jun 2.

Autoinflammatory pustular neutrophilic diseases.

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This article provides a new categorization of inflammatory pustular dermatoses in the context of recent genetic and biological insights. Monogenic diseases with pustular phenotypes are discussed, including deficiency of interleukin 1 receptor antagonist, deficiency of the interleukin 36 receptor antagonist, CARD14-associated pustular psoriasis, and pyogenic arthritis, pyoderma gangrenosum, and acne. How these new genetic advancements may inform how previously described pustular diseases are viewed, including pustular psoriasis and its clinical variants, with a focus on historical classification by clinical phenotype, is also discussed.



Published by Elsevier Inc.

DOI: 10.1016/j.det.2013.04.001

PMCID: PMC3703099

PMID: 23827244 [Indexed for MEDLINE]

2346. *Dermatol Clin.* 2013 Jul;31(3):387-404. doi: 10.1016/j.det.2013.04.005.

Autoinflammatory diseases in dermatology: CAPS, TRAPS, HIDS, FMF, Blau, CANDLE.

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Autoinflammatory diseases, including CAPS, TRAPS, HIDS, FMF, Blau, and CANDLE, have unique dermatologic presentations that can be a clue to diagnosis. Although these conditions are rare, the morbidity and mortality can be severe, and well-informed physicians can place these conditions in their differential diagnosis when familiar with the dermatologic manifestations. This review article presents a brief overview of each condition, clues to diagnosis that focus of dermatologic manifestations and clinical images, basic laboratory tests and follow-up, a brief review of treatments, and concludes with an overview for these autoinflammatory conditions and their differential diagnoses.

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DOI: 10.1016/j.det.2013.04.005

PMID: 23827243 [Indexed for MEDLINE]

2347. *Dermatol Clin.* 2013 Jul;31(3):363-85. doi: 10.1016/j.det.2013.04.010. Epub 2013 Jun 14.

Introduction to autoinflammatory syndromes and diseases.

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Autoinflammatory syndromes and diseases are a group of disorders of innate immunity. This group has grown rapidly in recent years as a result of research advancements in molecular biology and genetics. These diseases often present with skin manifestations and the dermatologist may not recognize the constellation of symptoms and medical history as a systemic inflammatory disease. Dermatologists would benefit from a deeper understanding of these diseases and the new treatments available for them.

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DOI: 10.1016/j.det.2013.04.010

PMID: 23827242 [Indexed for MEDLINE]

2348. Ren Fail. 2013 Aug;35(7):1013-6. doi: 10.3109/0886022X.2013.809096. Epub 2013 Jul 5.

Are systemic lupus erythematosus patients carrying MEFV gene less prone to renal involvement? Report of three cases and review of the literature.

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Familial Mediterranean fever (FMF) is an autosomal recessive auto inflammatory disease, characterized by acute attacks of serositis, arthritis or skin rash.

Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease characterized by multisystem inflammatory lesions affecting any organ systems in the body.

Coexistence of FMF and SLE is rare in literature. In this report, we present three patients with FMF associated with SLE.

DOI: 10.3109/0886022X.2013.809096

PMID: 23826804 [Indexed for MEDLINE]

2349. J Periodontol. 2014 May;85(5):706-12. doi: 10.1902/jop.2013.130230. Epub 2013 Jul 4.

Effect of chronic periodontitis on serum and gingival crevicular fluid oxidant and antioxidant status in patients with familial Mediterranean fever before and after periodontal treatment.

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**BACKGROUND:** The aim of this study is to investigate the impact of periodontal status on oxidant/antioxidant status in patients with chronic periodontitis (CP) who experienced familial Mediterranean fever (FMF) and their response to non-surgical periodontal therapy.

**METHODS:** Data were obtained from 13 patients with FMF with generalized CP (FMF-CP), 15 systemically healthy patients with generalized CP, 15 systemically and periodontal healthy controls (HCs), and 14 periodontally healthy patients with FMF (FMF-HC). Each participant's total oxidant status (TOS), total antioxidant status (TAS), and oxidative stress index (OSI) in their gingival crevicular fluid (GCF) and serum were recorded. Probing depth, clinical attachment level, and gingival and plaque indices in each participant were also measured. The GCF and clinical parameters at baseline and 6 weeks after periodontal treatment were recorded.

**RESULTS:** The study showed statistically significant improvement of clinical parameters in both FMF-CP and CP groups after periodontal treatment. The baseline GCF-TOS and OSI levels were significantly higher in the CP group compared with the FMF-CP group ( $P < 0.05$ ). After periodontal treatment, the GCF-TOS levels were significantly reduced in members of the FMF-CP group ( $P < 0.05$ ). The GCF-TAS levels in members of the FMF-CP group were significantly higher than those of members of the HC group at baseline ( $P < 0.05$ ). Serum-TAS levels in the FMF-CP group were significantly higher than those in the CP and HC groups at baseline ( $P < 0.05$ ). The GCF-TOS level in the FMF-CP group was significantly higher than that

in the FMF-HC group at baseline and 6 weeks. However, there were no significant differences in the serum-TOS and serum-OSI levels of those in the FMF-CP and CP groups at baseline and 6 weeks ( $P > 0.05$ ).

**CONCLUSION:** The results of the present study show that patients with FMF-CP displayed reduced oxidative stress and increased antioxidant status compared with those in the CP and HC groups.

DOI: 10.1902/jop.2013.130230

PMID: 23826647 [Indexed for MEDLINE]

2350. *Pediatr Emerg Care*. 2013 Jul;29(7):842-8; quiz 849-51. doi: 10.1097/PEC.0b013e318298df8b.

A taste of periodic fever syndromes.

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Periodic fevers are acquired or inherited disorders of innate immunity, which were first described in the 1940s. The patients are typically young at onset and have regularly recurring fevers for a few days to a few weeks with systemic inflammatory symptoms that are interrupted by symptom-free periods. There is a variety of clinical manifestations including gastrointestinal complaints, myalgias, arthralgias, and rash. A differential diagnosis in these patients may include recurrent infections, other inflammatory disorders, and neoplastic disease. This clinical review focuses on a sample of autoinflammatory disorders including familial Mediterranean fever, tumor necrosis factor receptor 1-associated periodic syndrome, hyperimmunoglobulinemia D syndrome, the cryopyrin-associated periodic syndrome, and periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome. We review the basics, pertinent clinical and laboratory features, and management of each entity.

DOI: 10.1097/PEC.0b013e318298df8b

PMID: 23823268 [Indexed for MEDLINE]

2351. Nat Rev Rheumatol. 2013 Sep;9(9):532-43. doi: 10.1038/nrrheum.2013.95. Epub 2013 Jul 2.

Vaccinations in juvenile chronic inflammatory diseases: an update.

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Vaccination is a powerful tool to reduce the burden of infectious diseases in paediatric patients with chronic rheumatic diseases. Live attenuated vaccines are not recommended for profoundly immunosuppressed patients, but nonlive vaccines have adequate safety and efficacy profiles in the few (admittedly underpowered) studies published to date. No severe vaccine-specific or disease-specific adverse events have been observed in patients with juvenile idiopathic arthritis (JIA) or childhood-onset systemic lupus erythematosus (SLE) who have been vaccinated with live or nonlive agents. The immune response to live vaccines is variable in these patients but generally adequate, despite concomitant use of immunosuppressive and biologic agents. The proposal that onset of autoimmune rheumatic diseases could be induced by vaccination is controversial and primarily based on case reports; however, patients with mevalonate kinase deficiency can experience febrile attacks after immunizations. Adequately powered studies of live and nonlive vaccination in patients with paediatric rheumatic diseases are necessary to clarify safety and efficacy issues. This narrative Review discusses vaccination in patients with JIA, childhood-onset SLE, juvenile dermatomyositis, juvenile systemic sclerosis, primary vasculitis and autoinflammatory syndromes. Vaccine safety, short-term and long-term changes in disease parameters, and the immunogenicity and influence of immunosuppressive agents are outlined for each combination of disease and vaccine.

DOI: 10.1038/nrrheum.2013.95

PMID: 23820860 [Indexed for MEDLINE]

2352. Int J Inflam. 2013;2013:183061. doi: 10.1155/2013/183061. Epub 2013 May 30.

Curbing inflammation in the ischemic heart disease.

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A modern concept considers acute coronary syndrome as an autoinflammatory disorder. From the onset to the healing stage, an endless inflammation has been presented with complex, multiple cross-talk mechanisms at the molecular, cellular, and organ levels. Inflammatory response following acute myocardial infarction has been well documented since the 1940s and 1950s, including increased erythrocyte sedimentation rate, the C-reactive protein analysis, and the determination of serum complement. It is surprising to note, based on a wide literature overview including the following 30 years (decades of 1960, 1970, and 1980), that the inflammatory acute myocardium infarction lost its focus, virtually disappearing from the literature reports. The reversal of this historical process occurs in the 1990s with the explosion of studies involving cytokines. Considering the importance of inflammation in the pathophysiology of ischemic heart disease, the aim of this paper is to present a conceptual overview in order to explore the possibility of curbing this inflammatory process.

DOI: 10.1155/2013/183061

PMCID: PMC3683484

PMID: 23819098

2353. Clin Rheumatol. 2013 Nov;32(11):1593-8. doi: 10.1007/s10067-013-2316-1. Epub 2013 Jun 29.

Does enthesopathy relate to M694V gene mutation in patients with Familial Mediterranean fever?

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Familial Mediterranean fever (FMF) is a systemic hereditary autoinflammatory disorder. The present study aimed to investigate the relationship of enthesitis to FMF and to search the potential association between enthesitis and MEFV gene missense variations in patients with FMF. The study consisted of 72 FMF patients (mean age  $29.12 \pm 11.47$  years, 32 females), 29 patients with ankylosing spondylitis (AS) (mean age  $34.14 \pm 11.73$  years, 16 females), and 34 healthy volunteers (mean age  $23.06 \pm 6.41$  years, 8 females). FMF patients were classified according to the kind of MEFV gene mutation. Doppler ultrasound was used to determine enthesitis based on the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) scoring system. OMERACT score was significantly different between FMF patients and control group ( $p < 0.001$  in all patients,  $p = 0.009$  in men, and  $p = 0.002$  in women). However, it was not significantly different between FMF and AS patients in both sexes. OMERACT score did not differ between FMF patients with and without M694V gene mutation. The best cutoff point of OMERACT score to predict enthesitis was found as  $\geq 0.5$  with sensitivity of 29 %, specificity of 100 %, positive predictive value of 100 %, and negative predictive value of 40 %.

DOI: 10.1007/s10067-013-2316-1

PMID: 23812619 [Indexed for MEDLINE]

2354. Clin Immunol. 2013 Aug;148(2):299-300. doi: 10.1016/j.clim.2013.05.020. Epub 2013 Jun 12.

Atypical presentation of a cryopyrin-associated periodic syndrome, revealing a novel NLRP3 mutation.

Canouï E, Maigné G, Jéru I, Amselem S, Koné-Paut I, Lambotte O.

DOI: 10.1016/j.clim.2013.05.020

PMID: 23811320 [Indexed for MEDLINE]

2355. Immunity. 2013 Jun 27;38(6):1154-63. doi: 10.1016/j.immuni.2013.05.015.

Omega-3 fatty acids prevent inflammation and metabolic disorder through inhibition of NLRP3 inflammasome activation.

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Comment in

Immunity. 2013 Jun 27;38(6):1088-90.

Omega-3 fatty acids ( $\omega$ -3 FAs) have potential anti-inflammatory activity in a variety of inflammatory human diseases, but the mechanisms remain poorly understood. Here we show that stimulation of macrophages with  $\omega$ -3 FAs, including eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and other family members, abolished NLRP3 inflammasome activation and inhibited subsequent caspase-1 activation and IL-1 $\beta$  secretion. In addition, G protein-coupled receptor 120 (GPR120) and GPR40 and their downstream scaffold protein  $\beta$ -arrestin-2 were shown to be involved in inflammasome inhibition induced by  $\omega$ -3 FAs. Importantly,  $\omega$ -3 FAs also prevented NLRP3 inflammasome-dependent inflammation and metabolic disorder in a high-fat-diet-induced type 2 diabetes model. Our results reveal a mechanism through which  $\omega$ -3 FAs repress inflammation and prevent inflammation-driven diseases and suggest the potential clinical use of  $\omega$ -3 FAs in gout, autoinflammatory syndromes, or other NLRP3 inflammasome-driven inflammatory diseases.

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DOI: 10.1016/j.immuni.2013.05.015

PMID: 23809162 [Indexed for MEDLINE]

2356. J Obstet Gynaecol Res. 2013 Aug;39(8):1314-8. doi: 10.1111/jog.12061. Epub 2013 Jun 26.



# Frequency of MEFV mutation and genotype-phenotype correlation in cases with dysmenorrhea.

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**AIM:** We aimed to investigate the relation between mutations and polymorphisms playing roles in the onset of clinical findings of Familial Mediterranean Fever (FMF) and clinical phenotypic reflections manifesting with painful episodes, such as dysmenorrhea.

**MATERIAL AND METHODS:** A total of 1000 female patients who had not responded well to non-steroidal anti-inflammatory drugs in the menstrual period, and who had presented to the emergency room with the complaint of recurrent pain episodes were included in the study. All the patients were Turkish women living in Istanbul. In this study, the mutations most frequently seen in the Mediterranean Fever Gene (MEFV), namely M694V, E148Q, M680I(G/C), V726A, P369S, R761H, A744S, M694I, K695R, F479L, M680I(G/A), and I692del were examined using the DNA sequence analysis following DNA isolation.

**RESULTS:** The number of individuals who had a mutation in at least one allele for FMF was 511 out of 1000 patients. Of these 511 patients, homozygous mutations were found in 21% (n = 109), compound heterozygous mutations were found in 27% (n = 136), and heterozygous mutations were found in 52% (n = 266). The most frequent homozygous genotype seen in our study population was M694V/M694V. The most common compound heterozygote genotypes were M694V/M680I, M694V/V726A, M694V/E148Q, and M680I/V726A; and 11.7% (n = 60) of the families in whom mutations were found had consanguinity.

**CONCLUSION:** Women who present to the emergency room with the complaint of dysmenorrhea that is irresponsive to non-steroidal anti-inflammatory drugs may have several types of MEFV mutations that are responsible for FMF.

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DOI: 10.1111/jog.12061

PMID: 23800337 [Indexed for MEDLINE]

2357. Int J Med Sci. 2013 Apr 30;10(7):836-9. doi: 10.7150/ijms.6116. Print 2013.

Increased levels of macrophage migration inhibitory factor in patients with familial mediterranean Fever.

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**OBJECTIVE:** To determine the level of macrophage migration inhibitory factor (MIF), its relationship with Mediterranean fever (MEFV) gene mutations and oxidative stress in familial Mediterranean fever (FMF).

**METHODS:** Fifty one unrelated attack free FMF patients (24 M and 27 F,  $32.8 \pm 8.7$  years) and 30 healthy controls (16 M and 14 F,  $32.7 \pm 7$  years) were included in the study. Serum MIF, total oxidant status (TOS) and total anti-oxidant status (TAS) were studied.

**RESULTS:** Age, sex distribution, anthropometrical indices, smoking status, serum lipids and TAS concentrations were similar between the patients and controls. However; erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), MIF, and TOS were significantly higher in the patients' group compared with healthy subjects. MIF, TOS and TAS levels were not different between patients with or without M694V mutations.

**CONCLUSION:** We found increased concentrations of MIF in patients with FMF. Increased MIF levels were significantly correlated with oxidative stress and in regression analysis MIF concentrations were independent from the inflammatory activity as assessed by ESR and CRP. M694V mutations seem no effect on MIF and oxidative stress.

DOI: 10.7150/ijms.6116

PMCID: PMC3689875

PMID: 23794947 [Indexed for MEDLINE]

2358. Inflammation. 2013 Dec;36(6):1357-62. doi: 10.1007/s10753-013-9675-2.

As a new inflammatory marker for familial Mediterranean fever:  
neutrophil-to-lymphocyte ratio.

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Comment in

Inflammation. 2014 Jun;37(3):833-4.

Familial Mediterranean fever (FMF), which is an autosomal recessive disease, is characterised by recurrent febrile episodes in association with peritonitis, pleuritis and arthritis and has ongoing subclinical inflammation during attack-free period. In this study, we aimed to investigate the relationship between FMF with neutrophil-to-lymphocyte ratio (NLR), which is determined in many chronic inflammations as a new potential inflammatory mediator. We included 62 patients and 41 healthy subjects who were similar in terms of age and sex. We found that the NLR values of the patients were significantly higher than those of the control group, and C-reactive protein values were correlated with NLR. Another finding was the NLR values were significantly higher in the FMF patient with M694V mutation than with other mutations. As a result, NLR might be used in the FMF patient as an indicator of the subclinical inflammation, and the FMF patients with M694V mutation should be followed up closely because of increased subclinical inflammation risk.

DOI: 10.1007/s10753-013-9675-2

PMID: 23794006 [Indexed for MEDLINE]

2359. Pediatr Res. 2013 Sep;74(3):266-71. doi: 10.1038/pr.2013.96. Epub 2013 Jun 12.

Mouse model of mevalonate kinase deficiency: comparison of cytokine and chemokine profile with that of human patients.

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**BACKGROUND:** Mevalonate kinase deficiency (MKD) is a rare genetic autoinflammatory disease caused by blocking of the enzyme mevalonate kinase in the pathway of cholesterol and isoprenoids. The pathogenic mechanism originating an immune response in MKD patients has not been clearly understood.

**METHODS:** We investigated the dysregulation of expression of selected cytokines and chemokines in the serum of MKD patients. The results have been compared with those observed in an MKD mouse model obtained by treating the mice with aminobisphosphonate, a molecule that is able to inhibit the cholesterol pathway, mimicking the genetic block characteristic of the disease.

**RESULTS:** Interleukin (IL)-1 $\beta$ , IL-5, IL-6, IL-9, IL-17, granulocyte colony-stimulating factor, monocyte chemotactic protein-1, tumor necrosis factor- $\alpha$ , and IL-4 expression were dysregulated in sera from MKD patients and mice. Moreover, geraniol, an exogenous isoprenoid, when administered to MKD mice, restored cytokines and chemokines levels with values similar to those of untreated mice.

**CONCLUSION:** Our findings, which were obtained in patients and a mouse model mimicking the human disease, suggest that these cytokines and chemokines could be MKD specific and that isoprenoids could be considered as potential therapeutic molecules. The mouse model, even if with some limitations, was robust and suitable for routine testing of potential MKD drugs.

DOI: 10.1038/pr.2013.96

PMID: 23760140 [Indexed for MEDLINE]

2360. *Pediatr Hematol Oncol*. 2014 Mar;31(2):129-30. doi: 10.3109/08880018.2013.800928. Epub 2013 Jun 12.

Leucopenia and familial Mediterranean Fever.

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Comment on

Pediatr Hematol Oncol. 2014 Mar;31(2):120-8.

DOI: 10.3109/08880018.2013.800928

PMID: 23758175 [Indexed for MEDLINE]

2361. Int J Immunopathol Pharmacol. 2013 Apr-Jun;26(2):315-26.

A roadmap for fever of unknown origin in children.

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Fever of unknown origin (FUO) in adults is conventionally defined by the occurrence of body temperatures above 38.3 degrees C (101 degrees F) for a period of 3 weeks without any identified etiology after a period of 1-week hospitalization. The issue of FUO in pediatrics is rather hazy and still represents a challenging diagnostic dilemma. Most of the available data are limited to nationwide cohorts of patients of any age. The major difficulty in establishing a diagnosis is that the characteristic features rendering specific disorders clinically recognizable are absent or subtle, hence only a painstaking questioning on family background may elicit the correct investigative path. No diagnostic algorithms are actually available and clinicians must rely on a very careful step-by-step evaluation of the single patient. The need for invasive diagnostic techniques should be closely taken into consideration when laboratory tests or simple imaging procedures fail to discern the origin of FUO. Fevers with no reasonable explanation and no localizing signs often conceal different common diseases in children, which tend to display an unusual or atypical pattern. The principal causes behind FUO in pediatric age remain infections, followed by collagen vascular diseases and neoplastic disorders, although most children with malignancies present other systemic signs or suggestive laboratory abnormalities. The possibility of autoinflammatory syndromes, drug fever, and factitious fever should also be taken into account.

DOI: 10.1177/039463201302600205

PMID: 23755747 [Indexed for MEDLINE]

2362. Proc Natl Acad Sci U S A. 2013 Jun 25;110(26):10723-8. doi: 10.1073/pnas.1307569110. Epub 2013 Jun 10.

Langerin(neg) conventional dendritic cells produce IL-23 to drive psoriatic plaque formation in mice.

Wohn C(1), Ober-Blöbaum JL, Haak S, Pantelyushin S, Cheong C, Zahner SP, Onderwater S, Kant M, Weighardt H, Holzmann B, Reizis B, Becher B, Prens EP, Clausen BE.

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Psoriasis is an autoinflammatory skin disease of unknown etiology. Topical application of Aldara cream containing the Toll-like receptor (TLR)7 agonist Imiquimod (IMQ) onto patients induces flares of psoriasis. Likewise, in mice IMQ triggers pathological changes closely resembling psoriatic plaque formation. Key cytokines like IL-23 and type-I IFN (IFN-I), both being produced mainly by dendritic cells (DCs), have been implicated in psoriasis. Although plasmacytoid DCs (pDCs) are the main source of IFN $\alpha$  and thought to initiate disease, conventional DCs (cDCs) appear to maintain the psoriatic lesions. Any role of cDCs during lesion formation remains elusive. Here, we report that selective activation of TLR7 signaling specifically in CD11c(+) DCs was sufficient to induce psoriasiform skin disease in mice. Intriguingly, both pDCs and the IFN-I pathway were dispensable for the development of local skin inflammation. Selective TLR7 triggering of Langerin(+) DCs resulted in attenuated disease, whereas their depletion did not alter the severity of skin lesions. Moreover, after IMQ-painting, IL-23 was exclusively produced by Langerin(neg) DCs in vivo. In conclusion, TLR7-activated Langerin(neg) cDCs trigger psoriatic plaque formation via IL-23-mediated activation of innate IL-17/IL-22-producing lymphocytes, independently of pDCs or IFN-I. These results suggest therapeutic targeting of IL-23 production by cDCs to refine current treatment strategies for psoriasis.

DOI: 10.1073/pnas.1307569110

PMCID: PMC3696803

PMID: 23754427 [Indexed for MEDLINE]

2363. Clin Rheumatol. 2013 Aug;32(8):1245-6. doi: 10.1007/s10067-013-2313-4. Epub 2013 Jun 11.

Mean platelet volume and amyloidosis in patients with familial Mediterranean fever.

Beyan C, Beyan E.

Comment on

Clin Rheumatol. 2013 Aug;32(8):1185-90.

DOI: 10.1007/s10067-013-2313-4

PMID: 23754246 [Indexed for MEDLINE]

2364. Intern Med J. 2013 Jun;43(6):725-7. doi: 10.1111/imj.12163.

Expanding spectrum of TNFRSF1A gene mutations among patients with idiopathic recurrent acute pericarditis.

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Although idiopathic recurrent acute pericarditis (IRAP) is generally presumed to derive from an autoimmune process, increasing interest is currently being devoted to autoinflammatory diseases, a group of disorders of the innate immune system caused by mutations of genes involved in the regulation or activation of the inflammatory response, without any apparent involvement of autoimmunity. The tumour necrosis factor receptor-1-associated periodic syndrome is the most common autosomal dominant autoinflammatory disorder and is caused by mutations in the TNFRSF1A gene encoding the 55-kD receptor for tumour necrosis factor- $\alpha$ . IRAP patients carrying TNFRSF1A gene mutations have been recently described. We report

herein the first IRAP patients carrying the rare R104Q and D12E TNFRSF1A gene mutations, thus expanding the spectrum of tumour necrosis factor receptor-1-associated periodic syndrome mutations in IRAP patients.

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DOI: 10.1111/imj.12163

PMID: 23745996 [Indexed for MEDLINE]

2365. Semin Arthritis Rheum. 2013 Dec;43(3):387-91. doi: 10.1016/j.semarthrit.2013.04.011. Epub 2013 Jun 3.

Evidence-based recommendations for the practical management of Familial Mediterranean Fever.

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**AIM:** Familial Mediterranean Fever (FMF) is the most common recurrent autoinflammatory fever syndrome. Still, many issues-e.g.: colchicine dosage adjustment, maximum dosage of colchicine in children and adults, definition of colchicine resistance, alternative treatment solutions in colchicine-resistant patients, and genetic screening for asymptomatic siblings-have not yet been standardized. The current paper aims at summarizing consensus recommendations to approach these issues.

**METHODS:** A literature review concerning these practical management questions was performed through PubMed. On the basis of this analysis, expert recommendations were developed during a consensus meeting of caregivers from France and Israel.

**RESULTS:** A patient experiencing more than four FMF attacks a year needs colchicine dose adjustment. In case of persistent attacks ( $\geq 6$  per year) in patients with maximum doses of colchicine (2 mg in children; 3 mg in adults), alternative treatment to colchicine with IL1 inhibitors should be considered.



Routine genetic testing for MEFV mutations in asymptomatic siblings of an index case is not recommended.

CONCLUSION: This is a first attempt to resolve practical questions in the daily management of FMF patients.

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DOI: 10.1016/j.semarthrit.2013.04.011

PMID: 23742958 [Indexed for MEDLINE]

2366. Rheumatol Int. 2014 Jun;34(6):883-4. doi: 10.1007/s00296-013-2791-3. Epub 2013 Jun 5.

Evaluation of mean platelet volume in familial Mediterranean fever; insight from the methodological aspect.

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Comment on

Rheumatol Int. 2013 Oct;33(10):2555-9.

DOI: 10.1007/s00296-013-2791-3

PMID: 23736276 [Indexed for MEDLINE]

2367. Gastroenterology. 2013 Sep;145(3):591-601.e3. doi: 10.1053/j.gastro.2013.05.047. Epub 2013 May 31.

Card9 mediates intestinal epithelial cell restitution, T-helper 17 responses, and control of bacterial infection in mice.

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**BACKGROUND & AIMS:** Caspase recruitment domain 9 (CARD9) is an adaptor protein that integrates signals downstream of pattern recognition receptors. CARD9 has been associated with autoinflammatory disorders, and loss-of-function mutations have been associated with chronic mucocutaneous candidiasis, but the role of CARD9 in intestinal inflammation is unknown. We characterized the role of Card9 in mucosal immune responses to intestinal epithelial injury and infection.

**METHODS:** We induced intestinal inflammation in Card9-null mice by administration of dextran sulfate sodium (DSS) or *Citrobacter rodentium*. We analyzed body weight, assessed inflammation by histology, and measured levels of cytokines and chemokines using quantitative reverse-transcription polymerase chain reaction and enzyme-linked immunosorbent assay. Cell populations were compared between wild-type and Card9-null mice by flow cytometry analysis.

**RESULTS:** Colon tissues and mesenteric lymph nodes of Card9-null mice had reduced levels of interleukin (IL)-6, interferon- $\gamma$ , and T-helper (Th)17 cytokines after administration of DSS, compared with wild-type mice. IL-17A and IL-22 expression were reduced in the recovery phase after DSS administration, coincident with decreased expression of antimicrobial peptides and the chemokine (C-C motif) ligand 20 (Ccl20). Although Card9-null mice had more intestinal fungi based on 18S analysis, their Th17 responses remained defective even when an antifungal agent was administered throughout DSS exposure. Moreover, Card9-null mice had impaired immune responses to *C. rodentium*, characterized by decreased levels of colonic IL-6, IL-17A, IL-22, and regenerating islet-derived 3 gamma (RegIII $\gamma$ ), as well as fewer IL-22-producing innate lymphoid cells (ILCs) in colon lamina propria.

**CONCLUSIONS:** The adaptor protein CARD9 coordinates Th17- and innate lymphoid cell-mediated intestinal immune responses after epithelial injury in mice.

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DOI: 10.1053/j.gastro.2013.05.047

PMCID: PMC3781941

PMID: 23732773 [Indexed for MEDLINE]

2368. Arch Argent Pediatr. 2013 Jun;111(3):237-43. doi: 10.1590/S0325-00752013000300011.

Autoinflammatory diseases in pediatrics.

[Article in English, Spanish]

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Monogenic autoinflammatory syndromes are caused by mutations in protein-coding genes that have a pivotal role in the regulation of the inflammatory response. Due to their genetic nature, most of these syndromes usually begin during childhood. They are clinically characterized by recurrent episodes of systemic inflammation (fever with different clinical manifestations, such as skin rash, serositis or arthritis) associated with elevation of acute phase reactants. During symptom-free intervals, patients achieve clinical well-being and normalize inflammatory parameters. Amyloidosis is a serious long-term complication. In this update we will discuss the clinical presentation and therapeutic strategies for these diseases in pediatrics.

DOI: 10.5546/aap.2013.237

PMID: 23732351 [Indexed for MEDLINE]

2369. J Pediatr Endocrinol Metab. 2013;26(9-10):877-82. doi: 10.1515/jpem-2013-0062.

Pigmentary hypertrichosis and non-autoimmune insulin-dependent diabetes mellitus (PHID) syndrome is associated with severe chronic inflammation and cardiomyopathy, and represents a new monogenic autoinflammatory syndrome.

Senniappan S, Hughes M, Shah P, Shah V, Kaski JP, Brogan P, Hussain K.

Mutations in SLC29A3 lead to pigmentary hypertrichosis and non-autoimmune insulin-dependent diabetes mellitus (PHID) and H syndromes, familial Rosai-Dorfman disease, and histiocytosis-lymphadenopathy plus syndrome. We report a new association of PHID syndrome with severe systemic inflammation, scleroderma-like changes, and cardiomyopathy. A 12-year-old girl with PHID syndrome presented with shortness of breath, hepatosplenomegaly, and raised

erythrocyte sedimentation rate and C-reactive protein. An echocardiogram showed biventricular myocardial hypertrophy, and cardiac magnetic resonance imaging showed circumferential late gadolinium enhancement of the myocardium. No systemic amyloid deposits were observed on a whole-body serum amyloid P scintigraphy scan. Abdominal ultrasound revealed intra-abdominal fat surrounding the solid organs, suggesting a possibility of evolving lipodystrophy with visceral adiposity. PHID syndrome is a novel monogenic autoinflammatory syndrome (AIS) associated with severe elevation of serum amyloid. Lipodystrophy, cutaneous sclerodermatous changes, and cardiomyopathy were also present in this case. In contrast to other AIS, blockade of interleukin-1 and tumor necrosis- $\alpha$  was ineffective.

DOI: 10.1515/jpem-2013-0062

PMID: 23729543 [Indexed for MEDLINE]

2370. Arthritis Res Ther. 2013;15(3):R64.

Treatment of Muckle-Wells syndrome: analysis of two IL-1-blocking regimens.

Kuemmerle-Deschner JB, Wittkowski H, Tyrrell PN, Koetter I, Lohse P, Ummenhofer K, Reess F, Hansmann S, Koitschev A, Deuter C, Bialkowski A, Foell D, Benseler SM.

**OBJECTIVES:** Muckle-Wells syndrome (MWS) is an autoinflammatory disease characterized by excessive interleukin-1 (IL-1) release, resulting in recurrent fevers, sensorineural hearing loss, and amyloidosis. IL-1 inhibition with anakinra, an IL-1 receptor antagonist, improves clinical symptoms and inflammatory markers. Subclinical disease activity is commonly observed. Canakinumab, a fully human IgG1 anti-IL-1 $\beta$  monoclonal antibody, can abolish excess IL-1 $\beta$ . The study aim was to analyze the efficacy and safety of these two anti-IL-1 therapies.

**METHODS:** Two cohorts of patients with severe MWS and confirmed NLRP3 mutation were treated with anakinra and/or canakinumab. Clinical and laboratory features including ESR, CRP, SAA, and the neutrophil marker S100A12 were determined serially. Disease activity was captured by MWS disease activity scores (MWS-DAS). Remission was defined as MWS-DAS  $\leq 5$  plus normal CRP and SAA. Treatment efficacy and safety were analyzed.

**RESULTS:** The study included 12 anakinra- and 14 canakinumab-treated patients; the median age was 33.5 years (3.0 years to 72.0 years); 57% were female patients.

Both treatment regimens led to a significant reduction of clinical disease activity and inflammatory markers. At last follow-up, 75% of anakinra-treated and 93% of canakinumab-treated patients achieved remission. During follow-up, S100A12 levels mirrored recurrence of disease activity. Both treatment regimens had favorable safety profiles.

CONCLUSIONS: IL-1 blockade is an effective and safe treatment in MWS patients. MWS-DAS in combination with MWS inflammatory markers provides an excellent monitoring tool set. Canakinumab led to a sustained control of disease activity even after secondary failure of anakinra therapy. S100A12 may be a sensitive marker to detect subclinical disease activity.

DOI: 10.1186/ar4237

PMCID: PMC4060562

PMID: 23718630 [Indexed for MEDLINE]

2371. Indian J Hum Genet. 2012 Sep;18(3):363-5. doi: 10.4103/0971-6866.108043.

Renal amyloidosis due to familial mediterranean fever misdiagnosed.

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Familial Mediterranean fever (FMF, MIM 249100) is an autosomal recessive disease affecting mainly patients of the Mediterranean basin. It is an autoinflammatory periodic disorder characterized by recurrent episodes of fever and abdominal pain, synovitis, and pleuritis. The major complication of FMF is the development of renal AA amyloidosis. Treatment with colchicine prevents the occurrence of recurrent seizures and renal amyloidosis. The disease is caused by mutations in the MEFV gene. We report here the cases of two unrelated patients, who have been late diagnosed with FMF complicated by renal amyloidosis. We focus on the importance of early diagnosis of FMF, both to start rapidly treatment with colchicine and avoid renal amyloidosis, and to provide genetic counseling to families.

DOI: 10.4103/0971-6866.108043

PMCID: PMC3656531

PMID: 23716950

2372. J Craniofac Surg. 2013 May;24(3):e258-60. doi: 10.1097/SCS.0b013e318287d252.

Surgical approach to oral lichen planus by submucosal autologous fat grafting.

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Oral lichen planus is a chronic autoinflammatory mucositis. Oral lesions are predominantly white; they tend to be bilateral while involving the buccal mucosa especially cheek, tongue, gums, lips, and palate. Many topical and systemic agents are currently used with unpredictable results. Fat grafting is characterized by the placement of multiple parcels of purified fat with blunt cannulas; at the beginning, it was introduced to improve facial aesthetics. Recently, it has been translated to other surgical cases such as posttraumatic deformities and craniofacial anomalies and as ancillary reconstructive procedure after tumor resections. The successful results of this procedure encouraged us to use this approach to a clinical case of oral lichen planus refractory to conventional therapy.

DOI: 10.1097/SCS.0b013e318287d252

PMID: 23714984 [Indexed for MEDLINE]

2373. Clin Immunol. 2013 Jun;147(3):155-74. doi: 10.1016/j.clim.2013.03.016. Epub 2013 Apr 9.

Monogenic autoinflammatory diseases: concept and clinical manifestations.

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The objective of this review is to describe the clinical manifestations of the growing spectrum of monogenic autoinflammatory diseases including recently described syndromes. The autoinflammatory diseases can be grouped based on clinical findings: 1. the three classic hereditary "periodic fever syndromes", familial Mediterranean Fever (FMF); TNF receptor associated periodic syndrome (TRAPS); and mevalonate kinase deficiency/hyperimmunoglobulinemia D and periodic fever syndrome (HIDS); 2. the cryopyrin associated periodic syndromes (CAPS), comprising familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and neonatal-onset multisystem inflammatory disease (NOMID) or CINCA, and; 3. pediatric granulomatous arthritis (PGA); 4. disorders presenting with skin pustules, including deficiency of interleukin 1 receptor antagonist (DIRA); Majeed syndrome; pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome; deficiency of interleukin 36 receptor antagonist (DITRA); CARD14 mediated psoriasis (CAMP5), and early-onset inflammatory bowel diseases (EO-IBD); 5. inflammatory disorders caused by mutations in proteasome components, the proteasome associated autoinflammatory syndromes (PRAAS) and 6. very rare conditions presenting with autoinflammation and immunodeficiency.

Published by Elsevier Inc.

DOI: 10.1016/j.clim.2013.03.016

PMCID: PMC3769788

PMID: 23711932 [Indexed for MEDLINE]

2374. Clin Exp Rheumatol. 2013 May-Jun;31(3 Suppl 77):93-5. Epub 2013 May 27.

Brain stem infarction associated with familial Mediterranean fever and central nervous system vasculitis.

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Familial Mediterranean fever (FMF) is an autoinflammatory autosomal recessive disease caused by mutations of the Mediterranean fever (MEFV) gene on chromosome 16p. Clinically, it is characterized by recurrent episodes of fever and painful polyserositis. An association of FMF with systemic vasculitis, namely Henoch-Schönlein purpura, polyarteritis nodosa and Behçet's disease has been described. Neurological manifestations of FMF occur rarely and include demyelinating (MS-like) lesions, posterior reversible encephalopathy syndrome, and pseudotumour cerebri. Hitherto hardly known, we herein present a young patient with a genetically proven FMF who suffered a brain stem infarction during a typical FMF attack. After a careful diagnostic workup including cerebrospinal fluid analysis, intra-arterial angiography and leptomeningeal biopsy, a FMF-associated central nervous system vasculitis was identified as the cause of stroke. The pathophysiological background and potential therapeutic strategies are discussed.

PMID: 23710607 [Indexed for MEDLINE]

2375. Clin Immunol. 2013 Jun;147(3):242-75. doi: 10.1016/j.clim.2013.04.008. Epub 2013 Apr 19.

Inflammasome and cytokine blocking strategies in autoinflammatory disorders.

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Autoinflammatory disorders are characterized by usually unprovoked recurrent episodes of features of inflammation caused by activation of the innate immune system. Many autoinflammatory disorders - the monogenetic defects in particular - are associated with alterations of inflammasomes. Inflammasomes are complex multimolecular structures, which respond to "danger" signals by activation of cytokines. Among these, IL-1 is the key player of the innate immune response and inflammation. Consequently, IL-1 blocking strategies are specific pathway targeting therapies in autoinflammatory diseases and applied in CAPS,



colchicine-resistant FMF, TRAPS, HIDS and DIRA. A number of rare genetic disorders involve inflammasome malfunction resulting in enhanced inflammatory response. IL-1 inhibition to date is the most successful specific therapy in autoinflammatory disorders. Here, current treatment strategies in autoinflammatory disorders are reviewed with a focus on inflammasome and cytokine inhibition.

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DOI: 10.1016/j.clim.2013.04.008

PMID: 23697917 [Indexed for MEDLINE]

2376. Turk J Pediatr. 2013 Jan-Feb;55(1):78-81.

Different presentations in patients with tumor necrosis factor receptor-associated periodic syndrome mutations: report of two cases.

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Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is an autosomal dominant autoinflammatory disorder caused by mutations in the TNFRSF1A gene encoding the 55-kDa receptor for tumor necrosis factor (TNF)- $\alpha$ . It is characterized by recurrent prolonged episodes of fever accompanied by abdominal pain, pleuritis, migratory skin rashes, fasciitis, headache, conjunctivitis, and periorbital edema. We report two children, one with a severe mutation in the TNFRSF1A gene causing the typical phenotype. The second patient had a homozygous R92Q-type mutation and displayed a periodic fever with aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome-like phenotype. In the eastern Mediterranean region, TRAPS is probably underdiagnosed because of the overwhelming frequency of familial Mediterranean fever (FMF). However, TRAPS should be sought for in patients with atypical symptoms for FMF.

PMID: 23692837 [Indexed for MEDLINE]

2377. Case Rep Rheumatol. 2013;2013:795027. doi: 10.1155/2013/795027. Epub 2013 Apr 16.

A case of hyperimmunoglobulinemia d syndrome successfully treated with canakinumab.

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Hyperimmunoglobulinemia D syndrome is a rare autosomal recessive autoinflammatory disorder caused by mutations in the mevalonate kinase gene (MVK). In a proportion of patients, however, no MVK mutations are detected. Although various standard anti-inflammatory drugs have been tried, until now there is no consensus about how HIDS should be treated. We present a case of HIDS in an 8-year-old girl whose clinical picture had started before the end of the first year of life. The patient had consistently elevated IgD levels but no mutations were found after a full-length analysis of the MVK gene. The method of MVK mutational analysis is presented in details. Treatment with canakinumab in a final single dose of 4 mg/kg every 4 weeks resulted in the disappearance of febrile attacks and a considerable improvement of patients' quality of life during a 12-month follow-up period. The drug has been well tolerated, and no side effects were observed.

DOI: 10.1155/2013/795027

PMCID: PMC3652103

PMID: 23691418

2378. Evid Based Complement Alternat Med. 2013;2013:418508. doi: 10.1155/2013/418508. Epub 2013 Apr 16.

The Inhibition of Inflammasome by Brazilian Propolis (EPP-AF).

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Propolis extracts have gained the attention of consumers and researchers due to their unique chemical compositions and functional properties such as its anti-inflammatory activity. Recently, it was described a complex that is also important in inflammatory processes, named inflammasome. The inflammasomes are a large molecular platform formed in the cell cytosol in response to stress signals, toxins, and microbial infections. Once activated, the inflammasome induces caspase-1, which in turn induces the processing of inflammatory cytokines such as IL-1  $\beta$  and IL-18. So, to understand inflammasomes regulation becomes crucial to treat several disorders including autoinflammatory diseases. Since green propolis extracts are able to regulate inflammatory pathways, this work purpose was to investigate if this extract could also act on inflammasomes regulation. First, the extract was characterized and it demonstrated the presence of important compounds, especially Artepillin C. This extract was effective in reducing the IL-1  $\beta$  secretion in mouse macrophages and this reduction was correlated with a decrease in activation of the protease caspase-1. Furthermore, we found that the extract at a concentration of 30  $\mu$ g/mL was not toxic to the cells even after a 18-hour treatment. Altogether, these data indicate that Brazilian green propolis (EPP-AF) extract has a role in regulating the inflammasomes.

DOI: 10.1155/2013/418508

PMCID: PMC3652175

PMID: 23690844

2379. J Dermatol Sci. 2013 Aug;71(2):83-8. doi: 10.1016/j.jdermsci.2013.04.009. Epub 2013 Apr 19.

Linkage of bacterial colonization of skin and the urticaria-like rash of NLRP3-mediated autoinflammatory syndromes through mast cell-derived TNF- $\alpha$ .

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As anti-cytokine therapies were developed for clinical use during the last decade, anti-IL-1 therapies have emerged as a highly effective treatment for cryopyrin-associated periodic syndromes (CAPSs), including the "urticaria-like rash." Based on clinical observations, we hypothesized that NLRP3 activation and IL-1 $\beta$  production, in particular in mast cells (MCs), are important for the development of this eruption, due to the observation that CAPS patients have gain-of-function mutations in NLRP3 that result in unregulated excess levels of IL-1 $\beta$ . To further address our hypothesis, we employed gene-targeted mice carrying Nlrp3 mutations and found that signaling in MCs following bacterial colonization of skin is essential for IL-1 $\beta$ -dependent inflammation. Intradermal administration of a molecule that induces the release of granule-associated molecules from MCs showed that MCs and TNF- $\alpha$  were necessary for the inflammation in CAPS-mimicking mice. However, adult CAPS mice exhibited a persistent skin phenotype and did not respond to anti-TNF- $\alpha$  antibody, indicating that TNF- $\alpha$  is important only for the onset of the disease and is dispensable during the chronic phase of CAPS. Thus, in this review, we highlight our recent findings on how MCs play an important role, not only in ordinary urticaria, but also in the "urticaria-like rash" associated with NLRP3 mutations.

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DOI: 10.1016/j.jdermsci.2013.04.009

PMID: 23684246 [Indexed for MEDLINE]

2380. Ren Fail. 2013 Jul;35(6):835-7. doi: 10.3109/0886022X.2013.794660. Epub 2013 May 17.

Serum soluble fas ligand levels in familial Mediterranean fever.

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**INTRODUCTION:** Fas/FasL system plays an important role in the regulation of cell life and death, and circulating levels of sFasL have been shown to increase in some inflammatory conditions. However, there is no sufficient information about the levels of sFasL in patients with FMF. This study was designed to evaluate the serum sFasL levels in patients with FMF during attack and attack-free periods.

**METHODS:** Twenty-five FMF patients in attack and forty-four in free-attack period, and 20 age-, sex-, and BMI-matched healthy controls were included in this study. Participants with any chronic diseases were excluded. Blood samples were obtained within the first 24 h of the attack period and between febrile attacks, and levels of WBC, ESR, Fibrinogen, hsCRP and sFasL were determined.

**RESULTS:** The levels of traditional acute phase reactants during the attack were significantly higher than the attack-free and controls ( $p < 0.05$ ). The serum sFasL levels in the FMF study groups did not differ from the control group ( $0.70 \pm 0.08$  vs.  $0.73 \pm 0.12$ ;  $0.70 \pm 0.08$  vs.  $0.83 \pm 0.14$ ;  $0.73 \pm 0.12$  vs.  $0.83 \pm 0.14$ , respectively,  $p > 0.05$ ). Moreover, the sFasL levels during the attack were not significantly different from those in attack-free patients ( $0.70 \pm 0.08$  vs.  $0.83 \pm 0.14$ ,  $p > 0.05$ ).

**CONCLUSION:** In this study, we demonstrated that serum sFasL levels were not markedly affected in FMF and cannot be used as a supportive marker to differentiate attacks from attack-free periods. However, further studies are needed to determine its usefulness as a marker in clinical practice.

DOI: 10.3109/0886022X.2013.794660

PMID: 23682624 [Indexed for MEDLINE]

2381. J Immunol. 2013 Jun 15;190(12):6488-500. doi: 10.4049/jimmunol.1203215. Epub 2013 May 15.

Pseudogout-associated inflammatory calcium pyrophosphate dihydrate microcrystals induce formation of neutrophil extracellular traps.

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Pseudogout is an autoinflammatory condition triggered by calcium pyrophosphate

dehydrate (CPPD) crystal deposition in the joints. The innate immune system is irritated by and responds to the presence of the crystals with an inflammatory response. The synovial fluid contains activated inflammatory macrophages and neutrophil granulocytes. Several details of crystal-induced macrophage activation were recently uncovered, but very little is known about interactions of CPPD crystals with neutrophils. In this study, we show that human neutrophils engulf CPPD crystals and form large amounts of neutrophil extracellular traps (NETs) in vitro. Released extracellular DNA binds myeloperoxidase and citrullinated histone H4. CPPD crystal-stimulated neutrophils and their nuclear DNA undergo morphological changes characteristic for NET formation. The ERK/MEK signaling pathway, heat shock protein 90, PI3K, and an intact cytoskeleton are required for CPPD-induced NET formation. Blocking crystal-activated respiratory burst has, however, no effect on NETs. Human neutrophils release IL-1 $\beta$  and IL-8 in response to CPPD crystals, and blocking CXCR2, the main IL-8R, diminishes NET formation. Proinflammatory cytokines, TNF- $\alpha$ , GM-CSF, and IL-1 $\beta$ , increase NET release by the crystals. Enhanced bacterial killing by CPPD-induced NETs demonstrates their ability to cause cellular damage. Our work documents and provides details about extracellular trap release in human neutrophils activated by CPPD microcrystals. We suggest that crystal-triggered NET formation can be a novel contributor to inflammatory conditions observed in CPPD crystal-driven synovitis.

DOI: 10.4049/jimmunol.1203215

PMID: 23677474 [Indexed for MEDLINE]

2382. Rheumatol Int. 2013 Oct;33(10):2555-9. doi: 10.1007/s00296-013-2775-3. Epub 2013 May 15.

Evaluation of the mean platelet volume in secondary amyloidosis due to familial Mediterranean fever.

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Comment in

Familial Mediterranean fever (FMF) is an inflammatory disorder that is leading cause of secondary amyloidosis (AA). This study was designed to investigate the level of mean platelet volume (MPV) in AA. Seventy-four FMF, 29 AA patients and 180 healthy controls, were included. There was no significant difference between the cases in terms of sex and age. MPV levels were measured in all groups. In the FMF group, MPV level was significantly higher when compared to the control group. MPV level was significantly lower in AA group in comparison with the FMF and healthy control groups. In summary, our present study showed low MPV values in AA due to FMF.

DOI: 10.1007/s00296-013-2775-3

PMID: 23673449 [Indexed for MEDLINE]

2383. J Dermatol. 2013 Jul;40(7):516-21. doi: 10.1111/1346-8138.12159. Epub 2013 May 10.

Association between MEFV gene mutations and recurrent aphthous stomatitis in a cohort of Turkish patients.

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Recurrent aphthous stomatitis (RAS) has a multifactorial etiopathogenesis, an interaction between predisposing factors and/or systemic conditions and immunological components in genetically predisposed subjects. The Mediterranean fever (MEFV) gene has already been identified as being responsible for familial Mediterranean fever. Because the association between MEFV gene mutations and Behçet's disease has been reported before in several studies, we considered that the role of MEFV gene mutations should be studied in patients with RAS, because of the clinical similarities of both diseases. The aim of this study was to explore the frequency and clinical significance of MEFV gene mutations in a cohort of Turkish patients with RAS. The study population comprised 100 unrelated patients with a clinical diagnosis of RAS and 156 healthy controls. Genomic DNA

was isolated and genotyped using polymerase chain reaction and restriction fragment length polymorphism for the four MEFV gene mutations (M694V, M680I, V726A and E148Q). There were statistically significant differences of the MEFV gene mutation carrier rates and allele frequencies between RAS patients and healthy controls ( $P = 0.042$ , odds ratio [OR] = 1.9, 95% confidence interval [CI] = 1.01-3.41; and  $P = 0.039$ , OR = 1.8, 95% CI = 1.02-3.14, respectively). Even if it is not statistically significant, the E148Q allele frequency was higher in patients with RAS than the control group. A statistically significant increased prevalence of MEFV variants in RAS patients was found. This is the first study to report that missense mutations of MEFV is associated with RAS in the Turkish population.

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DOI: 10.1111/1346-8138.12159

PMID: 23663176 [Indexed for MEDLINE]

2384. Turk Patoloji Derg. 2013;29(2):146-9. doi: 10.5146/tjpath.2013.01167.

[Diffuse lipid infiltration and squamous metaplasia accompanying amyloid goiter: case report].

[Article in Turkish]

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Systemic amyloidosis is one of the serious complications of Familial Mediterranean Fever (FMF). Amyloid accumulation secondary to FMF can cause pressure symptoms in thyroid gland rarely. A 17-year-old male patient with the diagnosis of FMF performed the complaints of dyspnea during his follow-up period. He has demonstrated a rapidly increasing mass localized in front of his neck within the last three months that was diagnosed as a diffuse, hyperplastic and pressuring thyroid gland. Total thyroidectomy was performed. Histopathological investigation of the material obtained after thyroidectomy revealed diffuse



lipid infiltration in parenchyma, intense amyloid accumulation around and between the follicles that caused pressure on the follicles, and cystic areas in the tissue. Squamous metaplasia foci in cyst epithelium were detected. Upon these findings the case was diagnosed as amyloid goiter accompanied by metaplastic variations. In conclusion, it can be appropriate to take into account the possibility that metaplastic variations could accompany amyloid goiter in patients with long-term FMF.

DOI: 10.5146/tjpath.2013.01167

PMID: 23661354 [Indexed for MEDLINE]

2385. Adv Exp Med Biol. 2013;764:99-107.

Chronic recurrent multifocal osteomyelitis.

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Chronic recurrent multifocal osteomyelitis (CRMO) is an autoinflammatory bone disease occurring primarily in children and adolescents. Episodes of systemic inflammation occur due to immune dysregulation without autoantibodies, pathogens or antigen-specific T cells. CRMO is characterised by the insidious onset of pain with swelling and tenderness over the affected bones. Clavicular involvement was the classical description; however, the metaphyses and epiphyses of long bones are frequently affected. Lesions may occur in any bone, including vertebrae. Characteristic imaging includes bone oedema, lytic areas, periosteal reaction and soft tissue reaction. Biopsies from affected areas display polymorphonuclear leucocytes with osteoclasts and necrosis in the early stages. Subsequently, lymphocytes and plasma cells predominate followed by fibrosis and signs of reactive new bone forming around the inflammation. Diagnosis is facilitated by the use of STIR MRI scanning, potentially obviating the need for biopsy and unnecessary long-term antibiotics due to incorrect diagnosis. Treatment options include non-steroidal anti-inflammatory drugs and bisphosphonates. Biologics have been tried in resistant cases with promising initial results. Gene identification has not proved easy although research in this area continues. Early descriptions of the disease suggested a benign course; however, longer-term follow up shows

that it can cause significant morbidity and longer-term disability. Although it has always been thought of as very rare, the prevalence is likely to be vastly underestimated due to poor recognition of the disease.

PMID: 23654059 [Indexed for MEDLINE]

2386. Curr Opin Pediatr. 2013 Jun;25(3):388-96. doi: 10.1097/MOP.0b013e328360c2fd.

Common presentations of pediatric rheumatologic diseases: a generalist's guide.

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**PURPOSE OF REVIEW:** To present a case-based approach of three common scenarios which often present to the primary care physician. The approach to these cases and the differential diagnosis are discussed for these common rheumatologic diseases.

**RECENT FINDINGS:** Numerous healthy children and adolescents are referred to pediatric rheumatologists for the evaluation of suspected rheumatologic diseases. Often, general rheumatologic laboratory tests are sent which are not necessarily specific to the clinical situation. There is a high false-positive rate associated with many of these tests and undue anxiety and referrals result from these. Directed laboratory studies based on history and exam findings are more prudent and useful in the evaluation of these children. Routine antinuclear antibody testing, for example, is not recommended without supportive symptoms or signs.

**SUMMARY:** A practical approach for primary care physicians is described for the evaluation of patients suspected of having some of the more common pediatric rheumatologic symptoms and diseases.

DOI: 10.1097/MOP.0b013e328360c2fd

PMID: 23652686 [Indexed for MEDLINE]

2387. Allergy. 2013 Jun;68(6):816-9. doi: 10.1111/all.12153. Epub 2013 May 6.

Practical algorithm for diagnosing patients with recurrent wheals or angioedema.

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**BACKGROUND:** Chronic urticaria is a common disorder characterized by recurrent wheals, angioedema, or both. Several differential diagnoses need to be considered in patients presenting with wheals and/or angioedema. These include rare diseases such as autoinflammatory syndromes and urticarial vasculitis in patients with recurrent wheals and bradykinin-mediated angioedema in patients with recurrent swellings. **AIM AND RESULT:** In order to not miss these conditions, we have developed a symptom-based diagnostic algorithm for the management of patients with wheals and/or angioedema.

**DISCUSSION AND CONCLUSION:** By asking the right questions and performing a limited diagnostic workup as suggested here, this algorithm may help to establish the right diagnosis and treat patients early and more effectively.

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DOI: 10.1111/all.12153

PMID: 23646863 [Indexed for MEDLINE]

2388. Gene. 2013 Sep 15;527(1):62-4. doi: 10.1016/j.gene.2013.04.020. Epub 2013 May 2.

Association between fibromyalgia syndrome and polymorphism of the IL-4 gene in a Turkish population.

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**PURPOSE:** Fibromyalgia (FM) syndrome is a form of non-articular rheumatism characterized by long term and widespread musculoskeletal pain, morning stiffness, sleep disturbance, paresthesia, and pressure hyperalgesia at characteristic sites, called soft tissue tender points. The etiology of FM is still obscure. Genetic factors may predispose individuals to FM. Cytokines may play a role in the pathophysiology of FM. The aim of this study was to investigate the interleukin-4 (IL-4) 70 bp VNTR variations in Turkish patients with FM and evaluate if there was an association with clinical features, especially between these polymorphisms.

**METHODS:** The study included 300 patients with FM and 270 healthy controls. Genomic DNA was isolated and genotyped using polymerase chain reaction (PCR) for the IL-4 gene 70 bp VNTR polymorphisms.

**RESULTS:** There was statistically significant difference between the groups with respect to IL-4 genotype distribution and allele frequencies ( $p < 0.0001$ ). The homozygous P1P1 genotype and P1 allele were significantly higher in FM patients than in healthy controls ( $p = 0.04$ ; OR: 3.25, 95% CI: 1-10,  $p < 0.0001$ ; OR: 4.84, 95% CI: 3-7.7). There was not any difference between the groups respect to IL-4 genotype distribution and allele frequencies ( $p > 0.05$ ) and clinical characteristics.

**CONCLUSION:** Our findings suggest that there is an association of IL-4 gene 70 bp VNTR polymorphism with susceptibility of a person for development of FM. As a result, further studies are necessary to determine whether IL-4 may be a genetic marker for FM in the Turkish population.

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DOI: 10.1016/j.gene.2013.04.020

PMID: 23644020 [Indexed for MEDLINE]

2389. J Plast Reconstr Aesthet Surg. 2013 Dec;66(12):1759-62. doi: 10.1016/j.bjps.2013.04.020. Epub 2013 May 2.

Autologous fat grafting for treatment of facial atrophy in Behcet's disease: a case report.

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Behcet's disease (BD) is an autoimmune & autoinflammatory disease of unclear etiology characterized by recurrent oral & genital ulcers as well as other systemic manifestations. A key pathogenesis is excessive inflammatory wound healing response. While descriptions of the cutaneous manifestations of disease are limited to short-term consequences such as extensive pustule and papule formation in response to minor tissue injury, the long-term consequences are significant fibrosis and scarring of epithelial tissue. We describe the case of a patient with Behcet's disease who presented with unilateral facial atrophy secondary to minor trauma to the oral mucosa. She was treated with autologous fat grafting. Though a rare disease, plastic surgeons should be aware of the entity of Behcet's disease and its complications of tissue atrophy that may require reconstructive surgery.

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DOI: 10.1016/j.bjps.2013.04.020

PMID: 23642794 [Indexed for MEDLINE]

2390. Eur Rev Med Pharmacol Sci. 2013 Apr;17(7):958-63.

Assesment life quality of familial Mediterranean fever patients by short form-36 and its relationship with disease parameters.

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**BACKGROUND:** Familial Mediterranean fever is an auto-inflammatory disorder. Long term complications of the disease include decreased quality of life. The measurement of quality of life in the patients with chronic disease has become an important research topic during the last years.

**AIM:** We aimed to evaluate life quality of the FMF patients by SF-36, and examine its relationship with the disease parameters.

**PATIENTS AND METHODS:** One hundred voluntary patients (69 female, 31 male) admitted to the rheumatology clinic were included in the study. The control group consisted of 100 healthy individuals. All subjects in the study were asked to complete SF-36 questionnaire. Age of onset of FMF, age at diagnosis, age at the beginning of colchicine therapy, number of attacks per month, family history of FMF and dialysis were inquired of patients with FMF. Disease severity was determined using the FMF severity score.

**RESULTS:** The mean age of the patient group was  $31 \pm 12$  and that of the control group was  $29 \pm 9$ . Sixty-nine patients (69%) were female, and 31 patients were male (31%) in both groups. The mean scores of the physical function, physical role function, emotional role function, mental health, and general health parameters of the patients were statistically significantly lower than those of healthy volunteers ( $p < 0.05$ ). The difference in social function and vitality between two groups was found to be insignificant ( $p > 0.05$ ).

**CONCLUSIONS:** We have shown that FMF had a negative impact on SF-36. FMF reduces quality of life both in physical and mental dimensions.

PMID: 23640444 [Indexed for MEDLINE]

2391. Gene. 2013 Jul 25;524(2):412-4. doi: 10.1016/j.gene.2013.04.039. Epub 2013 Apr 29.

Innate immunity functional gene polymorphisms and gout susceptibility.

Qing YF, Zhang QB, Zhou JG.

Gout is a common autoinflammatory disease characterized with elevated serum urate and recurrent attacks of intra-articular crystal deposition of monosodium urate.

Accumulating evidence has demonstrated that MSU crystal-induced inflammation is a paradigm of innate immunity and the TLRs, NALP3 inflammasome and IL1R pathways are involved in gout development. Innate immunity components containing TLR2, TLR4, CD14, NALP3, ASC, Caspase-1 and CARD-8 are essential in the development of gouty inflammation. Recent studies suggest that innate immunity component gene functional mutations contribute to the development of autoinflammatory diseases including hereditary periodic fever syndrome, arthritis as well as inflammatory bowel disease. Taking into account these genetic findings, we would like to propose a novel hypothesis that the gene functional mutations might make innate

immunity components as attractive susceptibility candidates and genetic markers for gout. Further clinical genetic studies need to be performed to confirm the role of innate immunity in the etiology of gout.

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DOI: 10.1016/j.gene.2013.04.039

PMID: 23639963 [Indexed for MEDLINE]

2392. Trends Immunol. 2013 Aug;34(8):371-8. doi: 10.1016/j.it.2013.04.001. Epub 2013 Apr 30.

From genetics of inflammatory bowel disease towards mechanistic insights.

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Advancements in human genetics now poise the field to illuminate the pathophysiology of complex genetic disease. In particular, genome-wide association studies (GWAS) have generated insights into the mechanisms driving inflammatory bowel disease (IBD) and implicated genes shared by multiple autoimmune and autoinflammatory diseases. Thus, emerging evidence suggests a central role for the mucosal immune system in mediating immune homeostasis and highlights the complexity of genetic and environmental interactions that collectively modulate the risk of disease. Nevertheless, the challenge remains to determine how genetic variation can precipitate and sustain the inappropriate inflammatory response to commensals that is observed in IBD. Here, we highlight recent advancements in immunogenetics and provide a forward-looking view of the innovations that will deliver mechanistic insights from human genetics.

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DOI: 10.1016/j.it.2013.04.001

PMCID: PMC3735683

PMID: 23639549 [Indexed for MEDLINE]

2393. Ned Tijdschr Geneeskd. 2013;157(18):A5784.

[Familial Mediterranean fever: not to be missed].

[Article in Dutch]

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Familial Mediterranean fever (FMF) is common among Turkish and Moroccan migrants. We describe three patients with FMF. A 3-year-old girl with recurrent fever and abdominal pain who was diagnosed early with FMF and treated effectively with colchicine. An adolescent girl who required interleukin (IL)-1 blockade to achieve disease remission. And a 37-year-old woman in whom the attacks of FMF had not been recognised, but who developed end-stage kidney failure due to AA amyloidosis. Mutations in the MEFV gene underlie the disease in most but not all patients. Therefore, FMF remains a clinical diagnosis. FMF patients suffer recurrent bouts of inflammation, often with fever, serositis or arthritis. The major complication is AA amyloidosis. The inflammatory process is mediated by IL-1 $\beta$ . When started early, colchicine prophylaxis can prevent amyloidosis. When colchicine fails, IL-1 blockade has shown promising results. Timely diagnosis and treatment can make the difference between near normal health and end-stage kidney failure.

PMID: 23635502 [Indexed for MEDLINE]

2394. Proc Natl Acad Sci U S A. 2013 May 14;110(20):8134-9. doi: 10.1073/pnas.1306352110. Epub 2013 Apr 30.

Targeted resequencing implicates the familial Mediterranean fever gene MEFV and the toll-like receptor 4 gene TLR4 in Behçet disease.



Kirino Y(1), Zhou Q, Ishigatsubo Y, Mizuki N, Tugal-Tutkun I, Seyahi E, Özyazgan Y, Ugurlu S, Erer B, Abaci N, Ustek D, Meguro A, Ueda A, Takeno M, Inoko H, Ombrello MJ, Satorius CL, Maskeri B, Mullikin JC, Sun HW, Gutierrez-Cruz G, Kim Y, Wilson AF, Kastner DL, Gül A, Remmers EF.

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Genome-wide association studies (GWAS) are a powerful means of identifying genes with disease-associated common variants, but they are not well-suited to detecting genes with disease-associated rare and low-frequency variants. In the current study of Behçet disease (BD), nonsynonymous variants (NSVs) identified by deep exonic resequencing of 10 genes found by GWAS (IL10, IL23R, CCR1, STAT4, KLRK1, KLRC1, KLRC2, KLRC3, KLRC4, and ERAP1) and 11 genes selected for their role in innate immunity (IL1B, IL1R1, IL1RN, NLRP3, MEFV, TNFRSF1A, PSTPIP1, CASP1, PYCARD, NOD2, and TLR4) were evaluated for BD association. A differential distribution of the rare and low-frequency NSVs of a gene in 2,461 BD cases compared with 2,458 controls indicated their collective association with disease. By stringent criteria requiring at least a single burden test with study-wide significance and a corroborating test with at least nominal significance, rare and low-frequency NSVs in one GWAS-identified gene, IL23R ( $P = 6.9 \times 10^{-5}$ ), and one gene involved in innate immunity, TLR4 ( $P = 8.0 \times 10^{-4}$ ), were associated with BD. In addition, damaging or rare damaging NOD2 variants were nominally significant across all three burden tests applied ( $P = 0.0063$ - $0.045$ ). Furthermore, carriage of the familial Mediterranean fever gene (MEFV) mutation Met694Val, which is known to cause recessively inherited familial Mediterranean fever, conferred BD risk in the Turkish population (OR, 2.65;  $P = 1.8 \times 10^{-12}$ ). The disease-associated NSVs in MEFV and TLR4 implicate innate immune and bacterial sensing mechanisms in BD pathogenesis.

DOI: 10.1073/pnas.1306352110

PMCID: PMC3657824

PMID: 23633568 [Indexed for MEDLINE]

2395. Front Immunol. 2013 Apr 23;4:96. doi: 10.3389/fimmu.2013.00096. eCollection 2013.

Caution Should be Used in the Recognition of Adult-Onset Autoinflammatory

## Disorders: Facts or Fiction?

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DOI: 10.3389/fimmu.2013.00096

PMCID: PMC3632798

PMID: 23630527

2396. Joint Bone Spine. 2013 Jul;80(4):353-4. doi: 10.1016/j.jbspin.2013.03.008. Epub 2013 Apr 23.

Chinese Shar-Pei dogs: a model for human Mediterranean fever?

Hayem G.

DOI: 10.1016/j.jbspin.2013.03.008

PMID: 23622734 [Indexed for MEDLINE]

2397. Curr Opin Immunol. 2013 Apr;25(2):277-83. doi: 10.1016/j.coi.2013.03.007. Epub 2013 Apr 23.

The repertoire of human tumor-associated epitopes--identification and selection of antigens and their application in clinical trials.

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In cancer patients, active immunotherapy has gained significant importance in recent years by implementation of novel substances into standard clinical care.

These new drugs represent strategies which either use defined cancer associated antigens as vaccines or induce tumor-directed immune responses through generation of a general inflammatory state which has extensive autoinflammatory side effects by induction of autoreactive immune cells. Hence, the definition of suitable target antigens for immunotherapy remains a major challenge. These antigens should ideally be specific markers for individual tumors or should be at least structures overexpressed on the tumor as compared to normal cells. Recent approaches have defined algorithms and refined analytical methods for antigen identification and immunological validation that have already been evaluated in clinical studies. This article summarizes recent developments in tissue analysis on genome, transcriptome and HLA-ligandome levels and of antigen application in recent clinical vaccination trials.

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DOI: 10.1016/j.coi.2013.03.007

PMID: 23619309 [Indexed for MEDLINE]

2398. Eur J Med Genet. 2013 Jul;56(7):351-5. doi: 10.1016/j.ejmg.2013.04.002. Epub 2013 Apr 18.

Comparative screening of FMF mutations in various communities of the Israeli society.

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Familial Mediterranean Fever (FMF) is an autosomal recessive disease that is widely spread in the populations of the Mediterranean region. It is characterized by recurrent fever and inflammatory attacks. A total of 1700 suspected patients, belonging to various communities in Israel: Jews (Ashkenazi and non-Ashkenazi), Arabs (Muslims and Christians) and Druze, was subjected to examination for FMF mutation screening. The patients were screened for the most common six MEFV gene mutations namely, M680I, M694V, M694I, V726A, E148Q and K695R. Fifty-five percent of the cases were confirmed to have MEFV mutations. The most common mutations

among all the cases studied were M694V, E148Q and V726A. The common mutations in the respective communities were: among the Jews M694V with a frequency of 69.9% (76.8% for non-Ashkenazi Jews and 43.6% for Ashkenazi Jews), among the Arabs V726A with a frequency of 32.7% (32.7% for Muslims and 32.1% for Christians) and among Druze it was E148Q with a frequency of 52.1%. The characteristic mutation present in Jews was K695R and the one in Arabs was M680I, while no characteristic mutation was found in Druze. On the other hand, mutation E148Q was observed to have a considerable occurrence in patients of all ethnic groups studied.

Furthermore, our results revealed that homozygous mutations accounted for 168 cases (18%). The homozygote mutation M694V was the most prevalent among Jews and the E148Q mutation was the most common among Druze, while, among Arabs there were three homozygous mutations having maximum prevalence, namely, V726A, M694V and M694I. Our study comprehensively provided a spectrum of FMF mutations in various communities of Israeli society.

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DOI: 10.1016/j.ejmg.2013.04.002

PMID: 23602951 [Indexed for MEDLINE]

2399. Clin Rheumatol. 2013 Aug;32(8):1185-90. doi: 10.1007/s10067-013-2257-8. Epub 2013 Apr 17.

Mean platelet volume as a potential predictor of proteinuria and amyloidosis in familial Mediterranean fever.

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Comment in

Clin Rheumatol. 2013 Aug;32(8):1245-6.

This study aims to compare the mean platelet volume (MPV) levels in children and adults diagnosed with familial Mediterranean fever (FMF) during attack-free periods in order to find out whether it reflects the emergence of

microalbuminuria/proteinuria and the development of amyloidosis or not. The study consisted of 63 pediatric patients (group 1), 50 adult patients (group 2), 50 healthy children (group 3), and 43 healthy adults (group 4). Demographic data, age at diagnosis, duration of the disease and colchicine treatment, and FMF gene mutations were recorded, and erythrocyte sedimentation rate, C-reactive protein, fibrinogen, hemoglobin, white blood cell count, platelet count, MPV, blood urea nitrogen, creatine, albumin, and urine microalbumin and protein levels were evaluated. According to the presence of microalbuminuria/proteinuria, patient groups were subgrouped into two by themselves as pediatric and adult groups with and without proteinuria. The most frequent mutation was M694V. MPV was significantly higher in FMF patients than those in the healthy control groups. Microalbuminuria/proteinuria were detected in 18 (28.57 %) of 63 pediatric patients and 26 (52 %) of 50 adult patients. Amyloidosis has been identified in 3 (16.6 %) of 18 pediatric patients and 18 (69.23 %) of 26 adult patients with proteinuria. Subgroup comparisons revealed that MPV levels were significantly higher in patients with proteinuria than patients without proteinuria in both pediatric and adult groups. Moreover, MPV levels were also significantly higher in adult patients with or without proteinuria than in pediatric patients with or without proteinuria. There were significant differences in terms of serum albumin levels between the groups with and without proteinuria as expected. The increase in MPV over the years of the disease, especially in groups with proteinuria, may be an important predictor of continuing increase of subclinical inflammation, the emergence of the microalbuminuria/proteinuria, and the developing of amyloidosis, but further studies are needed in order to support this proposal.

DOI: 10.1007/s10067-013-2257-8

PMID: 23592230 [Indexed for MEDLINE]

2400. Immunol Res. 2013 Jul;56(2-3):371-5. doi: 10.1007/s12026-013-8414-y.

E148Q MEFV mutation carriage and longevity in individuals of Ashkenazi origin.

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The high carriage rate of MEFV mutations in at risk populations suggests that they confer a selective advantage, possibly by way of protection from infections. Here, we sought to assess whether this putative protection contributes to longevity, by studying MEFV mutation status in nonagenarians and the association of mutation carriage with life-threatening conditions. DNA samples and a medical history questionnaire were obtained from 200 nonagenarians (>90 years of age), who received medical treatment at a large tertiary hospital in Israel. The prevalence of MEFV mutations in the study group was compared to the known prevalence, by ethnic group, in the Israeli population. The presence of associated diseases in mutation carriers versus noncarriers was compared. The majority of study subjects were females (67.5 %) of Ashkenazi origin (78%). A fifth carried an MEFV mutation, most commonly E148Q (73% of total mutations), followed by V726A (5%). Only the frequency of E148Q in Ashkenazi subjects was found to be higher than expected in the general Ashkenazi population (19.8 vs. 2.6%,  $p < 0.0001$ ). Cardiac arrhythmias and hypothyroidism were more common in mutation carriers, while no difference was noted, between carriers and noncarriers, in the rates of ischemic heart disease, diabetes, stroke and a wide range of other serious conditions. Our findings suggest that E148Q carriage contributes to longevity in the Ashkenazi population, perhaps by enhancing resistance to infections.

DOI: 10.1007/s12026-013-8414-y

PMID: 23592051 [Indexed for MEDLINE]

2401. J Pediatr Gastroenterol Nutr. 2013 Sep;57(3):319-23. doi: 10.1097/MPG.0b013e318295fc65.

Gastrointestinal mucosal involvement without amyloidosis in children with familial Mediterranean fever.

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BACKGROUND AND OBJECTIVES: Familial Mediterranean fever (FMF) and inflammatory bowel disease togetherness is well described in the literature. Abdominal pain

and various gastrointestinal manifestations may arise directly from FMF or secondary to FMF-associated diseases such as inflammatory bowel disease, vasculitides, or amyloidosis. The aim of the study was to document gastrointestinal involvement in familial Mediterranean fever.

**METHODS:** The medical files of the patients who were diagnosed as having FMF at the Department of Pediatric Gastroenterology, Gazi University School of Medicine between 2007 and 2012 were examined retrospectively. FMF diagnosis was made through performing clinical, laboratory, colonoscopy, endoscopy, and genetic analysis.

**RESULTS:** Thirty-six patients were diagnosed as having FMF during this period. Among them, 11 patients were admitted with vomiting or diarrhea. Colonoscopy and upper gastrointestinal endoscopy were performed. Colonic inflammation and multiple gastric aphthous ulcerations were observed.

**CONCLUSIONS:** In this report, we described 11 patients who presented with gastrointestinal symptoms and eventually diagnosed as having FMF. Gastrointestinal mucosal involvement without amyloidosis is documented by endoscopic and histopathologic investigations in these patients. We concluded that mucosal involvement of the gastrointestinal tract may be attack-related manifestations in these patients.

DOI: 10.1097/MPG.0b013e318295fc65

PMID: 23591909 [Indexed for MEDLINE]

2402. J Eur Acad Dermatol Venereol. 2014 Jun;28(6):741-6. doi: 10.1111/jdv.12169. Epub 2013 Apr 17.

Clinical profile of generalized vitiligo patients with associated autoimmune/autoinflammatory diseases.

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**BACKGROUND:** The significance of associated autoimmune/autoinflammatory diseases in generalized vitiligo patients with respect to their clinical profile has not yet been completely established.

**OBJECTIVE:** The objective of this study was to evaluate the clinical significance

of associated autoimmune/autoinflammatory diseases in generalized vitiligo patients with respect to some general clinical variables, distribution pattern, disease activity and treatment response.

**METHODS:** Seven hundred generalized vitiligo patients were included in this retrospective observational cohort study.

**RESULTS:** Associated autoimmune/autoinflammatory diseases were present in 15.4% of the patient population and were more common in women compared with men, especially concerning thyroid disease. Only vitiligo patients with thyroid disease had clear different clinical characteristics. The percentage of total body surface area involvement was significantly ( $P = 0.005$ ) higher in the presence of thyroid disease which was more pronounced in women compared with men. Patients with thyroid disease had a particular predisposition to acral and joint depigmentations. No clear differences in disease activity or response to therapy were observed in vitiligo patients with or without autoimmune/autoinflammatory disorders.

**CONCLUSION:** The presence of associated autoimmune/autoinflammatory diseases seems to influence the clinical profile of generalized vitiligo patients. Our results support the hypothesis that in the presence of a thyroid disorder, the disease activity of vitiligo is more extensive, in particular on areas prone to friction.

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© 2013 European Academy of Dermatology and Venereology.

DOI: 10.1111/jdv.12169

PMID: 23590677 [Indexed for MEDLINE]

2403. Eur J Pediatr. 2013 Aug;172(8):1061-7. doi: 10.1007/s00431-013-2003-x. Epub 2013 Apr 16.

MEFV gene mutations in Turkish children with juvenile idiopathic arthritis.

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Mutations of the Mediterranean fever (MEFV) gene, which encodes pyrin protein,



leads to familial Mediterranean fever (FMF) and a connection between MEFV mutations and rheumatic diseases has been suggested. The aim of this study was to explore the frequency and clinical significance of MEFV mutations in children with juvenile idiopathic arthritis (JIA). In this study, children with JIA, who had no typical symptoms of FMF, were screened for the mutations in exons 2 and 10 of the MEFV gene by direct sequencing. A total of 96 children, 56 girls (58.3%), with a median age of 11 years (2-18 years) were included. Patients were classified according to JIA subgroups as oligoarthritis in 43 (44.8%), rheumatoid factor-negative polyarthritis in 22 (22.9%), rheumatoid factor-positive polyarthritis in 2 (2.1%), systemic arthritis in 12 (12.5%) patients, enthesitis-related arthritis in 16 (16.7%), and psoriatic arthritis 1 (1.04%). A total of 31 children (32.3%) had MEFV mutations: 25 heterozygous, 2 homozygous, and 4 compound heterozygous. There were 22 (11.4%) exon 10 mutations (M694V, R761H, K695R, V726A, R653H) and 15 (7.8%) exon 2 mutations (E148Q, G304R, E148V, T267I). The allele frequencies of MEFV mutations were found to be 19.27%, which is higher than the general population [ $p = 0.03$ , (odds ratio (OR):1.93, 95% confidence interval (CI): 1.09-3.41)]. MEFV mutation carrier rates were significantly higher in antinuclear antibody (ANA) negative than in ANA positive patients [ $p = 0.01$ , (OR: 0.25, 95% CI: 0.085-0.74)] and in males than in females [ $p = 0.001$ , (OR: 0.197, 95% CI: 0.078-0.495)]. Also, there was a statistically significant difference between the MEFV mutation carrier rates and the subgroups of JIA ( $p = 0.005$ ). CONCLUSION: These findings suggest that mutations of the MEFV gene may be responsible for rheumatic diseases other than FMF, and patients with JIA especially males, ANA negatives, and ERA subgroups should be screened for MEFV gene mutations in countries where FMF is frequent.

DOI: 10.1007/s00431-013-2003-x

PMID: 23588594 [Indexed for MEDLINE]

2404. G Ital Dermatol Venereol. 2013 Apr;148(2):185-96.

Neutrophilic dermatoses and inflammatory bowel diseases.

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Pyoderma gangrenosum (PG) and Sweet's Syndrome (SS) are inflammatory skin diseases caused by the accumulation of neutrophils in the skin and, rarely, in internal organs, which led to coining the term of neutrophilic dermatoses (ND) to define these conditions. Recently, ND have been included among the autoinflammatory diseases, which are forms due to mutations of genes regulating the innate immune responses. Both PG and SS are frequently associated with inflammatory bowel diseases (IBD), a group of chronic intestinal disorders which comprises ulcerative colitis and Crohn's disease and whose pathogenesis involves both the innate and adaptive immunity in genetically prone individuals. Patients with IBD develop PG in 1-3% of cases, while SS is rarer. PG presents with deep erythematous-to-violaceous painful ulcers with undermined borders, but bullous, pustular, and vegetative variants can also occur. SS, also known as acute febrile neutrophilic dermatosis, is characterized by the abrupt onset of fever, peripheral neutrophilia, tender erythematous skin lesions and a diffuse neutrophilic dermal infiltrate. In this review that will be focused on PG and SS, we will describe also the aseptic abscesses syndrome, a new entity within the spectrum of ND which frequently occurs in association with IBD and is characterized by deep abscesses mainly involving the spleen and skin and by polymorphic cutaneous manifestations including PG- and SS-like lesions.

PMID: 23588144 [Indexed for MEDLINE]

2405. Clin Immunol. 2013 Jun;147(3):151-4. doi: 10.1016/j.clim.2013.03.006. Epub 2013 Mar 26.

Bridging the gap between autoinflammation and autoimmunity.

Hedrich CM, Tsokos GC.

DOI: 10.1016/j.clim.2013.03.006

PMID: 23587745 [Indexed for MEDLINE]

2406. Rheumatology (Oxford). 2013 Nov;52(11):2095-7. doi: 10.1093/rheumatology/ket143. Epub 2013 Apr 12.

Distal lower extremity swelling as a prominent phenotype of NOD2-associated autoinflammatory disease.

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DOI: 10.1093/rheumatology/ket143

PMID: 23584365 [Indexed for MEDLINE]

2407. Immunol Res. 2013 Jul;56(2-3):317-24. doi: 10.1007/s12026-013-8404-0.

Autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA syndrome) in commercial sheep.

Luján L(1), Pérez M, Salazar E, Álvarez N, Gimeno M, Pinczowski P, Irusta S, Santamaría J, Insausti N, Cortés Y, Figueras L, Cuartielles I, Vila M, Fantova E, Chapullé JL.

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We describe a form of the autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA syndrome) in commercial sheep, linked to the repetitive inoculation of aluminum-containing adjuvants through vaccination. The syndrome shows an acute phase that affects less than 0.5% of animals in a given herd, it appears 2-6 days after an adjuvant-containing inoculation and it is characterized by an acute neurological episode with low response to external stimuli and acute meningoencephalitis, most animals apparently recovering afterward. The chronic phase is seen in a higher proportion of flocks, it can follow the acute phase, and it is triggered by external stimuli, mostly low temperatures. The chronic phase begins with an excitatory phase, followed by weakness, extreme cachexia, tetraplegia and death. Gross lesions are related to a cachectic process with muscular atrophy, and microscopic lesions are mostly linked to a

neurodegenerative process in both dorsal and ventral column of the gray matter of the spinal cord. Experimental reproduction of ovine ASIA in a small group of repeatedly vaccinated animals was successful. Detection of Al(III) in tissues indicated the presence of aluminum in the nervous tissue of experimental animals. The present report is the first description of a new sheep syndrome (ovine ASIA syndrome) linked to multiple, repetitive vaccination and that can have devastating consequences as it happened after the compulsory vaccination against bluetongue in 2008. The ovine ASIA syndrome can be used as a model of other similar diseases affecting both human and animals. A major research effort is needed in order to understand its complex pathogenesis.

DOI: 10.1007/s12026-013-8404-0

PMID: 23579772 [Indexed for MEDLINE]

2408. JAMA Dermatol. 2013 Jun;149(6):762-4. doi: 10.1001/jamadermatol.2013.2907.

Pyogenic arthritis, pyoderma gangrenosum, acne, and hidradenitis suppurativa (PAPASH): a new autoinflammatory syndrome associated with a novel mutation of the PSTPIP1 gene.

Marzano AV, Trevisan V, Gattorno M, Ceccherini I, De Simone C, Crosti C.

DOI: 10.1001/jamadermatol.2013.2907

PMID: 23571383 [Indexed for MEDLINE]

2409. Curr Pharm Des. 2014;20(4):552-66.

Platelets in rheumatic diseases: friend or foe?

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Platelets are intimately involved in hemostasis, inflammation, innate and

adaptive immunity, tissue regeneration and other physiological and pathological processes. Their granular structure is programmed to release a wide range of bioactive substances in response to agonists. Upon activation, platelet membranes display thrombotic and inflammatory agents, which may take an active part in the pathophysiology of autoimmune and autoinflammatory disorders. The aim of this review is to analyze current evidence of platelet (dys)function in inflammatory rheumatic diseases and overview platelet-targeting mechanisms of antirheumatic drug therapies. A comprehensive search through Medline/PubMed, SciVerse/Scopus and Web of Science was performed for English-language original research papers, using the keywords related to platelets in autoimmune and autoinflammatory rheumatic disorders. Additionally, the Cochrane Collaboration database was searched for the literature on the effects of antirheumatic drugs on platelet function. A variety of platelet markers have been tested in systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, spondyloarthropathies, vasculitides, and some autoinflammatory disorders. It has been shown that platelets circulate in an activated state in most of these disorders and tend to form complexes with other inflammatory and immune cells. Thrombotic and inflammatory agents, released from platelets, may trigger disease-specific complications (e.g., extraarticular features, fibrosis in systemic sclerosis) and propagate endothelial dysfunction. Whether platelet activation is a primary or secondary feature in rheumatic disorders remains to be elucidated. Some widely used antirheumatic drugs may suppress thrombopoiesis and platelet activity, however the clinical implications of this effect have yet to be examined in specifically designed prospective studies. Large retrospective cohort studies supported the use of low-dose aspirin for suppressing platelet function and preventing cerebrovascular events in giant-cell arteritis. However, emerging data suggest that the release rate of activated platelets applied topically to the inflamed cartilage in arthritis or skin ulcers in scleroderma may suppress the inflammation and facilitate tissue repair. Taken together, current evidence necessitates a balanced approach to platelet-activating and suppressing drug therapies in inflammatory rheumatic diseases.

PMID: 23565634 [Indexed for MEDLINE]

2410. *Pediatr Hematol Oncol*. 2014 Mar;31(2):120-8. doi: 10.3109/08880018.2013.782082. Epub 2013 Apr 5.

Leukopenia in familial Mediterranean fever: case series and literature review with special emphasis on pathogenesis.

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Comment in

Pediatr Hematol Oncol. 2014 Mar;31(2):129-30.

Leukopenia is a blood disease in which the number of circulating white blood cells diminishes. All underlying causes of leukopenia are not yet known. The subjects of this study are 15 leukopenic patients who were assessed by a systemic workup, including physical examination, blood tests, and molecular analysis. A common and unusual cause was revealed in all patients. This cause was a disorder with a laboratory characteristic of leukocytosis, namely familial Mediterranean fever (FMF). It was discussed that leukopenia arising in the context of FMF is mainly due to autophagy and apoptosis processes. These two pathophysiological characteristics of FMF were thought to explain the particular (episodic and self-limited) leukopenia in this disorder. Based on the results of this study in conjunction with the currently existing literature data, we suggest that FMF causes leukopenia. Leukopenic cases should be investigated for FMF, particularly if the leukopenia is episodic in nature. Early recognition of FMF would help to skip unnecessary invasive procedures and to prevent the development of amyloidosis, the devastating complication of FMF.

DOI: 10.3109/08880018.2013.782082

PMID: 23560861 [Indexed for MEDLINE]

2411. Clin Exp Rheumatol. 2013 May-Jun;31(3 Suppl 77):15-9. Epub 2013 Apr 2.

Oral health and oral quality of life in inactive patients with familial Mediterranean fever without amyloidosis.

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**OBJECTIVES:** The aim of this study was to investigate oral and general health-related quality of life (QoL) in patients with familial Mediterranean fever (FMF) disease.

**METHODS:** In this cross-sectional study, 45 patients with FMF, 50 age- and sex-matched healthy controls (HC), and 50 patients with Behçet's disease (BD) as the disease control group were included. FMF disease activity was evaluated by using the FMF-severity score, as well as with erythrocyte sedimentation rate (ESR), and serum C-reactive protein and fibrinogen levels. Oral health-related QoL and general QoL were evaluated using oral health impact profile-14 (OHIP-14) and Medical Outcomes Short-Form Health Survey Questionnaire 36 (SF-36), respectively.

**RESULTS:** Only the numbers of extracted teeth ( $4.13 \pm 4.72$  vs.  $1.55 \pm 3.6$ ) and filled teeth ( $2.33 \pm 3.19$  vs.  $0.66 \pm 1.46$ ) were significantly higher in FMF group compared to HC group ( $p=0.005$  and  $p=0.013$ , respectively). OHIP-14 score was significantly higher in FMF and BD groups compared to HC group. In FMF patients, OHIP-14 score was positively correlated with the number of extracted teeth ( $r=0.38$ ,  $p=0.010$ ), while the number of carious teeth was positively correlated with ESR ( $r=0.43$ ,  $p=0.003$ ). When FMF patients were sub-classified according to disease severity, no significant difference was observed with respect to oral health status.

**CONCLUSIONS:** In patients with FMF, some of the parameters of oral health status were found to be worse compared to HC group. Tooth loss appears to be a critical factor contributing to impaired oral QoL. In general, oral health status in FMF patients is better than in BD patients.

PMID: 23557976 [Indexed for MEDLINE]

2412. Clin Genet. 2013 Jun;83(6):582-3. doi: 10.1111/cge.12135. Epub 2013 Apr 5.

Response to Zizzo et al.

Simsek I, Yilmaz S, Cinar M, Erdem H, Pay S.

Comment on

Clin Genet. 2013 Jun;83(6):576-81.

DOI: 10.1111/cge.12135

PMID: 23557211 [Indexed for MEDLINE]

2413. Blood. 2013 Jul 4;122(1):112-23. doi: 10.1182/blood-2012-08-439083. Epub 2013 Apr 3.

A novel syndrome of congenital sideroblastic anemia, B-cell immunodeficiency, periodic fevers, and developmental delay (SIFD).

Wiseman DH(1), May A, Jolles S, Connor P, Powell C, Heeney MM, Giardina PJ, Klaassen RJ, Chakraborty P, Geraghty MT, Major-Cook N, Kannengiesser C, Thuret I, Thompson AA, Marques L, Hughes S, Bonney DK, Bottomley SS, Fleming MD, Wynn RF.

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Congenital sideroblastic anemias (CSAs) are a heterogeneous group of inherited disorders identified by pathological erythroid precursors with perinuclear mitochondrial iron deposition in bone marrow. An international collaborative group of physicians and laboratory scientists collated clinical information on cases of CSA lacking known causative mutations, identifying a clinical subgroup of CSA associated with B immunodeficiency, periodic fevers, and development delay. Twelve cases from 10 families were identified. Median age at presentation was 2 months. Anemia at diagnosis was sideroblastic, typically severe (median hemoglobin, 7.1 g/dL) and markedly microcytic (median mean corpuscular volume, 62.0 fL). Clinical course involved recurrent febrile illness and gastrointestinal disturbance, lacking an infective cause. Investigation revealed B-cell lymphopenia (CD19<sup>+</sup> range, 0.016-0.22 × 10<sup>9</sup>/L) and panhypogammaglobulinemia in most cases. Children displayed developmental delay alongside variable neurodegeneration, seizures, cerebellar abnormalities, sensorineural deafness, and other multisystem features. Most required regular blood transfusion, iron chelation, and intravenous immunoglobulin replacement. Median survival was 48 months, with 7 deaths caused by cardiac or multiorgan failure. One child underwent bone marrow transplantation aged 9 months, with apparent cure of the



hematologic and immunologic manifestations. We describe and define a novel CSA and B-cell immunodeficiency syndrome with additional features resembling a mitochondrial cytopathy. The molecular etiology is under investigation.

DOI: 10.1182/blood-2012-08-439083

PMCID: PMC3761334

PMID: 23553769 [Indexed for MEDLINE]

2414. Pharmacotherapy. 2013 Jul;33(7):744-53. doi: 10.1002/phar.1265. Epub 2013 Apr 3.

Role of interleukin-1 inhibitors in the management of gout.

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Erratum in

Pharmacotherapy. 2014 Feb;34(2):212.

Interleukin-1 (IL-1) inhibitors potentially have a role as antiinflammatory agents in refractory gout or for patients who are unable to tolerate conventional therapy, such as nonsteroidal antiinflammatory drugs (NSAIDs), colchicine, or glucocorticoids, for acute attacks. Additionally, IL-1 inhibitors may also help patients with polyarticular and tophaceous gout by making them less vulnerable to breakthrough attacks during initiation of chronic urate-lowering treatment, the mainstay of gout therapy. Because evidence highlights the role of proinflammatory cytokine IL-1 in the inflammation process during an acute gouty attack, IL-1 inhibitors are used to modulate the pathogenesis of a variety of autoinflammatory diseases, providing support for its potential role in the inflammatory process of gout. After NSAIDs, colchicine, and steroids, IL-1 inhibitors are beneficial as fourth-line therapy for acute gout attacks due to their high cost and limited clinical experience. The IL-1 inhibitors used in gout are anakinra, canakinumab, and rilonacept. Based on published evidence, anakinra has limited support in the form of anecdotal case reports to justify its use for treating gout.

Canakinumab's toxic profile in clinical trials precludes its use in treating

patients for gout, and rilonacept shows promise with a few well-designed studies to support its use in gout patients initiating urate-lowering treatment. When combined with current traditional therapies, these newer agents present clinicians and patients with more potential treatment options in the difficult-to-treat gout population.

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DOI: 10.1002/phar.1265

PMID: 23553601 [Indexed for MEDLINE]

2415. Z Rheumatol. 2013 May;72(4):332-8. doi: 10.1007/s00393-012-1061-1.

[Genetic fever syndromes. Hereditary recurrent (periodic) fever syndromes].

[Article in German]

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Genetic fever syndromes or hereditary recurrent fever syndromes (HRF) are considered to be part of the autoinflammatory diseases (AID) which result from errors in the innate immune system. Patients typically have self-limiting episodes of fever and high levels of inflammation markers. The mode of inheritance is autosomal recessive or autosomal dominant. The diseases of the HRF include familial Mediterranean fever, tumor necrosis factor receptor 1-associated periodic syndrome, hyper-IgD syndrome and cryopyrin-associated periodic fever syndromes. The disease known as deficiency of interleukin 1 (IL1) receptor antagonist does not fully belong to this group because fever is not a typical symptom. The therapy depends on the type and severity of the disease. Effective prophylaxis is possible for FMF. Biologicals, especially IL1 blocking agents are highly effective in very severe fever syndromes. In order to collect more information on AID, to establish a biobank and coordinate research in this field the AID-Net project was founded. Currently 606 patients with AID are registered

of whom 381 have HRF.

DOI: 10.1007/s00393-012-1061-1

PMID: 23552978 [Indexed for MEDLINE]

2416. Kidney Blood Press Res. 2013;37(1):33-42. doi: 10.1159/000343398. Epub 2013 Mar 12.

Renal involvement in AA amyloidosis: clinical outcomes and survival.

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**BACKGROUND:** The natural history of AA amyloidosis is typically progressive, leading to multiple organ failure and death. We analyzed the etiology as well as clinical and laboratory features of patients with biopsy-proven AA amyloidosis and evaluated the ultimate outcome.

**METHODS:** Seventy-three patients (24 female; mean age  $41.85 \pm 15.89$  years) were analyzed retrospectively. Demographic, clinical and laboratory features were studied and the outcome was assessed.

**RESULTS:** Familial Mediterranean Fever and tuberculosis were the most frequent causes of amyloidosis. Mean serum creatinine and proteinuria at diagnosis were  $4.65 \pm 4.89$  mg/dl and  $8.04 \pm 6.09$  g/day, respectively; and stage I, II, III, IV and V renal disease were present in 19.2%, 13.7%, 16.4%, 11%, and 39.7% of the patients, respectively. ESRD developed in 16 patients during the follow-up period. All of the ESRD patients started a dialysis programme. Thirty patients (41%) died during the follow-up period; median patient survival was  $35.9 \pm 6.12$  months. Old age, tuberculosis etiology, advanced renal disease and low serum albumin levels were associated with a worse prognosis. Serum albumin was a predictor of mortality in logistic regression analysis.

**CONCLUSION:** The ultimate outcome of the patients with AA amyloidosis is poor, possibly due to the late referral to the nephrology clinics. Early referral may be helpful to improve prognosis.

2417. *Pediatr Rheumatol Online J.* 2013 Apr 2;11(1):14. doi: 10.1186/1546-0096-11-14.

Autoinflammatory gene polymorphisms and susceptibility to UK juvenile idiopathic arthritis.

Hinks A(1), Martin P, Thompson SD, Sudman M, Stock CJ, Thomson W, Day TG, Packham J; Childhood arthritis prospective study (CAPS); BSPAR study group, Ramanan AV, Donn RP.

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**BACKGROUND:** To investigate the autoinflammatory hereditary periodic fever syndrome genes MVK and TNFRSF1A, and the NLRP1 and IL1 genes, for association with juvenile idiopathic arthritis (JIA).

**METHODS:** For MVK, TNFRSF1A and NLRP1 pair-wise tagging SNPs across each gene were selected and for IL1A SNPs from a prior meta-analysis were included. 1054 UK Caucasian JIA patients were genotyped by Sequenom iPLEX MassARRAY and allele and genotype frequencies compared with 5380 unrelated healthy UK Caucasian controls.

**RESULTS:** Four SNPs were significantly associated with UK JIA: rs2071374 within intron 4 of IL1A (ptrend=0.006), rs2228576 3' of TNFRSF1A (ptrend=0.009) and 2 SNPs, rs11836136 and rs7957619, within MVK (ptrend=0.006, ptrend=0.005 respectively). In all cases the association appeared to be driven by the systemic-onset JIA (SoJIA) subtype. Genotype data for the two MVK SNPs was available in a validation cohort of 814 JIA (oligoarticular and RF negative polyarticular) cases and 3058 controls from the US. Replication was not confirmed, however, further suggesting that this association is specific to SoJIA.

**CONCLUSIONS:** These findings extend the observations of the relevance of studying monogenic loci as candidates for complex diseases. We provide novel evidence of association of MVK and TNFRSF1A with UK JIA, specifically driven by association

with SoJIA and further confirm that the IL1A SNP association with SoJIA is subtype specific. Replication is required in independent cohorts.

DOI: 10.1186/1546-0096-11-14

PMCID: PMC3621775

PMID: 23547563

2418. Rev Invest Clin. 2012 Sep-Oct;64(5):477-86.

[Autoinflammatory diseases: a glimpse at the innate immunity and its pathology].

[Article in Spanish]

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PMID: 23544310 [Indexed for MEDLINE]

2419. Auto Immun Highlights. 2012 Dec 15;4(1):33-8. doi: 10.1007/s13317-012-0044-1. eCollection 2013 Apr.

Autoimmunity in connection with a metal implant: a case of autoimmune/autoinflammatory syndrome induced by adjuvants.

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Autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA) has been recently proposed by Shoenfeld and Agmon-Levin as a new entity that comprises several conditions: the macrophagic-myofasciitis syndrome, the Gulf War syndrome, silicosis and post-vaccination phenomena, autoimmunity related to infectious fragments, hormones, aluminum, silicone, squalene oil, and pristane. We report the case of a 23-year-old woman who developed serial episodes of high fever, extreme fatigue, transient thrombocytopenia, multiple cervical adenopathies, hepatosplenomegaly, anemia, neutropenia, severe proteinuria and urine sediment abnormalities, elevated serum ferritin levels, and transient low positive antinuclear antibodies 1 year after she had a nickel-titanium chin implant for cosmetic reasons. The clinical picture simulated a variety of probable diseases: systemic lupus erythematosus, Kikuchi-Fujimoto syndrome, adult onset Still's disease, antiphospholipid syndrome, and hemophagocytic syndrome, among others, so she underwent an extensive medical investigation including two lymph node biopsies. She received treatment accordingly with steroids, methotrexate, and mofetil mycophenolate, with initial improvement of her symptoms, which recurred every time the dose was reduced. Two and a half years later the patient decided to retire the chin implant and afterwards all her systemic symptoms have disappeared. She remains in good health, without recurrence of any symptom and off medications until today. Albeit this patient fulfills proposed major ASIA criteria, to our knowledge it would be the first description of systemic features of autoinflammation in connection with a metal implant.

DOI: 10.1007/s13317-012-0044-1

PMCID: PMC4389082

PMID: 26000140

2420. J Med Genet. 2013 Jun;50(6):349-59. doi: 10.1136/jmedgenet-2013-101577. Epub 2013 Mar 27.

Inheritance of autoinflammatory diseases: shifting paradigms and nomenclature.

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Over 15 years have passed since the discovery of the first autoinflammatory gene, MEFV, responsible for familial Mediterranean fever. The identification of another gene, TNFRSF1A, in 1999 led to the concept of autoinflammation which characterises rheumatological conditions triggered by a defective innate immunity. Substantive progress has been made since then with the identification of 18 autoinflammatory genes accounting for up to 24 disease entities showing overlapping symptoms. The accumulation of studies reporting patients with missing or excess mutations as compared with expected numbers favours the hypothesis that these diseases are distributed along a continuum ranging from monogenic to multifactorial conditions, rather than featuring only classical modes of inheritance. Moreover, the probable interactions of environmental and epigenetic factors further obscure our understanding of the mechanisms underlying the phenotypic expression of patients. This review explores the history of autoinflammatory gene discovery, discusses the nosological disparities stemming from the clinical versus pathophysiological definition of autoinflammatory diseases and summarises various inheritance patterns. This review calls for a consistent disease nomenclature and presents a reconciling hypothesis which places different sequence variants within the autoinflammatory disease continuum. Integrating these new concepts should help to facilitate communication between health professionals and promote personalised patient care.

DOI: 10.1136/jmedgenet-2013-101577

PMID: 23536687 [Indexed for MEDLINE]

2421. ISRN Dermatol. 2013;2013:907189. doi: 10.1155/2013/907189. Epub 2013 Feb 25.

Effect of Infliximab on the UVB-Induced Apoptosis of Keratinocytes Infected by HPV38 E6/E7.

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The question of the effect of anti-TNF-alpha in skin carcinogenesis is especially relevant in view of the increased use of these drugs for the treatment of

autoinflammatory immune diseases. Since ultraviolet radiation and human papillomavirus are involved in skin carcinogenesis, we wished to investigate the effect of TNF-alpha antagonists on the UVB-induced apoptosis of keratinocytes infected by HPV38. Our results indicate that anti-TNF agent, infliximab, does not contribute to the survival of HPV38-transduced keratinocytes with UVB-induced DNA damages.

DOI: 10.1155/2013/907189

PMCID: PMC3596906

PMID: 23533798

2422. Anadolu Kardiyol Derg. 2013 Jun;13(4):357-62. doi: 10.5152/akd.2013.103. Epub 2013 Mar 26.

Relationship of paraoxonase-1, malondialdehyde and mean platelet volume with markers of atherosclerosis in familial Mediterranean fever: an observational study.

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Comment in

Anadolu Kardiyol Derg. 2013 Sep;13(6):608-9.

Anadolu Kardiyol Derg. 2014 Nov;14(7):659-60.

Anadolu Kardiyol Derg. 2013 Sep;13(6):609.

Anadolu Kardiyol Derg. 2014 Nov;14(7):660.

**OBJECTIVE:** There are many studies demonstrating deteriorated ventricle and endothelium functions in familial Mediterranean fever (FMF) patients. As FMF is an autoinflammatory disease with an ongoing inflammatory activity and inflammation plays an important role in the development and progression of atherosclerosis in some of the rheumatic diseases, we aimed to investigate the early markers of atherosclerosis in patients with FMF by the measurements of serum paraoxonase-1 (PON-1) activity, mean platelet volume (MPV) and malondialdehyde (MDA) level.



**METHODS:** This study is a cross-sectional, observational study. Forty consecutive patients with FMF and twenty healthy volunteers were selected to form the study population. The diagnosis of FMF was based on Tel-Hashomer criteria. Serum PON-1 activity, MPV and MDA level were determined to examine their association with FMF. Student's t-test, Mann-Whitney U test, Pearson correlation analysis were used for statistical analysis.

**RESULTS:** The mean PON-1 activity in FMF patients was significantly lower than in the healthy population ( $141.46 \pm 38.29$  vs.  $179.62 \pm 10.73$  U/l,  $p < 0.01$ ). Serum MDA levels were the same between the groups ( $1.08 \pm 0.66$  vs.  $1.08 \pm 0.33$  nmol/mL,  $p = 0.99$ ). MPV was higher in FMF patients than in the control I group ( $8.87 \pm 0.99$  vs.  $8.22 \pm 0.45$  fl,  $p = 0.04$ ). PON, MPV and MDA levels were the same in FMF patients with acute attack and attack -free period.

**CONCLUSION:** Our results show that PON-1 activity is lower in patients with FMF. Reduced PON-1 activity and increased MPV, independent of the oxidative stress status of these patients, may lead to increased atherosclerotic propensity in FMF.

**Publisher: AMAÇ:** Ailevi Akdeniz Ateşi (AAA) hastalarında bozulmuş ventrikül ve endotel fonksiyonlarını gösteren pek çok çalışma bulunmaktadır. AAA devamlı enflamatuvar aktivite ile seyreden bir otoenflamatuvar hastalık olduğundan ve bazı romatizmal hastalıklarda enflamasyon ateroskleroz gelişimi ve ilerlemesinde önemli rol oynadığından, AAA hastalarında serum paraoksonaz-1 (PON-1) aktivitesi, ortalama trombosit hacmi (OTH) ve malondialdehit (MDA) seviyesi ölçerek aterosklerozun erken belirteçlerini araştırmayı amaçladık. **YÖNTEM:** Bu çalışma kesitsel ve gözlemsel bir çalışmadır. Kırk AAA'lı hasta ve yirmi sağlıklı gönüllü çalışma topluluğunu oluşturmak için seçildi. AAA tanısı Tel-Hashomer kriterlerine göre konuldu. AAA, MDA seviyesi, OTH ve PON-1 aktivitesi arasındaki ilişkiyi araştırmak için serum PON-1 aktivitesi ve MDA seviyesi ve OTH ölçüldü. İstatistiksel analiz için Student's t-testi, Mann-Whitney U testi, Pearson korelasyon analizi kullanıldı. **BULGULAR:** AAA hastalarında ortalama PON-1 aktivitesi normal bireylere göre önemli olarak daha düşüktü ( $141.46 \pm 38.29$  karşın  $179.62 \pm 10.73$  U/L,  $p < 0.01$ ). Gruplar arasında serum MDA seviyeleri aynıydı ( $1.08 \pm 0.66$  karşın  $1.08 \pm 0.33$  nmol/mL,  $p = 0.99$ ). OTH normal bireylere göre önemli olarak daha yüksekti ( $8.87 \pm 0.99$  vs.  $8.22 \pm 0.45$  fl,  $p = 0.04$ ). AAA hastalarında akut atak sırasında ve ataksız dönemlerde PON-1 aktivitesi, MDA seviyeleri ve OTH aynıydı. **SONUÇ:** Sonuçlar göstermektedir ki AAA hastalarında PON-1 aktivitesi düşüktür. Azalmış PON-1 aktivitesi ve artmış OTH bu hastalarda, oksidatif stres durumundan bağımsız olarak, AAA'de artmış ateroskleroz yatkınlığına işaret ediyor olabilir.

DOI: 10.5152/akd.2013.103

PMID: 23531873 [Indexed for MEDLINE]

2423. Pediatrics. 2013 Apr;131(4):e1308-13. doi: 10.1542/peds.2012-2255. Epub 2013 Mar 25.

Mutation in the SLC29A3 gene: a new cause of a monogenic, autoinflammatory condition.

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Germline mutations in the SLC29A3 gene result in a range of recessive, clinically related syndromes: H syndrome, pigmented hypertrichosis with insulin-dependent diabetes mellitus syndrome, Faisalabad histiocytosis, and sinus histiocytosis with massive lymphadenopathy. The main symptoms of these diseases are hyperpigmentation with hypertrichosis, sensorineural deafness, diabetes, short stature, uveitis, and Rosai-Dorfman like histiocytosis. Here, we report the case of an 11-month-old boy with early-onset, recurrent episodes of unprovoked fever lasting 7 to 10 days and associated with pericardial effusion, abdominal pain, diarrhea, and inflammation. Physical examination revealed hyperpigmentation with hypertrichosis, dysmorphic features, and spleen and liver enlargement. Failure to thrive, sensorineural deafness, retarded psychomotor development, and a Rosai-Dorfman like cheek lesion developed subsequently. The febrile episodes did not respond to tumor necrosis factor  $\alpha$  antagonists and interleukin-1. Sequencing of the SLC29A3 gene revealed a homozygous missense mutation c.1088G>A (p.Arg363Gln). These observations suggest that a newly identified mutation in the SLC29A3 gene may be associated with an autoinflammatory disorder. Genetic defects in SLC29A3 should be considered in patients with autoinflammatory manifestations, recurrent febrile attacks, and 1 or more of the symptoms found in the broad spectrum of SLC29A3-related disorders (especially hyperpigmentation with hypertrichosis).

DOI: 10.1542/peds.2012-2255

PMID: 23530176 [Indexed for MEDLINE]

2424. Hautarzt. 2013 Apr;64(4):274-9. doi: 10.1007/s00105-012-2460-6.

[Uncommon acne-associated syndromes and their significance in understanding the pathogenesis of acne].

[Article in German]

Hong JB(1), Prucha H, Melnik B, Ziai M, Ring J, Chen W.

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Acne is an intriguing model for the study of interactions between hormones, innate immunity, inflammation and wound healing (scarring). The manifestations and involvement of acne in different systemic diseases and some rare syndromes demonstrate its multifaceted nature.

Synovitis-Acne-Pustulosis-Hyperostosis-Osteitis (SAPHO) and Pyogenic Arthritis-Pyoderma gangrenosum-Acne (PAPA) syndromes, both regarded as autoinflammatory diseases, highlight the attributes of inflammation in acne. While SAPHO syndrome can be used to explore the pathogenic role of *Propionibacterium acnes* in acne, PAPA syndrome and Apert syndrome can help understand the genetic influence on acne. The genetic defects in the gain-of-function of FGFR2 mutations in Apert syndrome and acne nevus of Munro lend further support to the hypothesis that the interaction of forkhead box class O (FoxOs)-mediated transcriptional regulation with androgen receptor transactivation and insulin/insulin like growth factor-1(IGF-1)-signaling is crucial in acne pathogenesis. Novel biologics, such as tumor necrosis factor (TNF) blockers and IL-1 inhibitors, appear promising in opposing the inflammation associated with SAPHO and PAPA syndromes, but it remains to be seen if they can also improve severe acne particularly in the long term.

DOI: 10.1007/s00105-012-2460-6

PMID: 23525534 [Indexed for MEDLINE]

2425. Clin Immunol. 2013 Apr;147(1):58-60. doi: 10.1016/j.clim.2013.02.016. Epub 2013 Mar 5.

Familial Mediterranean fever mutations in a patient with recurrent episodes of acute respiratory distress syndrome.

Arai Y, Yamashita K, Mizugishi K, Watanabe T, Kondo T, Kitano T, Kawabata H, Kadowaki N, Takaori-Kondo A.

DOI: 10.1016/j.clim.2013.02.016

PMID: 23524442 [Indexed for MEDLINE]

2426. J Cutan Pathol. 2013 Jun;40(6):585-90. doi: 10.1111/cup.12132. Epub 2013 Mar 23.

Erysipelas-like erythema of familial Mediterranean fever syndrome: a case report with emphasis on histopathologic diagnostic clues.

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We report histopathological findings in a case of familial Mediterranean fever (FMF) syndrome with an erysipelas-like erythema (ELE). ELE is the only pathognomic cutaneous manifestation of FMF. ELE is characterized by well-demarcated, tender, erythematous and infiltrated plaques recurring on the same site and resolving spontaneously within 48-72 h. FMF is a monogenic autoinflammatory syndrome highlighted by recurrent fever associated with polyserositis involving mainly the peritoneum, synovium and pleura. FMF results from a mutation of the MEFV gene, which encodes for pyrin, leading to IL-1 $\beta$  activation and promoting neutrophil migration into the dermis. Histopathological findings in our case showed a sparse superficial perivascular and interstitial lymphocytic infiltrate admixed with some neutrophils, no eosinophils and mild papillary dermal edema. Venules and lymphatics were dilated, though no vasculitis was identified. Neutrophils are the most common cutaneous marker of autoinflammation, and cutaneous manifestations of monogenic autoinflammatory syndromes are represented by the spectrum of aseptic neutrophilic dermatoses.

Neutrophils in the presence of recurrent fever and in the correct clinical context of recurrent erysipelas in the same site are a diagnostic clue for FMF.

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DOI: 10.1111/cup.12132

PMID: 23521609 [Indexed for MEDLINE]

2427. Turk Kardiyol Dern Ars. 2013 Jan;41(1):38-44. doi: 10.5543/tkda.2013.10179.

Heart-type fatty acid binding protein level in familial Mediterranean fever.

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**OBJECTIVES:** Familial Mediterranean fever (FMF) is an autosomal recessive disorder and the most frequent periodic syndrome characterized by recurrent attacks of polyserositis. Heart-type fatty acid-binding protein (h-FABP) is an intracellular molecule engaged in the transport of fatty acids through the myocardial cytoplasm and a rapid marker of myocardial injury. FMF is an autoinflammatory disease characterized by ongoing inflammatory activity. Inflammation also plays an important role in the development and progression of atherosclerosis in some rheumatic diseases. We aimed to investigate markers of atherosclerosis in patients with FMF by the measurement of serum h-FABP and malondialdehyde levels (MDA).

**STUDY DESIGN:** Forty consecutive patients with FMF and twenty healthy volunteers were selected to participate in the study. The diagnosis of FMF was based on Tel-Hashomer criteria. Serum h-FABP and MDA levels were determined to examine the association.

**RESULTS:** The mean h-FABP level in FMF patients was significantly higher than the normal population ( $4.89 \pm 0.83$  vs.  $3.06 \pm 2.13$  ng/ml,  $p < 0.01$ ). The mean platelet volume was significantly higher in FMF patients than in the normal group ( $8.87 \pm 0.99$  vs.  $8.22 \pm 0.45$  fl,  $p = 0.04$ ). Serum MDA levels were the same between the groups ( $1.08 \pm 0.66$  vs.  $1.08 \pm 0.33$  nmol/ml,  $p = 0.99$ ). h-FABP and MDA levels were the same in FMF patients with an acute attack and during an attack free period.

CONCLUSION: Our results show that h-FABP increases in patients with FMF. Higher h-FABP levels may lead to increased atherosclerotic propensity in FMF, independent of the oxidative stress status of these patients.

DOI: 10.5543/tkda.2013.10179

PMID: 23518937 [Indexed for MEDLINE]

2428. Nihon Rinsho. 2012 Nov;70 Suppl 8:561-8.

[Autoinflammatory syndrome].

[Article in Japanese]

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PMID: 23513902 [Indexed for MEDLINE]

2429. Nat Commun. 2013;4:1611. doi: 10.1038/ncomms2608.

TRPM2 links oxidative stress to NLRP3 inflammasome activation.

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Exposure to particulate crystals can induce oxidative stress in phagocytes, which triggers NLRP3 inflammasome-mediated interleukin-1 $\beta$  secretion to initiate undesirable inflammatory responses that are associated with both autoinflammatory and metabolic diseases. Although mitochondrial reactive oxygen species have a central role in NLRP3 inflammasome activation, how reactive oxygen species signal

assembly of the NLRP3 inflammasome remains elusive. Here, we identify liposomes as novel activators of the NLRP3 inflammasome and further demonstrate that liposome-induced inflammasome activation also requires mitochondrial reactive oxygen species. Moreover, we find that stimulation with liposomes/crystals induced reactive oxygen species-dependent calcium influx via the TRPM2 channel and that macrophages deficient in TRPM2 display drastically impaired NLRP3 inflammasome activation and interleukin-1 $\beta$  secretion. Consistently, Trpm2(-/-) mice are resistant to crystal-/liposome-induced interleukin-1 $\beta$ -mediated peritonitis in vivo. Together, these results identify TRPM2 as a key factor that links oxidative stress to the NLRP3 inflammasome activation. Therefore, targeting TRPM2 may be effective for the treatment of NLRP3 inflammasome-associated inflammatory disorders.

DOI: 10.1038/ncomms2608

PMCID: PMC3605705

PMID: 23511475 [Indexed for MEDLINE]

2430. Arthritis Rheum. 2013 Jun;65(6):1654-62. doi: 10.1002/art.37935.

Familial Mediterranean fever in heterozygotes: are we able to accurately diagnose the disease in very young children?

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**OBJECTIVE:** Familial Mediterranean fever (FMF) is an autosomal-recessive autoinflammatory disease due to mutations in MEFV. Descriptions of disease manifestations among patients carrying a single mutated MEFV allele are becoming more frequent, although no data are available on the long-term outcome. We undertook this study to assess the accuracy of clinical diagnosis in children carrying a single mutated MEFV allele with symptoms of recurrent autoinflammatory disorder.

**METHODS:** We performed a retrospective single-center study of 33 patients with autoinflammatory disorders age <6 years at disease onset with 1 mutated MEFV allele. The phenotype of the patients was investigated in detail, and the

clinical picture and outcome of 18 patients with an initial FMF diagnosis according to current clinical criteria were compared to those of 25 homozygous or compound heterozygous FMF patients.

**RESULTS:** No major differences in presenting signs or initial response to colchicine were observed between patient groups. During followup, heterozygotes had a milder disease course compared to homozygotes and were less prone than homozygotes to experience new clinical signs of FMF. At puberty, clinical signs of FMF completely disappeared in 5 of 18 heterozygotes, allowing them to discontinue colchicine without recurrence of symptoms or increases in inflammatory marker levels.

**CONCLUSION:** Our data suggest that the clinical diagnosis of FMF in very young heterozygous children should be made with caution. At this young age they can present with an FMF-like disease-similar to that seen in patients carrying 2 mutated alleles-that is not necessarily predictive of life-long illness.

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DOI: 10.1002/art.37935

PMID: 23508419 [Indexed for MEDLINE]

2431. Springerplus. 2013 Dec;2(1):42. doi: 10.1186/2193-1801-2-42. Epub 2013 Feb 8.

Lack of HLA predominance and HLA shared epitopes in biliary Atresia.

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Biliary atresia (BA) is characterized by progressive inflammation and fibrosis of bile ducts. A theory of pathogenesis entails autoimmune-mediated injury targeting bile duct epithelia. One of the strongest genetic associations with autoimmunity is with HLA genes. In addition, apparently dissimilar HLA alleles may have similar antigen-binding sites, called shared epitopes, that overlap in their



capacity to present antigens. In autoimmune disease, the incidence of the disease may be related to the presence of shared epitopes, not simply the HLA allelic association. AIM: To determine HLA allele frequency (high-resolution genotyping) and shared epitope associations in BA.

RESULTS: Analysis of every allele for HLA-A, -B, -C, -DRB1, -DPB1 and -DQB1 in 180 BA and 360 racially-matched controls did not identify any significant HLA association with BA. Furthermore, shared epitope analysis of greater than 10 million possible combinations of peptide sequences was not different between BA and controls.

CONCLUSIONS: This study encompasses the largest HLA allele frequency analysis for BA in the United States and is the first study to perform shared epitope analysis. When controlling for multiple comparisons, no HLA allele or shared epitope association was identified in BA. Future studies of genetic links to BA that involve alterations of the immune response should include investigations into defects in regulatory T cells and non-HLA linked autoinflammatory diseases.

DOI: 10.1186/2193-1801-2-42

PMCID: PMC3595468

PMID: 23505615

2432. Ann Rheum Dis. 2014 Jan;73(1):290-7. doi: 10.1136/annrheumdis-2012-203023. Epub 2013 Mar 16.

Identification of a new exon 2-skipped TNFR1 transcript: regulation by three functional polymorphisms of the TNFR-associated periodic syndrome (TRAPS) gene.

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BACKGROUND: Mutations in the TNFRSF1A gene encoding the tumour necrosis factor  $\alpha$  cell surface receptor, TNFR1, cause TNFR-associated periodic syndrome (TRAPS) and polymorphisms in TNFRSF1A, including rs4149570, rs767455 and rs1800692, are associated with inflammatory diseases.

OBJECTIVES: To describe a new exon 2-spliced transcript-TNFR1-d2-and the impact

of these three single nucleotide polymorphisms on exon 2 splicing, transcriptional activity of TNFRSF1A and TRAPS phenotype.

**METHODS:** Expression of TNFRSF1A transcripts was performed by reverse-transcription-PCR in a range of human cells and tissues. Exon 2 splicing and transcriptional activity were analysed in HEK293T and SW480 cells by in vitro alternative splicing and luciferase assays, respectively. We constructed haplotypes containing rs4149570, rs767455 and rs1800692 in controls (n=72), patients with TRAPS (n=111) and in TRAPS-like patients (n=450) to compare their distribution and association with clinical features of TRAPS.

**RESULTS:** TNFR1-d2 was expressed in a tissue-specific manner, whereas TNFR1 expression was ubiquitous. Alternative splicing assays showed that the T-A-T haplotype at rs4149570-rs767455-rs1800692 had a significantly higher expression of exon 2-skipping product ( $p=0.02$ ) compared with the G-G-C haplotype.

Transcriptional activity from the T-T haplotype at rs4149570-rs1800692 was increased compared with the G-C haplotype ( $p=0.03$ ). In patients with TRAPS, rs1800692 T/T homozygotes were excessively rare ( $p<10^{-4}$ ) and TRAPS-like patients with this genotype experienced less fever.

**CONCLUSIONS:** Our study provides a new mechanism of TNFRSF1A regulation whereby three polymorphisms in the promoter, exon 1 and intron 4 have a functional and combined effect on exon 2 splicing, via a coupling mechanism between transcription and splicing. These polymorphisms may affect the phenotype of TRAPS and TRAPS-like patients.

DOI: 10.1136/annrheumdis-2012-203023

PMID: 23505244 [Indexed for MEDLINE]

2433. Ann Rheum Dis. 2014 Feb;73(2):462-9. doi: 10.1136/annrheumdis-2012-202774. Epub 2013 Mar 16.

Increased NLRP3-dependent interleukin 1 $\beta$  secretion in patients with familial Mediterranean fever: correlation with MEFV genotype.

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**OBJECTIVES:** To define in patients affected by familial Mediterranean fever (FMF)

whether or not interleukin (IL)-1 $\beta$  secretion (1) is enhanced, (2) correlates with the type of MEFV mutation and (3) is mediated by NLRP3.

**METHODS:** Freshly isolated monocytes from 21 patients with FMF (12 homozygous and 9 heterozygous), 14 MEFV healthy carriers and 30 healthy donors (HDs), unstimulated or after lipopolysaccharide (LPS)-induced activation, were analysed for redox state (production of reactive oxygen species (ROS) and antioxidant responses) and IL-1 $\beta$  and IL-1 receptor antagonist (IL-1Ra) secretion. NLRP3 down-modulation was induced by in vitro silencing of the NLRP3 gene.

**RESULTS:** LPS-stimulated monocytes from patients with FMF displayed enhanced IL-1 $\beta$  secretion, which correlated with number and penetrance of MEFV mutations.

Silencing of NLRP3 consistently inhibited IL-1 $\beta$  secretion. As in other autoinflammatory diseases, FMF monocytes produced more ROS than genetically negative cells from HDs. Unlike in cryopyrin-associated periodic fever syndromes (CAPS), however, they were characterised by a conserved and sustained antioxidant response. Consistent with this finding, activated MEFV-mutated monocytes did not exhibit the functional indicators of oxidative stress observed in CAPS, including accelerated IL-1 $\beta$  secretion and deficient production of IL-1Ra.

**CONCLUSIONS:** MEFV-mutated monocytes display enhanced IL-1 $\beta$  secretion, which correlates with number of high-penetrance mutations and level of endogenous ROS. Unlike NLRP3-mutated cells, monocytes carrying MEFV mutations withstand oxidative stress and preserve IL-1Ra production, thereby limiting inflammation. Finally, in contrast with that found in the animal model, the increased secretion of IL-1 $\beta$  by LPS-stimulated FMF monocytes is NLRP3-dependent.

DOI: 10.1136/annrheumdis-2012-202774

PMID: 23505242 [Indexed for MEDLINE]

2434. Ann Rheum Dis. 2014 Feb;73(2):455-61. doi: 10.1136/annrheumdis-2012-202580. Epub 2013 Mar 16.

MEFV mutations affecting pyrin amino acid 577 cause autosomal dominant autoinflammatory disease.

Stoffels M(1), Szperl A, Simon A, Netea MG, Plantinga TS, van Deuren M, Kamphuis S, Lachmann HJ, Cuppen E, Kloosterman WP, Frenkel J, van Diemen CC, Wijmenga C, van Gijn M, van der Meer JW.

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**OBJECTIVES:** Autoinflammatory disorders are disorders of the innate immune system. Standard genetic testing provided no correct diagnosis in a female patient from a non-consanguineous family of British descent with a colchicine-responsive autosomal dominant periodic fever syndrome. We aimed to unravel the genetic cause of the symptoms.

**METHODS:** Whole exome sequencing was used to screen for novel sequence variants, which were validated by direct Sanger sequencing. Ex vivo stimulation with peripheral blood mononuclear cells was performed to study the functional consequences of the mutation. mRNA and cytokine levels were measured by quantitative PCR and ELISA, respectively.

**RESULTS:** Whole exome sequencing revealed a novel missense sequence variant, not seen in around 6800 controls, mapping to exon 8 of the MEFV gene (c.1730C>A; p.T577N), co-segregating perfectly with disease in this family. Other mutations at the same amino acid (c.1730C>G; p.T577S and c.1729A>T; p.T577S) were found in a family of Turkish descent, with autosomal dominant inheritance of familial Mediterranean fever (FMF)-like phenotype, and a Dutch patient, respectively. Moreover, a mutation (c.1729A>G; p.T577A) was detected in two Dutch siblings, who had episodes of inflammation of varying severity not resembling FMF. Peripheral blood mononuclear cells from one patient of the index family showed increased basal interleukin 1 $\beta$  mRNA levels and cytokine responses after lipopolysaccharide stimulation. Responses normalised with colchicine treatment.

**CONCLUSIONS:** Heterozygous mutations at amino acid position 577 of pyrin can induce an autosomal dominant autoinflammatory syndrome. This suggests that T577, located in front of the C-terminal B30.2/SPRY domain, is crucial for pyrin function.

DOI: 10.1136/annrheumdis-2012-202580

PMID: 23505238 [Indexed for MEDLINE]

2435. Ann Rheum Dis. 2014 Apr;73(4):704-9. doi: 10.1136/annrheumdis-2012-202932. Epub 2013 Mar 16.

Mortality risk factors associated with familial Mediterranean fever among a cohort of 1.25 million adolescents.

Twig G(1), Livneh A, Vivante A, Afek A, Shamiss A, Derazne E, Tzur D, Ben-Zvi I, Tirosh A, Barchana M, Shohat T, Golan E, Amital H.

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**OBJECTIVE:** There are limited data on long-term comorbidities and mortality among patients with familial Mediterranean fever (FMF). Our objective was to evaluate comorbidities and death rates among individuals with FMF.

**METHODS:** We studied a nationwide, population-based, retrospective cohort of 1225 individuals with FMF (59% men) in a database of 1 244 350 adolescents (16-20 years of age) medically evaluated for military service between 1973 and 1997. This cohort was linked with the national mortality, cancer and end-stage renal disease (ESRD) registries in Israel. Study outcomes were all-cause mortality, occurrence of ESRD and malignancy by the age of 50 years.

**RESULTS:** During 30 years of follow-up, death rates were 8.73/10(4) versus 4.32/10(4) person-years in the FMF and control groups, respectively ( $p=0.002$ ). In a multivariable analysis adjusted for age, birth year, socio-economic status, education, ethnicity and body mass index, FMF was associated with increased mortality in men ( $HR=1.705$  (95% CI 1.059 to 2.745),  $p=0.028$ ) and women ( $HR=2.48$  (1.032 to 5.992),  $p=0.042$ ). Renal amyloidosis accounted for 35% and 60% of deaths in men and women, respectively. FMF was not associated with an increased incidence of cancer.

**CONCLUSIONS:** FMF is associated with increased all-cause mortality that is likely attributed to reduced colchicine compliance or responsiveness. Individuals with FMF do not have an increased incidence of cancer. These results support the awareness among medical community to decrease the higher than average mortality rate among participants with FMF.

DOI: 10.1136/annrheumdis-2012-202932

PMCID: PMC4934385

PMID: 23505237 [Indexed for MEDLINE]

2436. J Neuroinflammation. 2013 Mar 16;10:39. doi: 10.1186/1742-2094-10-39.

Corticosteroid therapy in a patient with cerebral amyloid angiopathy-related inflammation.

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We studied longitudinal changes of the levels of anti-amyloid  $\beta$  (anti-A $\beta$ ) antibody, amyloid  $\beta$  (A $\beta$ ) protein, and interleukin 8 (IL-8) in cerebrospinal fluid (CSF) of a patient with cerebral amyloid angiopathy-related inflammation (CAA-ri) in whom steroid treatment resulted in clinical improvement. The diagnosis of CAA-ri was established with brain biopsy. Levels of anti-A $\beta$  42 antibody, A $\beta$  40, A $\beta$  42 and IL-8 in CSF were measured in the CAA-ri patient at 23 time points in the 8-month clinical course. These CSF samples were divided into 2 groups: those obtained before (n = 12) and those after (n = 11) oral corticosteroid therapy was started. We compared these levels between CSF samples obtained before and after therapy. The mean levels of anti-A $\beta$  42 antibody and IL-8 were significantly higher in CSF samples of the CAA-ri patient before oral corticosteroid therapy than those after therapy. A positive correlation was noted between levels of anti-A $\beta$  42 antibodies and IL-8 in CSF of this patient. There were no significant differences of mean levels of A $\beta$  40 and A $\beta$  42 between CSF samples obtained before and after oral corticosteroid therapy. It was possible that the autoinflammatory process with anti-A $\beta$  42 antibodies and IL-8 may have been involved in the pathogenesis of CAA-ri, and that corticosteroid therapy directly affected levels of anti-A $\beta$  42 antibody and IL-8. In summary, CAA-ri encephalopathy is a relapsing or progressive disorder and may be treatable by adequate immunosuppressive therapy. The anti-A $\beta$  42 antibody in CSF is a useful biological marker for therapeutic monitoring of CAA-ri.

DOI: 10.1186/1742-2094-10-39

PMCID: PMC3635896

PMID: 23497126 [Indexed for MEDLINE]

2437. J Pediatr Gastroenterol Nutr. 2014 Jul;59(1):e11-3. doi: 10.1097/MPG.0b013e3182906d8f.

Esophagitis and widespread aphthous ulcerations in gastric mucosa in an infant with familial Mediterranean fever.

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DOI: 10.1097/MPG.0b013e3182906d8f

PMID: 23492736 [Indexed for MEDLINE]

2438. J Gastroenterol Hepatol. 2013 Jul;28(7):1076-86. doi: 10.1111/jgh.12193.

Proteomics and metabolomics in inflammatory bowel disease.

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Genome-wide studies in inflammatory bowel disease (IBD) have allowed us to understand Crohn's disease and ulcerative colitis as forms of related autoinflammatory disorders that arise from a multitude of pathogenic origins. Proteomics and metabolomics are the offspring of genomics that possess unprecedented possibilities to characterize unknown pathogenic pathways. It has been about a decade since proteomics was first applied to IBD, and 5 years for metabolomics. These techniques have yielded novel and potentially important findings, but turning these results into beneficial patient outcomes remains challenging. This review recounts the history and context of clinical IBD developments before and after proteomics and metabolomics IBD in this field, discusses the challenges in consolidating high complexity data with physiological understanding, and provides an outlook on the emerging principles that will help interface the bioanalytical laboratory with IBD prognosis.

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DOI: 10.1111/jgh.12193

PMID: 23489082 [Indexed for MEDLINE]

2439. Int J Dermatol. 2014 Feb;53(2):e121-2. doi: 10.1111/j.1365-4632.2012.05618.x. Epub 2013 Mar 14.

A case of Beau's lines associated with familial Mediterranean fever.

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DOI: 10.1111/j.1365-4632.2012.05618.x

PMID: 23488825 [Indexed for MEDLINE]

2440. Islets. 2012 Nov-Dec;4(6):417-22. doi: 10.4161/isl.23541.

The lysine deacetylase inhibitor Givinostat inhibits  $\beta$ -cell IL-1 $\beta$  induced IL-1 $\beta$  transcription and processing.

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AIMS: Pro-inflammatory cytokines and chemokines, in particular IL-1 $\beta$ , IFN $\gamma$ , and CXCL10, contribute to  $\beta$ -cell failure and loss in DM via IL-1R, IFN $\gamma$ R, and TLR4 signaling. IL-1 signaling deficiency reduces diabetes incidence, islet IL-1 $\beta$  secretion, and hyperglycemia in animal models of diabetes. Further, IL-1R antagonism improves normoglycemia and  $\beta$ -cell function in type 2 diabetic patients. Inhibition of lysine deacetylases (KDACi) counteracts  $\beta$ -cell toxicity induced by the combination of IL-1 and IFN $\gamma$  and reduces diabetes incidence in non-obese diabetic (NOD) mice. We hypothesized that KDACi breaks an autoinflammatory circuit by differentially preventing  $\beta$ -cell expression of the



$\beta$ -cell toxic inflammatory molecules IL-1 $\beta$  and CXCL10 induced by single cytokines. RESULTS: CXCL10 did not induce transcription of IL-1 $\beta$  mRNA. IL-1 $\beta$  induced  $\beta$ -cell IL-1 $\beta$  mRNA and both IL-1 $\beta$  and IFN $\gamma$  individually induced Cxcl10 mRNA transcription. Givinostat inhibited IL-1 $\beta$ -induced IL-1 $\beta$  mRNA expression in INS-1 and rat islets and IL-1 $\beta$  processing in INS-1 cells. Givinostat also reduced IFN $\gamma$  induced Cxcl10 transcription in INS-1 cells but not in rat islets, while IL-1 $\beta$  induced Cxcl10 transcription was unaffected in both.

MATERIALS AND METHODS: INS-1 cells and rat islets of Langerhans were exposed to IL-1 $\beta$ , IFN $\gamma$  or CXCL10 in the presence or absence of KDACi (givinostat). Cytokine and chemokine mRNA expressions were quantified by real-time qPCR, and IL-1 $\beta$  processing by western blotting of cell lysates.

CONCLUSION/INTERPRETATION: Inhibition of  $\beta$ -cell IL-1 $\beta$  expression and processing and Cxcl10 transcription contributes to the  $\beta$ -cell protective actions of KDACi.

In vitro  $\beta$ -cell destructive effects of CXCL10 are not mediated via IL-1 $\beta$  transcription. The differential proinflammatory actions of KDACs may be attractive novel drug targets in DM.

DOI: 10.4161/isl.23541

PMCID: PMC3605170

PMID: 23486342 [Indexed for MEDLINE]

2441. Biomed Res Int. 2013;2013:501305. doi: 10.1155/2013/501305. Epub 2013 Jan 1.

Clinical genetic testing of periodic fever syndromes.

Marcuzzi A(1), Piscianz E, Kleiner G, Tommasini A, Severini GM, Monasta L, Crovella S.

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Periodic fever syndromes (PFSs) are a wide group of autoinflammatory diseases. Due to some clinical overlap between different PFSs, differential diagnosis can be a difficult challenge. Nowadays, there are no universally agreed recommendations for most PFSs, and near half of patients may remain without a genetic diagnosis even after performing multiple-gene analyses. Molecular analysis of periodic fevers' causative genes can improve patient quality of life

by providing early and accurate diagnosis and allowing the administration of appropriate treatment. In this paper we focus our discussion on effective usefulness of genetic diagnosis of PFSs. The aim of this paper is to establish how much can the diagnostic system improve, in order to increase the success of PFS diagnosis. The mayor expectation in the near future will be addressed to the so-called next generation sequencing approach. Although the application of bioinformatics to high-throughput genetic analysis could allow the identification of complex genotypes, the complexity of this definition will hardly result in a clear contribution for the physician. In our opinion, however, to obtain the best from this new development a rule should always be kept well in mind: use genetics only to answer specific clinical questions.

DOI: 10.1155/2013/501305

PMCID: PMC3581266

PMID: 23484126 [Indexed for MEDLINE]

2442. J Biol Chem. 2013 Apr 19;288(16):11378-83. doi: 10.1074/jbc.M112.448795. Epub 2013 Mar 11.

Ribotoxic stress through p38 mitogen-activated protein kinase activates in vitro the human pyrin inflammasome.

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Human pyrin with gain-of-function mutations in its B30.2/SPRY domain causes the autoinflammatory disease familial Mediterranean fever by assembling an ASC-dependent inflammasome that activates caspase-1. Wild-type human pyrin can also form an inflammasome complex with ASC after engagement by autoinflammatory PSTPIP1 mutants. How the pyrin inflammasome is activated in the absence of disease-associated mutations is not yet known. We report here that ribotoxic stress triggers the assembly of the human pyrin inflammasome, leading to ASC oligomerization and caspase-1 activation in THP-1 macrophages and in a 293T cell line stably reconstituted with components of the pyrin inflammasome. Knockdown of

pyrin and selective inhibition of p38 MAPK greatly attenuated caspase-1 activation by ribotoxic stress, whereas expression of the conditional mutant  $\Delta$ MEKK3:ER\* allowed the activation of caspase-1 without ribotoxic stress. Disruption of microtubules by colchicine also inhibited pyrin inflammasome activation by ribotoxic stress. Together, our results indicate that ribotoxic stress activates the human pyrin inflammasome through a mechanism that requires p38 MAPK signaling and microtubule stability.

DOI: 10.1074/jbc.M112.448795

PMCID: PMC3630843

PMID: 23479736 [Indexed for MEDLINE]

2443. J Clin Endocrinol Metab. 2013 Apr;98(4):1361-75. doi: 10.1210/jc.2012-4075. Epub 2013 Mar 7.

Endocrine side effects induced by immune checkpoint inhibitors.

Corsello SM(1), Barnabei A, Marchetti P, De Vecchis L, Salvatori R, Torino F.

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CONTEXT: In recent years, progress has been made in cancer immunotherapy by the development of drugs acting as modulators of immune checkpoint proteins, such as the cytotoxic T-lymphocyte antigen-4 (CTLA4) and programmed death-1 (PD-1), two co-inhibitory receptors that are expressed on T cells upon activation. These molecules play crucial roles in maintaining immune homeostasis by down-regulating T-cell signaling, thereby preventing unbridled T-cell proliferation while maintaining tolerance to self-antigens, such as tumor-associated antigens. CTLA4 blockade through systemic administration of the CTLA4-blocking antibody ipilimumab was shown to confer significant survival benefit and prolonged stable disease in patients affected by advanced cutaneous melanoma. Other immune checkpoint inhibitors are under clinical evaluation. However, immune checkpoint blockade can lead to the breaking of immune self-tolerance, thereby inducing a novel syndrome of autoimmune/autoinflammatory side effects, designated as "immune-related adverse events," mainly including rash, colitis, hepatitis, and endocrinopathies.

DATA ACQUISITION: We searched the medical literature using the words "hypophysitis," "hypopituitarism," "thyroid," "adrenal insufficiency," and "endocrine adverse events" in association with "immune checkpoint inhibitors," "ipilimumab," "tremelimumab," "PD-1," and "PD-1-L."

EVIDENCE SYNTHESIS: The spectrum of endocrine disease experienced by patients treated with ipilimumab includes most commonly hypophysitis, more rarely thyroid disease or abnormalities in thyroid function tests, and occasionally primary adrenal insufficiency. Hypophysitis has emerged as a distinctive side effect of CTLA4-blocking antibodies, establishing a new form of autoimmune pituitary disease. This condition, if not promptly recognized, may be life-threatening (due to secondary hypoadrenalism). Hypopituitarism caused by these agents is rarely reversible, and prolonged or lifelong substitutive hormonal treatment is often required. The precise mechanism of injury to the endocrine system triggered by these drugs is yet to be fully elucidated.

CONCLUSIONS: Although reports of endocrine side effects caused by cancer immune therapy are abundant, their exact prevalence and mechanism are unclear. Well-designed correlative studies oriented to finding and validating predictive factors of autoimmune toxicity are urgently needed.

DOI: 10.1210/jc.2012-4075

PMID: 23471977 [Indexed for MEDLINE]

2444. Genes Immun. 2013 Jun;14(4):212-6. doi: 10.1038/gene.2013.6. Epub 2013 Mar 7.

T helper 17 polarization in familial Mediterranean fever.

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Autoinflammatory attacks in familial Mediterranean fever (FMF) are accompanied by elevated levels of interleukin-6 (IL-6), and are controllable by IL-1-targeting drugs. In combination, IL-6 and IL-1 are known to be potent inducers of T helper (Th) 17 cells development. Therefore, we studied the Th17 population size, and activation potential, of FMF patients. Based on the relative mRNA expression of

the Th1, Th2, Treg and Th17 transcription factors T-bet, GATA3, FOXP3 and retinoic acid-related orphan receptor  $\gamma$ T (ROR $\gamma$ T), respectively, the Th17 population in peripheral blood mononuclear cells (PBMCs) of healthy subjects was estimated at 2.5% of the entire Th population and 4.4% in FMF patients in remission (n=6 for each group, P=0.03). IL-17 secretion after universal stimulation of the T-cell receptor in PBMCs culture was twice higher in cultures of patients with frequent attacks (n=18) than in those of patients with infrequent attacks (n=10, 1124 $\pm$ 266 vs 615 $\pm$ 196 pg ml<sup>-1</sup>, P=0.009). IL-17 secretion correlated well with IL17A mRNA level. Part of the increased secretion was related to the deleterious, MEFV p.M694V homozygous genotype (n=19, 1.5-fold, P=0.03). Almost all IL-17 producer cells were CD4-positive (CD4(+)/IL-17(+)). In conclusion, frequent attacks and the deleterious FMF genotype appear to drive FMF patients to a heightened Th17 response.

DOI: 10.1038/gene.2013.6

PMID: 23466494 [Indexed for MEDLINE]

2445. Ann Rheum Dis. 2014 Apr;73(4):662-7. doi: 10.1136/annrheumdis-2012-202708. Epub 2013 Mar 5.

Results from a multicentre international registry of familial Mediterranean fever: impact of environment on the expression of a monogenic disease in children.

Ozen S(1), Demirkaya E, Amaryan G, Koné-Paut I, Polat A, Woo P, Uziel Y, Modesto C, Finetti M, Quartier P, Papadopoulou-Alataki E, Al-Mayouf SM, Fabio G, Gallizzi R, Cantarini L, Frenkel J, Nielsen S, Hofer M, Insalaco A, Acikel C, Ozdogan H, Martini A, Ruperto N, Gattorno M; Paediatric Rheumatology International Trials Organisation; Eurofever Project.

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Comment in

Ann Rheum Dis. 2014 Aug;73(8):e53.

Ann Rheum Dis. 2014 Aug;73(8):e52.

BACKGROUND AND AIM: Familial Mediterranean fever (FMF) is an autoinflammatory

disease caused by mutations of the MEFV gene. We analyse the impact of ethnic, environmental and genetic factors on the severity of disease presentation in a large international registry.

**METHODS:** Demographic, genetic and clinical data from validated paediatric FMF patients enrolled in the Eurofever registry were analysed. Three subgroups were considered: (i) patients living in the eastern Mediterranean countries; (ii) patients with an eastern Mediterranean ancestry living in western Europe; (iii) Caucasian patients living in western European countries. A score for disease severity at presentation was elaborated.

**RESULTS:** Since November 2009, 346 FMF paediatric patients were enrolled in the Eurofever registry. The genetic and demographic features (ethnicity, age of onset, age at diagnosis) were similar among eastern Mediterranean patients whether they lived in their countries or western European countries. European patients had a lower frequency of the high penetrance M694V mutation and a significant delay of diagnosis ( $p < 0.002$ ). Patients living in eastern Mediterranean countries had a higher frequency of fever episodes/year and more frequent arthritis, pericarditis, chest pain, abdominal pain and vomiting compared to the other two groups. Multivariate analysis showed that the variables independently associated with severity of disease presentation were country of residence, presence of M694V mutation and positive family history.

**CONCLUSIONS:** Eastern Mediterranean FMF patients have a milder disease phenotype once they migrate to Europe, reflecting the effect of environment on the expression of a monogenic disease.

DOI: 10.1136/annrheumdis-2012-202708

PMID: 23463692 [Indexed for MEDLINE]

2446. Amyloid. 2013 Jun;20(2):122-6. doi: 10.3109/13506129.2013.775119. Epub 2013 Mar 6.

Systemic AA amyloidosis as a unique manifestation of a combined mutation of TNFRSF1A and MEFV genes.

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We report the case of a 22-year-old Caucasian woman presenting with a new-onset nephrotic syndrome with normal renal function during the 35th week of pregnancy. AA (secondary) amyloidosis was further diagnosed at the renal biopsy. Extensive genetic testing revealed that the patient was heterozygous for both TNFRSF1A p.R92Q and MEFV p.M694I mutations leading to an autoinflammatory syndrome characterized by amyloid deposition as the sole manifestation.

DOI: 10.3109/13506129.2013.775119

PMID: 23461592 [Indexed for MEDLINE]

2447. Internist (Berl). 2013 Apr;54(4):408-15. doi: 10.1007/s00108-012-3186-3.

[Interleukin-1-mediated diseases].

[Article in German]

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Interleukin-1 (IL-1)-mediated diseases are caused by an inappropriately high production and release of IL-1 beta which results in a multitude of symptoms, e.g. arthritis, exanthema, conjunctivitis, serositis, fever and loss of hearing. If IL-1-mediated diseases remain unrecognized or are recognized and treated too late, long-term complications, such as amyloidosis may occur. In recent years the diagnostic and therapeutic options with respect to IL-1-mediated diseases have drastically improved. These diseases often manifesting in childhood can now be treated with monoclonal antibodies against IL-1 or with IL-1 receptor antagonists. Increased IL-1 secretion does not only play a role in relatively rare hereditary diseases, such as cryopyrin-associated periodic fever syndromes or familial Mediterranean fever but also in widespread diseases, such as gout or type 2 diabetes. This article will focus on pathogenic, diagnostic and therapeutic aspects of IL-1-mediated inflammatory diseases.

DOI: 10.1007/s00108-012-3186-3

PMID: 23460390 [Indexed for MEDLINE]

2448. Arch Pediatr. 2013 Apr;20(4):382-5. doi: 10.1016/j.arcped.2013.01.053. Epub 2013 Mar 1.

[Cutaneous polymorph manifestations of familial Mediterranean fever in a child].

[Article in French]

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We describe the case of a 4-year-old child with Mediterranean fever characterized by cutaneous features. Familial Mediterranean fever is an autosomal recessive disorder characterized by recurrent attacks of fever and polyserositis including peritonitis, pleuritis, and arthritis. Skin involvement is less common. In our case, the successively patient presented erysipelas-like erythema, edemas of the palmar and plantar regions, and purpuric lesions. From these clinical observations, several diagnoses were raised: infectious erysipelas, Kawasaki disease, Henoch-Schönlein purpura, and familial Mediterranean fever. Only the latter diagnosis was confirmed after exploration and then confirmed with genetic analysis, which found a M694V homozygous mutation. Erysipelas-like erythema is the most frequent cutaneous sign reported in the literature and the only one to be associated with the M694V homozygous mutation. The originality of this case is the dominancy and polymorphism of the skin lesions.

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DOI: 10.1016/j.arcped.2013.01.053

PMID: 23453719 [Indexed for MEDLINE]

2449. J Am Acad Dermatol. 2013 May;68(5):834-53. doi: 10.1016/j.jaad.2012.11.002. Epub 2013 Feb 28.



Autoinflammation: From monogenic syndromes to common skin diseases.

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Autoinflammation is characterized by aberrant regulation of the innate immune system and often manifests as periodic fevers and systemic inflammation involving multiple organs, including the skin. Mutations leading to abnormal behavior or activity of the interleukin 1 beta (IL-1 $\beta$ )-processing inflammasome complex have been found in several rare autoinflammatory syndromes, for which anticytokine therapy such as IL-1 or tumor necrosis factor- $\alpha$  inhibition may be effective. It is becoming clear that features of autoinflammation also affect common dermatoses, some of which were previously thought to be solely autoimmune in origin (eg, vitiligo, systemic lupus erythematosus). Recognizing the pathogenetic role of autoinflammation can open up new avenues for the targeted treatment of complex, inflammatory dermatoses.

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DOI: 10.1016/j.jaad.2012.11.002

PMID: 23453357 [Indexed for MEDLINE]

2450. Expert Opin Biol Ther. 2013 Apr;13(4):615-22. doi: 10.1517/14712598.2013.778239. Epub 2013 Mar 4.

Canakinumab in pediatric rheumatic diseases.

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INTRODUCTION: Hitherto, some of the most severe forms of arthritis with onset in

the neonatal period and early childhood have been resistant to conventional and anti-tumour necrosis factor agents. Recent results from drug trials of novel monoclonal antibodies will significantly alter the treatment of two of these diseases. This review is for canakinumab, a new monoclonal antibody to interleukin 1 $\beta$  that has been shown to be specifically efficacious in two groups of arthritis with systemic features.

**AREAS COVERED:** The clinical features and treatment to-date in the autoinflammatory disease, cryopyrin associated periodic fever syndrome and systemic juvenile idiopathic arthritis are briefly reviewed. An overview of current IL-1 inhibitors is provided. Clinical trials of Canakinumab in the treatment of these two diseases are evaluated.

**EXPERT OPINION:** The last decade has seen a major advance in treatment leading to remission while on therapy for many children with CAPS and sJIA. The outcomes of the anti-IL-1 $\beta$  and the anti-IL-6 trials for sJIA are quite similar and do not enable preferential use of either biological in a given patient.

DOI: 10.1517/14712598.2013.778239

PMID: 23451862 [Indexed for MEDLINE]

2451. J Clin Pharm Ther. 2013 Jun;38(3):243-5. doi: 10.1111/jcpt.12047. Epub 2013 Mar 1.

Colchicine toxicity precipitated by interaction with sunitinib.

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**WHAT IS KNOWN AND OBJECTIVE:** Colchicine is an anti-inflammatory agent used primarily in treatment of gout and familial Mediterranean fever. Toxicity is uncommon, and depends on dose, hepatic or renal impairment, co-administration with P-glycoprotein or CYP3A4 inhibitors and route of administration. In patients taking p-glycoprotein inhibitors, maximum recommended dose is 0.3 mg per day. In renal or hepatic impairment, recommendation is to avoid concomitant administration of p-glycoprotein inhibitors and colchicine.

**CASE SUMMARY:** We present an 82 year old patient, with a history of gout, chronic

kidney disease and recurrent renal cell carcinoma who was admitted with features of colchicine toxicity after taking a cumulative dose of 41.4 mg over ten days, and taking sunitinib 50 mg daily from day seven of his high dose colchicine regimen. Symptoms started after commencing his cycle of sunitinib, which he had taken in 14 day cycles for many years. He developed severe diarrhea, normal anion gap metabolic acidosis, fever, pneumonia, white cell abnormalities including 30% bands and toxic granulation with Dohle bodies. Red cell abnormalities included anemia, burr cells and acanthocytosis. He also developed acute cardiovascular collapse with hypotension and acute systolic heart failure. Cardiac catheterization showed previously known coronary artery disease, with no significant progression to explain degree of cardiovascular collapse.

WHAT IS NEW AND CONCLUSION: P-glycoprotein inhibition by sunitinib has been demonstrated. Interaction with colchicine metabolism precipitated colchicine toxicity in this case. Knowledge of p-glycoprotein and its role in drug interactions and potential drug toxicity may not be widespread among clinicians. We report the first case of colchicine toxicity precipitated by interaction with a tyrosine kinase inhibitor.

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DOI: 10.1111/jcpt.12047

PMID: 23448320 [Indexed for MEDLINE]

2452. Arthritis Rheum. 2013 Mar;65(3):824-31. doi: 10.1002/art.37810.

Hearing loss in Muckle-Wells syndrome.

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OBJECTIVE: Muckle-Wells syndrome (MWS) is an inherited autoinflammatory disease characterized by fevers, rashes, arthralgia, conjunctivitis, and sensorineural hearing loss. In MWS, NLRP3 gene mutations are associated with excessive interleukin-1 release. The aims of this study were to determine the otologic characteristics of MWS, define trajectories of hearing loss, and explore the

association with distinct NLRP3 genotypes.

**METHODS:** A prospective observational cohort study of children and adults diagnosed as having MWS was conducted at a single center. NLRP3 gene mutations were determined. Patients underwent standardized clinical, laboratory, and otologic assessments, including pure tone audiometry, vestibular organ testing, and tinnitus evaluation. Trajectories of hearing loss were defined for each genotype. The genotype-specific risk of progression of hearing loss was determined.

**RESULTS:** A total of 33 patients ages 3-75 years who were members of 5 families with 4 different NLRP3 gene mutations were included. The majority of patients (67%) experienced bilateral sensorineural hearing loss. Even in cases of profound hearing loss vestibular reactivity remained normal. Fourteen adult patients reported nondebilitating tinnitus. Overall, hearing impairment progressed with age. Patients with the T348M mutation were at highest risk of rapid progression of sensorineural hearing loss.

**CONCLUSION:** Patients with MWS are at risk of developing progressive sensorineural hearing loss without vestibular involvement. Hearing impairment starts at high frequencies and can subsequently progress to profound hearing loss. Progression is age dependent. Patients with different NLRP3 mutations had distinctly different trajectories of hearing loss, suggesting a mutation-specific risk that should be considered when making treatment decisions.

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DOI: 10.1002/art.37810

PMID: 23440695 [Indexed for MEDLINE]

2453. PLoS One. 2013;8(2):e55227. doi: 10.1371/journal.pone.0055227. Epub 2013 Feb 20.

The contribution of SAA1 polymorphisms to Familial Mediterranean fever susceptibility in the Japanese population.

Migita K(1), Agematsu K, Masumoto J, Ida H, Honda S, Jiuchi Y, Izumi Y, Maeda Y, Uehara R, Nakamura Y, Koga T, Kawakami A, Nakashima M, Fujieda Y, Nonaka F, Eguchi K, Furukawa H, Nakamura T, Nakamura M, Yasunami M.

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**BACKGROUND/AIMS:** Familial Mediterranean Fever (FMF) has traditionally been considered to be an autosomal-recessive disease, however, it has been observed that substantial numbers of patients with FMF possess only 1 demonstrable MEFV mutation. The clinical profile of familial Mediterranean fever (FMF) may be influenced by MEFV allelic heterogeneity and other genetic and/or environmental factors.

**METHODOLOGY/PRINCIPAL FINDINGS:** In view of the inflammatory nature of FMF, we investigated whether serum amyloid A (SAA) and interleukin-1 beta (IL-1 $\beta$ ) gene polymorphisms may affect the susceptibility of Japanese patients with FMF. The genotypes of the -13C/T SNP in the 5'-flanking region of the SAA1 gene and the two SNPs within exon 3 of SAA1 (2995C/T and 3010C/T polymorphisms) were determined in 83 Japanese patients with FMF and 200 healthy controls. The same samples were genotyped for IL-1 $\beta$ -511 (C/T) and IL-1 receptor antagonist (IL-1Ra) variable number of tandem repeat (VNTR) polymorphisms. There were no significant differences between FMF patients and healthy subjects in the genotypic distribution of IL-1 $\beta$ -511 (C/T), IL-1Ra VNTR and SAA2 polymorphisms. The frequencies of SAA1.1 allele were significantly lower (21.7% versus 34.0%), and inversely the frequencies of SAA1.3 allele were higher (48.8% versus 37.5%) in FMF patients compared with healthy subjects. The frequency of -13T alleles, associated with the SAA1.3 allele in the Japanese population, was significantly higher (56.0% versus 41.0%,  $p=0.001$ ) in FMF patients compared with healthy subjects.

**CONCLUSIONS/SIGNIFICANCE:** Our data indicate that SAA1 gene polymorphisms, consisting of -13T/C SNP in the 5'-flanking region and SNPs within exon 3 (2995C/T and 3010C/T polymorphisms) of SAA1 gene, are associated with susceptibility to FMF in the Japanese population.

DOI: 10.1371/journal.pone.0055227

PMCID: PMC3577815

PMID: 23437051 [Indexed for MEDLINE]

2454. Mod Rheumatol. 2013 Feb 24. [Epub ahead of print]

MEFV gene variations in patients with systemic lupus erythematosus.

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**OBJECTIVE:** The aim of this study was to investigate the frequency of familial Mediterranean fever (FMF)-associated MEFV gene variations in patients with systemic lupus erythematosus (SLE). **METHODS:** The study group comprised 190 SLE patients and 101 healthy controls of Turkish origin with no clinical features of FMF. All individuals were genotyped for the four most common MEFV gene variations (M694V, M680I, V726A and E148Q) by PCR-restriction fragment length polymorphism analysis. **RESULTS:** The frequency of carrying any of the four MEFV gene variations under study was 15 % in patients with SLE and 10 % in the healthy controls ( $p = 0.23$ ). After the exclusion of the less penetrant E148Q variation, re-analysis for the three penetrant mutations revealed a significant association between exon 10 variations and pericarditis [ $p = 0.038$ , odds ratio (OR) 3.5, 95 % confidence interval (CI) 1.0-12.1], and pleural effusion ( $p = 0.043$ , OR 5.2, 95 % CI 0.8-30.9). No significant association was detected between the MEFV gene variations and a higher acute phase response. **CONCLUSIONS:** The MEFV gene variations analyzed in our study do not seem to increase the overall susceptibility to SLE and do not have any strong association with its clinical manifestations. The possibility of a modest effect of penetrant exon 10 MEFV variants on the development of serosal effusions needs to be explored in a larger series of patients.

DOI: 10.1007/s10165-013-0848-5

PMID: 23436028

2455. J Neuroinflammation. 2013 Feb 21;10:29. doi: 10.1186/1742-2094-10-29.

An autoinflammatory neurological disease due to interleukin 6 hypersecretion.

Salsano E(1), Rizzo A, Bedini G, Bernard L, Dall'olio V, Volorio S, Lazzaroni M, Ceccherini I, Lazarevic D, Cittaro D, Stupka E, Paterra R, Farina L, Savoiaro M, Pareyson D, Sciacca FL.

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Autoinflammatory diseases are rare illnesses characterized by apparently unprovoked inflammation without high-titer auto-antibodies or antigen-specific T cells. They may cause neurological manifestations, such as meningitis and hearing loss, but they are also characterized by non-neurological manifestations. In this work we studied a 30-year-old man who had a chronic disease characterized by meningitis, progressive hearing loss, persistently raised inflammatory markers and diffuse leukoencephalopathy on brain MRI. He also suffered from chronic recurrent osteomyelitis of the mandible. The hypothesis of an autoinflammatory disease prompted us to test for the presence of mutations in interleukin-1-pathway genes and to investigate the function of this pathway in the mononuclear cells obtained from the patient. Search for mutations in genes associated with interleukin-1-pathway demonstrated a novel NLRP3 (CIAS1) mutation (p.I288M) and a previously described MEFV mutation (p.R761H), but their combination was found to be non-pathogenic. On the other hand, we uncovered a selective interleukin-6 hypersecretion within the central nervous system as the likely pathogenic mechanism. This is also supported by the response to the anti-interleukin-6-receptor monoclonal antibody tocilizumab, but not to the recombinant interleukin-1-receptor antagonist anakinra. Exome sequencing failed to identify mutations in other genes known to be involved in autoinflammatory diseases. We propose that the disease described in this patient might be a prototype of a novel category of autoinflammatory diseases characterized by prominent neurological involvement.

DOI: 10.1186/1742-2094-10-29

PMCID: PMC3601972

PMID: 23432807 [Indexed for MEDLINE]

2456. Antiinflamm Antiallergy Agents Med Chem. 2013;12(2):165-72.

Neutrophil F-actin dynamics in Familial Mediterranean Fever: the unequal effect of colchicine on activated neutrophils.

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In the innate immune system, cellular adaptation regulates neutrophil activation and chemotaxis, which have a pivotal role in Familial Mediterranean Fever (FMF) pathogenesis. We investigated neutrophil F-actin, phagocytosis and macropinocytosis dynamics during neutrophil chemoattractant-dependent activation in FMF patients carrying mutations in the MEFV locus. We found that while a non-stimulated neutrophil shows an increased overall F-actin content in patients with FMF, the activation-dependent F-actin dynamics in the presence of chemoattractant peptide is significantly reduced. Neither overall F-actin content nor F-actin dynamics was changed in FMF patient's neutrophils in the presence of double doses of chemoattractant, while in healthy donors it occurred with significant reduction of F-actin content and dynamics. The neutrophil shows increased phagocytosis and macropinocytosis dynamics for a relatively short period, which may contribute to the decreasing of plasticity of the cellular cytoskeleton during FMF. Colchicine causes reduction of overall F-actin content and shows a distinctively unequal effect on chemoattractant-activated neutrophil F-actin dynamics in FMF patients compared with healthy donors. These data suggested that mutations in MEFV cause the dissolution of cellular adaptation to chemoattractant stimuli due to alterations in neutrophil F-actin and phagocytosis dynamics, which could serve as a major target for FMF treatment.

PMID: 23432575 [Indexed for MEDLINE]

2457. *Pediatr Infect Dis J.* 2013 Jul;32(7):789-92. doi: 10.1097/INF.0b013e31828df4d1.

Successful immunotherapy in life-threatening parvovirus B19 infection in a child.

Butin M(1), Mekki Y, Phan A, Billaud G, Di Filippo S, Javouhey E, Cochat P, Belot A.

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We report a case of an immunocompetent child who developed parvovirus B19 infection complicated by autoinflammatory disease with myocarditis, tamponade and macrophage activation syndrome. He recovered with immunotherapy including prednisone, immunoglobulins, cyclosporin and anakinra (anti-interleukin-1). The report shows that parvovirus can provoke severe systemic inflammation with acute heart injury and that anti-interleukin-1 might be considered in such parvovirus-related inflammation.

DOI: 10.1097/INF.0b013e31828df4d1

PMID: 23429554 [Indexed for MEDLINE]

2458. Eur Rev Med Pharmacol Sci. 2013 Feb;17(3):375-8.

Paraoxonase 1 and arylesterase levels in children with familial Mediterranean fever.

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**BACKGROUND:** The pathogenesis of Familial Mediterranean Fever (FMF) is not clearly elucidated. It emerges as a result of triggering of the several environmental factors at the people who are genetically vulnerable.

**OBJECTIVES:** To evaluate the anti-oxidant enzymes at the remission period of familial mediterranean fever (FMF).

**MATERIALS AND METHODS:** Study group is consisted of 80 patients between the age of 2 and 16 years old who are routinely followed up. The control group is consisted of 80 healthy children whose physical examination is normal, and whose demographic findings are similar to the study group. Paraoxonase 1 (PON1) and arylesterase (ARE) levels are measured at both study and control group.

**RESULTS:** The difference between the levels of ARE and PON1 are statistically significant between the FMF and control group ( $p = 0.007$ ,  $p = 0.001$ ). According to the weight scoring, ARE and PON1 levels of light cases are higher versus the levels of moderate cases ( $p < 0.01$ ).

**CONCLUSIONS:** Endogenous anti-oxidants Paraoxonase 1 and arylesterase levels are important in evaluating the inflammation at the remission period of FMF.

PMID: 23426541 [Indexed for MEDLINE]

2459. JAMA Dermatol. 2013 Feb;149(2):209-15. doi: 10.1001/2013.jamadermatol.717.

Identification of a homozygous PSTPIP1 mutation in a patient with a PAPA-like syndrome responding to canakinumab treatment.

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**BACKGROUND:** Pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome (OMIM 604416) is a rare autosomal dominant inherited autoinflammatory syndrome characterized by pyogenic sterile arthritis and less frequently accompanied by pyoderma gangrenosum and acne. It is associated with dominant missense mutations in the proline-serine-threonine phosphatase-interacting protein 1 gene (PSTPIP1) located on chromosome 15. The patient was diagnosed as having features of a PAPA-like syndrome in which cutaneous manifestations, such as pyoderma gangrenosum and acne fulminans, predominated.

**OBSERVATIONS:** Sequencing of the PSTPIP1 gene was performed in the patient and his extended family. The patient's DNA analysis revealed a homozygous nucleotide exchange c.773G>C in the PSTPIP1 gene, leading to the substitution of glycine 258 by alanine (p.Gly258Ala), a previously reported heterozygous polymorphism. Heterozygous changes were identified in both of the patient's parents and in 7 other family members, all of whom were asymptomatic. The patient was treated with canakinumab, a human anti-interleukin 1 $\beta$  monoclonal antibody, which led to rapid remission of the symptoms.

**CONCLUSIONS:** To our knowledge, this is the first reported case of the resolution of dermatological symptoms associated with a PAPA-like syndrome using canakinumab treatment. Further study of the p.Gly258Ala variant is warranted to determine whether this mutation has a role in causing an apparently recessive cutaneous syndrome resembling PAPA syndrome.

2460. Arthritis Res Ther. 2013 Feb 19;15(1):R30. doi: 10.1186/ar4171.

Clinical characteristics in subjects with NLRP3 V198M diagnosed at a single UK center and a review of the literature.

Rowczenio DM, Trojer H, Russell T, Baginska A, Lane T, Stewart NM, Gillmore JD, Hawkins PN, Woo P, Mikoluc B, Lachmann HJ.

**INTRODUCTION:** Mutations in the NLRP3 gene are associated with the dominantly inherited cryopyrin-associated periodic syndrome (CAPS). The significance of the V198M variant is unclear; it has been reported in association with various CAPS phenotypes and as a variant of uncertain consequence. The aim of this study was to characterize the clinical phenotypes and treatments in individuals with V198M assessed in a single UK center.

**METHODS:** DNA samples from 830 subjects with fever syndromes or a family history of CAPS were screened for mutations in the NLRP3 gene with polymerase chain reaction (PCR) and sequencing. A detailed medical history was available in all cases. Inflammatory disease activity was monitored monthly with measurements of serum amyloid A protein (SAA) and C-reactive protein (CRP) in symptomatic individuals.

**RESULTS:** NLRP3 V198M was identified in 19 subjects. It was found in association with CAPS in five cases, in one patient with Schnitzler syndrome, in three patients who also had a nucleotide alteration in another fever gene, and in three other patients with evidence of an autoinflammatory phenotype. Seven asymptomatic individuals were detected during screening of family members.

**CONCLUSIONS:** The NLRP3 V198M variant shows variable expressivity and reduced penetrance. It may be associated with classical inherited or apparently sporadic CAPS and with atypical autoinflammatory disease of varying severity, intriguingly including Schnitzler syndrome. The factors that influence the pathogenic consequences of this variant remain unknown. However, the remarkable response to interleukin 1 (IL-1) blockade in all but one individual in our series confirms that their clinical features are indeed mediated by IL-1.

PMCID: PMC3672677

PMID: 23421920 [Indexed for MEDLINE]

2461. Arch Immunol Ther Exp (Warsz). 2013 Jun;61(3):175-86. doi: 10.1007/s00005-013-0216-3. Epub 2013 Feb 16.

Impact of microbes on autoimmune diseases.

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Autoimmune and autoinflammatory diseases arise as a consequence of complex interactions of environmental factors with genetic traits. Although specific allelic variations cluster in predisposed individuals and promote the generation and/or expansion of autoreactive T and B lymphocytes, autoimmunity appears in various disease phenotypes and localizes to diverging tissues. Furthermore, the discovery that allelic variations within genes encoding components of the innate immune system drive self-reactive immune responses as well, led to the distinction of immune responses against host tissues into autoimmune and autoinflammatory diseases. In both categories of disorders, different pathogenic mechanisms and/or subsequent orders of tissue assaults may underlie the target cell specificity of the respective autoimmune attack. Furthermore, the transition from the initial tissue assault to the development of full-blown disease is likely driven by several factors. Thus, the development of specific forms of autoimmunity and autoinflammation reflects a multi-factorial process. The delineation of the specific factors involved in the pathogenic process is hampered by the fact that certain symptoms are assembled under the umbrella of a specific disease, although they might originate from diverging pathogenic pathways. These multi-factorial triggers and pathogenic pathways may also explain the inter-individual divergent courses and outcomes of diseases among humans. Here, we will discuss the impact of different environmental factors in general and microbial pathogens in particular on the regulation/expression of genes encoded within susceptibility alleles, and its consequences on subsequent autoimmune and/or autoinflammatory tissue damage utilizing primarily the chronic

cholestatic liver disease primary biliary cirrhosis as model.

DOI: 10.1007/s00005-013-0216-3

PMCID: PMC4134873

PMID: 23417246 [Indexed for MEDLINE]

2462. Int J Hematol. 2013 Apr;97(4):498-504. doi: 10.1007/s12185-013-1281-4. Epub 2013 Feb 15.

New paraneoplastic syndrome in chronic basophilic leukemia.

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Chronic basophilic leukemia (CBL) is an extremely rare disorder. A female patient presented with recurrent attacks of chills, fever and abdominal pain was found to have simultaneous cyclic oscillation in leukocyte counts and C-reactive protein values. She was initially diagnosed with familial Mediterranean fever and treated with colchicine. Diagnosis of CBL was established by morphologic studies of peripheral blood and bone marrow. Her febrile attacks recurred with marked elevation in serum interleukin-6 (IL-6) level when basophil counts climbed to peak levels during cyclic oscillation. Molecular studies by real-time PCR showed IL-6 gene expression in neoplastic basophils separated by magnetic-activated cell sorting infiltrating the bone marrow, suggesting that IL-6 is released by neoplastic basophils of an underlying CBL, resulting in a new paraneoplastic syndrome that mimics autoinflammatory disorders.

DOI: 10.1007/s12185-013-1281-4

PMID: 23413035 [Indexed for MEDLINE]

2463. Clin Immunol. 2013 Jun;147(3):175-84. doi: 10.1016/j.clim.2013.01.006. Epub 2013 Feb 4.

Contribution of the inflammasomes to autoinflammatory diseases and recent mouse

models as research tools.

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Inflammasomes are multiprotein complexes that serve as activating platforms for the enzyme caspase-1 in response to various danger signals. Active caspase-1 can cleave the precursors of the pro-inflammatory cytokines IL-1 $\beta$  and IL-18 and thereby activate them. Deregulation of this cascade caused by mutations in genes coding for inflammasomal components and their interaction partners can lead to severe disease. This review summarizes the contribution of deregulated inflammasomes to the field of autoinflammatory syndromes. In addition, it gives insight into currently available mouse models that are used to study and characterize the role of the inflammasome components in the pathophysiology of these diseases.

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DOI: 10.1016/j.clim.2013.01.006

PMID: 23411032 [Indexed for MEDLINE]

2464. Genet Mol Res. 2013 Jan 24;12(3):3521-8. doi: 10.4238/2013.January.24.2.

Lack of an effect of CYP3A4 and MDR1 gene polymorphisms on colchicine pharmacogenetics in the treatment of Familial Mediterranean fever.

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The P-gp/MDR1 multidrug transporter mediates detoxification of numerous drugs, including colchicine, and CYP3A4 is key to the biotransformation of colchicine.

We investigated the effects of CYP3A4 and P-gp/MDR1 polymorphisms on bioavailability of colchicine in patients with Familial Mediterranean fever (FMF). Forty-eight Turkish patients with FMF treated with colchicine were genotyped for 3435C>T, (-)1A>G, 61A>G, 1199G>A, 1236C>T, 2677G>A, 2677G>T polymorphisms in the P-gp/MDR1 gene and 3435C>T, 1B(-392A>G), 2(15713T>C), 3(23171T>C), 12(21896C>T), 17(15615T>C) polymorphisms in the CYP3A4 gene. Doses of colchicine administered to patients did not differ with respect to P-gp/MDR1 or CYP3A4 gene polymorphism. We also determined the genotype distributions of CYP3A4 and P-gp/MDR1 genes among FMF patients. There was no significant gender difference in the P-gp/MDR1 polymorphism, whereas there were significant gender differences in the frequencies of 15713T>C and 15615T>C polymorphisms in the CYP3A4 gene. No significant relationship was found between colchicine doses that would introduce optimal clinical response and affect the therapeutic dose and CYP3A4 and P-gp/MDR1 gene polymorphisms in these FMF patients.

DOI: 10.4238/2013.January.24.2

PMID: 23408444 [Indexed for MEDLINE]

2465. Case Rep Pulmonol. 2013;2013:315751. doi: 10.1155/2013/315751. Epub 2013 Jan 17.

A very rare cause of pleuritic chest pain: bilateral pleuritis as a first sign of familial mediterranean Fever.

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The familial Mediterranean fever (FMF), also called recurrent polyserositis, is characterized by recurrent episodes of serositis at pleura, peritoneum, and synovial membrane and fever. We present a patient with recurrent bilateral pleural effusion due to serositis attacks as a first sign of FMF. A 59-year-old Turkish man suffered from recurrent pleuritic chest pain due to pleural effusion and atelectasis. The etiology was not found, and his symptoms were spontaneously recovered during several weeks. The pleuritic chest pain was associated with abdominal pain in the last attack. The gene mutation analysis revealed the homozygosity of FMF (F479L) gene mutation in both our patient and his grandchild. After the colchicine treatment, the attack has not developed. In conclusion,

recurrent pleural effusion and pleuritic chest pain may be the first signs of the FMF.

DOI: 10.1155/2013/315751

PMCID: PMC3562611

PMID: 23401829

2466. Arthritis Rheum. 2013 May;65(5):1137-47. doi: 10.1002/art.37882.

Beyond the NLRP3 inflammasome: autoinflammatory diseases reach adolescence.

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DOI: 10.1002/art.37882

PMID: 23400910 [Indexed for MEDLINE]

2467. J Korean Med Sci. 2013 Feb;28(2):328-30. doi: 10.3346/jkms.2013.28.2.328. Epub 2013 Jan 29.

Extensive thrombosis in a patient with familial Mediterranean fever, despite hyperimmunoglobulin D state in serum. [corrected].

Joo K(1), Park W, Chung MH, Lim MJ, Jung KH, Heo Y, Kwon SR.

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Erratum in

J Korean Med Sci. 2013 Mar;28(3):493.

Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent episodes of fever accompanied by peritonitis, pleuritis, arthritis, or erysipelas-like erythema. It is known to occur mainly among Mediterranean and Middle Eastern populations such as non-Ashkenazi Jews,



Arabs, Turks, and Armenians. FMF is not familiar to clinicians beyond this area and diagnosing FMF can be challenging. We report a 22-yr old boy who presented with fever, arthralgia and abdominal pain. He had a history of recurrent episodes of fever associated with arthralgia which would subside spontaneously or by antipyretics. Autosomal recessive periodic fever syndromes were suspected. Immunoglobulin D (IgD) level in the serum was elevated and DNA analysis showed complex mutations (p.Glu148Gln, p.Pro369Ser, p.Arg408Gln) in the MEFV gene. 3D angio computed tomography showed total thrombosis of splenic vein with partial thrombosis of proximal superior mesenteric vein, main portal vein and intrahepatic both portal vein. This is a case of FMF associated with multiple venous thrombosis and elevated IgD level. When thrombosis is associated with elevated IgD, FMF should be suspected. This is the first adult case reported in Korea.

DOI: 10.3346/jkms.2013.28.2.328

PMCID: PMC3565148

PMID: 23400211 [Indexed for MEDLINE]

2468. Clin Rheumatol. 2013 Jun;32(6):853-61. doi: 10.1007/s10067-013-2209-3. Epub 2013 Feb 10.

Inflammatory immune cell responses and Toll-like receptor expression in synovial tissues in rheumatoid arthritis patients treated with biologics or DMARDs.

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Comment in

Clin Rheumatol. 2014 Feb;33(2):291-2.

Biologic antirheumatic drugs (BIO) have been reported to be potent therapeutic agents in the prevention of inflammatory joint destruction in rheumatoid arthritis (RA). The aim of this study was to investigate the immune-inflammatory cells, including Toll-like receptor (TLR)-equipped cells, in synovial tissue

samples from RA patients on BIO compared to patients, who are only on conventional disease-modifying antirheumatic drug (DMARD). We analyzed immune-inflammatory cells in RA synovitis in patients of BIO group (n = 20) or DMARD group (n = 20). The grading scores of synovitis was 1.7 and 1.8 in each BIO and DMARD group and correlated best with the CD3(+) T ( $r = 0.71/0.70$ ,  $p < 0.05$ ) and CD20(+) B ( $r = 0.80/0.84$ ,  $p < 0.05$ ) cells in the both groups, but less well with the CD68(+) macrophages and S-100(+) dendritic cells (DCs). Interestingly, both T (116 vs. 242,  $p < 0.05$ ) and B (80 vs. 142,  $p < 0.05$ ) cell counts were lower in the BIO than in the DMARD group, whereas macrophage and DC counts did not differ. In contrast, the C-reactive protein (CRP) and disease activity score DAS28-CRP did not show clear-cut correlations with the inflammatory grade of the synovitis ( $r$  range, 0-0.35). Similar numbers of cells immunoreactive for TLR-1 to TLR-6 and TLR-9 were found in synovitis in both groups. Patients clinically responding to biologics might still have the potential of moderate/severe local joint inflammation, composed in particular of and possibly driven by the autoinflammatory TLR(+) cells.

DOI: 10.1007/s10067-013-2209-3

PMID: 23397147 [Indexed for MEDLINE]

2469. Semin Immunol. 2012 Dec;24(6):384-92. doi: 10.1016/j.smim.2013.01.002. Epub 2013 Feb 4.

New tricks from an old dog: mitochondrial redox signaling in cellular inflammation.

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Reactive oxygen species (ROS) such as superoxide ( $O(2)(-)$ ) and hydrogen peroxide ( $H(2)O(2)$ ) have long been implicated as pro-inflammatory, yet the sources of ROS and the molecular mechanisms by which they enhance inflammation have been less clear. Recent advances in the understanding of the molecular basis of inflammation mediated by the innate immune system have allowed these issues to be

revisited. Although the Nox2 NADPH oxidases generate the bulk of ROS for antimicrobial host defense, recent studies have found that NADPH oxidase-dependent ROS production can actually dampen macrophage inflammatory responses to sterile pro-inflammatory stimuli. Instead, production of mitochondrial ROS has emerged as an important factor in both host defense and sterile inflammation. Excess mitochondrial ROS can be generated by either damage to the respiratory chain or by alterations of mitochondrial function such as those that increase membrane potential and reduce respiratory electron carriers. In autoinflammatory diseases, where key components of innate immune responses are activated by genetic mutations or environmental stimuli, inflammation has been found to be particularly sensitive to inhibition of mitochondrial ROS production. These findings have highlighted mitochondrial ROS as a novel generator of pro-inflammatory ROS and a potential therapeutic target in inflammatory diseases.

Published by Elsevier Ltd.

DOI: 10.1016/j.smim.2013.01.002

PMCID: PMC3650900

PMID: 23391428 [Indexed for MEDLINE]

2470. Front Immunol. 2013 Feb 6;4:25. doi: 10.3389/fimmu.2013.00025. eCollection 2013.

Tailoring gut immune responses with lipoteichoic acid-deficient *Lactobacillus acidophilus*.

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As highlighted by the development of intestinal autoinflammatory disorders when tolerance is lost, homeostatic interactions between gut microbiota, resident immune cells, and the gut epithelium are key in the maintenance of gastrointestinal health. Gut immune responses, whether stimulatory or regulatory, are dictated by the activated dendritic cells (DCs) that first interact with

microorganisms and their gene products to then elicit T and B cell responses. Previously, we have demonstrated that treatment with genetically modified *Lactobacillus acidophilus* is sufficient to tilt the immune balance from proinflammatory to regulatory in experimental models of colitis and colon cancer. Given the significant role of DCs in efficiently orchestrating intestinal immune responses, characterization of the signals induced within these cells by the surface layer molecules, such as lipoteichoic acid (LTA), and proteins of *L. acidophilus* is critical for future treatment and prevention of gastrointestinal diseases. Here, we discuss the potential regulatory pathways involved in the downregulation of pathogenic inflammation in the gut, and explore questions regarding the immune responses to LTA-deficient *L. acidophilus* that require future studies.

DOI: 10.3389/fimmu.2013.00025

PMCID: PMC3565175

PMID: 23390423

2471. Eur Rev Med Pharmacol Sci. 2013 Jan;17(2):261-5.

Serum 17-OH progesterone and free testosterone levels in women patients with Familial Mediterranean Fever: a pivotal study.

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**BACKGROUND:** Familial Mediterranean Fever (FMF) is an autosomal recessive disease characterized by short lived, febrile serosae inflammatory attacks. FMF has various effects in multiple systems and organs.

**AIM:** In the present study, our aim was to evaluate adrenal steroidogenesis in female FMF patients.

**PATIENTS AND METHODS:** There were 71 women in the study including 41 women with FMF and 30 women as healthy control group (HC group). Of 41 FMF patients, twenty were evaluated in attack period (AP-FMF group) whereas 21 of them were evaluated in attack-free period (AFP-FMF group). In all subjects; serum free testosterone, 17-OHP levels as hormones, IL-1 beta, TNF-alpha, IL-6, IL-18 as proinflammatory

cytokines, CRP, fibrinogen, white blood cell (WBC) counts, and erythrocyte sedimentation rate (ESR) as acute phase reactants were measured in samples of venous blood taken in the morning before breakfast.

RESULTS: Serum 17-OHP levels in AP-FMF group and AFP-FMF group were higher than in HC group ( $p < 0.001$ ). A positive correlation was detected between serum levels of 17-OHP and IL-1 beta in FMF patients ( $p = 0.006$ ;  $r = 0.486$ ). There was no difference between FMF patients and HC group in terms of free testosterone levels ( $p > 0.05$ ).

CONCLUSIONS: Our results showed an increase in 17-OHP levels in FMF patients. These results may indicate that, regardless to the attack period adrenal steroidogenesis could be affected negatively in FMF patients.

PMID: 23377818 [Indexed for MEDLINE]

2472. Eur Rev Med Pharmacol Sci. 2013 Jan;17(2):253-60.

Cystatin C in serum as an early marker of renal involvement in Familial Mediterranean Fever patients.

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BACKGROUND: The major renal involvement in Familial Mediterranean Fever (FMF) is the occurrence of amyloidosis that primarily affects the kidneys manifested by proteinuria and ending in death from renal failure.

AIM: This study aims to investigate whether serum cystatin (cys-C) levels could be used as an early marker of renal involvement in FMF patients.

PATIENTS AND METHODS: Forty-six patients with FMF during the attack period (AP), and 41 patients with FMF during attack-free periods (AFP), and 11 patients with FMF associated amyloidosis, and 38 healthy controls were enrolled in the study. We determined cys-C levels in the serum of FMF patients and healthy controls.

RESULTS: Serum cys-C levels were significantly increased in patients with FMF and secondary amyloidosis, and serum cys-C is a more accurate and efficient marker for detecting renal involvement than estimated glomerular filtration rate (e-GFR)

in patients with FMF.

CONCLUSIONS: We propose a cutoff level of the serum cys-C of 876.5 pg/mL for screening renal involvement in patients with FMF, and amyloidosis should be strongly suspected when the serum cys-C reaches 1565.5 pg/mL.

PMID: 23377817 [Indexed for MEDLINE]

2473. J Autoimmun. 2013 Mar;41:100-10. doi: 10.1016/j.jaut.2012.12.010. Epub 2013 Feb 1.

The pathogenesis of neonatal autoimmune and autoinflammatory diseases: a comprehensive review.

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Autoimmune and autoinflammatory diseases are two distinct disease entities that can present in the neonate. Autoimmune diseases of the newborn primarily include neonatal lupus and neonatal anti-phospholipid syndrome, but other diseases have been reported as well. The pathogenic mechanisms behind autoimmune diseases of the newborns are unknown, but an association with antibodies to Ro and La is present in most cases. The extent to which these antibodies play a pathogenic role is unknown. Because the phenotype of clinical neonatal lupus is variable in many mothers who possess the antibodies, other mechanisms may be necessary to confer disease. The primary theories include apoptosis of cardiac cells, maternal microchimerism, cross-reactivity of the autoantibodies with cardiac tissue, T cell dysregulation and inhibitory receptors, and a genetic predisposition. The autoinflammatory diseases are unrelated to neonatal autoimmune diseases and include the cryopyrin-associated periodic syndromes (CAPS). These diseases include familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome and neonatal onset multisystem inflammatory disease (NOMID). All of these diseases share a defect in a common gene--the CIAS1 or NALP3 gene on chromosome 1. The diseases vary in severity and involvement of different physiologic systems, with

FCAS being the mildest form and NOMID being the most severe form with involvement of the neurologic and hematologic systems. Aberrant functioning of the inflammasome may play a role in the pathogenesis of autoinflammatory diseases.

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DOI: 10.1016/j.jaut.2012.12.010

PMID: 23375846 [Indexed for MEDLINE]

2474. Mol Genet Metab. 2013 Mar;108(3):166-71. doi: 10.1016/j.ymgme.2013.01.004. Epub 2013 Jan 15.

Long chain fatty acid (Lcfa) abnormalities in hyper IgD syndrome (Hids) and Familial Mediterranean Fever (Fmf): new insight into heritable periodic fevers.

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**OBJECTIVE:** To examine essential fatty acids (EFAs) in hyper-IgD syndrome (HIDS) and Familial Mediterranean Fever (FMF).

**METHODS:** EFAs were determined in sera derived from an archival, cross-sectional group of HIDS/FMF patients, stratified for presence and absence of fever. Control populations included healthy afebrile adults, and individuals with non-periodic fever (septic shock). EFAs were quantified using isotope dilution gas chromatography-mass spectrometry and data analyzed employing a Kruskal-Wallis non-parametric ANOVA with Dunn's post-hoc test.

**RESULTS:** Sera samples derived from HIDS patients showed significantly decreased C20, C26, phytanic and pristanic acids during febrile crises that normalized in the afebrile state, and a significantly increased afebrile C22\_4ω6 level that normalized with fever. Samples derived from FMF patients revealed increased ω-oxidized LCFAs as compared to controls, and the trend was for these same species to be increased in comparison to febrile, but not afebrile, HIDS patients. Individuals with non-periodic fever demonstrated global decreases in C10-C24 fatty acids, both saturated and unsaturated, accompanied by an elevated triene/tetraene ratio.

**CONCLUSIONS:** Our results suggest that different mechanisms are active in hereditary periodic fever syndromes that appear unrelated to fever, including depletion of very long chain fatty acids (VLCFAs) in febrile HIDS patients and increased  $\omega$ -oxidized LCFAs in patients with FMF. These findings underscore new roles for EFAs in the potential production of inflammatory species in patients with hereditary periodic fever.

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DOI: 10.1016/j.ymgme.2013.01.004

PMCID: PMC3654528

PMID: 23375471 [Indexed for MEDLINE]

2475. Front Cell Infect Microbiol. 2013 Jan 28;3:2. doi: 10.3389/fcimb.2013.00002. eCollection 2013.

Management of familial Mediterranean fever by colchicine does not normalize the altered profile of microbial long chain fatty acids in the human metabolome.

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In our previous works we established that in an autoinflammatory condition, familial Mediterranean fever (FMF), the gut microbial diversity is specifically restructured, which also results in the altered profiles of microbial long chain fatty acids (LCFAs) present in the systemic metabolome. The mainstream management of the disease is based on oral administration of colchicine to suppress clinical signs and extend remission periods and our aim was to determine whether this therapy normalizes the microbial LCFA profiles in the metabolome as well.

Unexpectedly, the treatment does not normalize these profiles. Moreover, it results in the formation of new distinct microbial LCFA clusters, which are well separated from the corresponding values in healthy controls and FMF patients without the therapy. We hypothesize that the therapy alters the proinflammatory



network specific for the disease, with the concomitant changes in gut microbiota and the corresponding microbial LCFAs in the metabolome.

DOI: 10.3389/fcimb.2013.00002

PMCID: PMC3556566

PMID: 23373011 [Indexed for MEDLINE]

2476. Intern Med. 2013;52(3):385-8. Epub 2013 Feb 1.

Familial Mediterranean fever occurring in an elderly Japanese woman with recent-onset rheumatoid arthritis.

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A 60-year-old woman with a two-year history of rheumatoid arthritis (RA) developed recurrent two- to three-day attacks of fever ( $>38^{\circ}\text{C}$ ) accompanied by monoarthritis of the right hip joint. The first attack occurred two months after beginning anti-tumor necrosis factor- $\alpha$  therapy. Since a diagnosis of infectious arthritis was suspected, the therapy was discontinued. Thereafter, the patient repeated similar episodes; however, oral colchicine effectively controlled the attacks. The patient was diagnosed to have familial Mediterranean fever (FMF). The clinical manifestations of FMF mimic infectious complications during anti-RA therapy. Clinicians should therefore consider the possibility of FMF development in RA patients exhibiting recurrent febrile attacks.

PMID: 23370751 [Indexed for MEDLINE]

2477. Clin Immunol. 2013 Jun;147(3):185-96. doi: 10.1016/j.clim.2012.12.012. Epub 2013 Jan 5.

Autoinflammatory bone disorders.

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Autoinflammatory bone disorders are characterized by chronic non-infectious osteomyelitis and inflammation-induced bone resorption and result from aberrant activation of the innate immune system. Sporadic chronic non-bacterial osteomyelitis (CNO) is the most common disease subtype. The clinical picture is highly variable and the exact underlying pathophysiology remains to be determined. Recently, novel insights in the pathophysiology of sterile bone inflammation have been gathered by analyzing patients with rare, monogenic inflammatory diseases. In this overview CNO and Majeed syndrome, cherubism, hypophosphatasia and primary hypertrophic osteoarthropathy will be discussed. For the latter four disorders, a genetic cause affecting bone metabolism and leading to chronic bone inflammation has been described. The exact pathophysiology of CNO remains to be determined. Insights from monogenic autoinflammatory bone diseases and the identification of distinct inflammatory pathways may help to understand the pathogenesis of bone inflammation and inflammation-induced bone resorption in more common diseases.

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DOI: 10.1016/j.clim.2012.12.012

PMID: 23369460 [Indexed for MEDLINE]

2478. BMJ Case Rep. 2013 Jan 29;2013. pii: bcr2012007991. doi: 10.1136/bcr-2012-007991.

Hypoadrenal syndrome in a patient with amyloidosis secondary to familial Mediterranean fever.

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Amyloidosis is a common complication of poorly controlled familial Mediterranean

fever (FMF). A variety of organs including kidneys, heart, liver, thyroid and adrenal glands may be clinically affected. However, involvement of adrenal glands leading to significant inefficiency is rarely seen in FMF patients with amyloidosis. The impairment of neuroendocrine immune system in FMF together with proteinuria in renal amyloidosis is a challenge while interpreting adrenal function tests. Here we present a case report of a 42-year-old man with FMF and renal failure due to amyloidosis whose disease course was complicated by adrenal insufficiency.

DOI: 10.1136/bcr-2012-007991

PMCID: PMC3604423

PMID: 23365166 [Indexed for MEDLINE]

2479. Brain. 2013 Jan;136(Pt 1):245-58. doi: 10.1093/brain/aws321.

Chronic exposure of astrocytes to interferon- $\alpha$  reveals molecular changes related to Aicardi-Goutieres syndrome.

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Aicardi-Goutières syndrome is a genetically determined infantile encephalopathy, manifesting as progressive microcephaly, psychomotor retardation, and in ~25% of patients, death in early childhood. Aicardi-Goutières syndrome is caused by mutations in any of the genes encoding TREX1, RNASEH2-A, -B, -C and SAMHD1, with protein dysfunction hypothesized to result in the accumulation of nucleic acids within the cell, thus triggering an autoinflammatory response with increased interferon- $\alpha$  production. Astrocytes have been identified as a major source of interferon- $\alpha$  production in the brains of patients with Aicardi-Goutières syndrome. Here, we study the effect of interferon- $\alpha$  treatment on astrocytes derived from immortalized human neural stem cells. Chronic interferon- $\alpha$  treatment promoted astrocyte activation and a reduction in cell proliferation. Moreover, chronic exposure resulted in an alteration of genes and proteins involved in the

stability of white matter (ATF4, eIF2B $\alpha$ , cathepsin D, cystatin F), an increase of antigen-presenting genes (human leukocyte antigen class I) and downregulation of pro-angiogenic factors and other cytokines (vascular endothelial growth factor and IL-1). Interestingly, withdrawal of interferon- $\alpha$  for 7 days barely reversed these cellular alterations, demonstrating that the interferon- $\alpha$  mediated effects persist over time. We confirmed our in vitro findings using brain samples from patients with Aicardi-Goutières syndrome. Our results support the idea of interferon- $\alpha$  as a key factor in the pathogenesis of Aicardi-Goutières syndrome relating to the observed leukodystrophy and microangiopathy. Because of the sustained interferon- $\alpha$  effect, even after withdrawal, therapeutic targets for Aicardi-Goutières syndrome, and other interferon- $\alpha$ -mediated encephalopathies, may include downstream interferon- $\alpha$  signalling cascade effectors rather than interferon- $\alpha$  alone.

DOI: 10.1093/brain/aws321

PMID: 23365100 [Indexed for MEDLINE]

2480. J Investig Med. 2013 Mar;61(3):593-6. doi: 10.2310/JIM.0b013e318280a96e.

Association of MEFV gene mutations with rheumatoid factor levels in patients with rheumatoid arthritis.

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**PURPOSE:** Rheumatoid arthritis (RA) is a systemic autoimmune disease primarily affecting the joints. Arthritis disorders are associated with mutations of the Mediterranean fever (MEFV) gene. This gene has already been identified as being responsible for familial Mediterranean fever. The aim of this study was to explore the frequency and clinical significance of MEFV gene mutations in a cohort of Turkish patients with RA.

**METHODS:** The study included 101 patients with RA and 110 healthy controls. Genomic DNA was isolated and genotyped using polymerase chain reaction and restriction fragment length polymorphism for the 5 MEFV gene mutations (M694V, M680I, V726A, E148Q, and P369S).

RESULTS: Carrier rates of MEFV gene mutations were 31 (30.7%) of 101 and 26 (23.6%) of 110 in the RA and healthy control groups, respectively ( $P > 0.05$ ; odds ratio, 1.4; 95% CI, 0.77-2.65). Whereas deformed joint count was relatively higher in the mutation carrier group than those of the noncarrier group, the rheumatoid factor levels were significantly higher in the carrier group of patients with RA ( $P = 0.001$ ).

CONCLUSIONS: The results of this study suggest that MEFV gene mutations are not positively associated with a predisposition to develop RA but might increase the severity of RA. Further research is needed to determine the actual pathogenic role of MEFV mutations in this disease.

DOI: 10.2310/JIM.0b013e318280a96e

PMID: 23360841 [Indexed for MEDLINE]

2481. Int Rev Immunol. 2013 Feb;32(1):68-75. doi: 10.3109/08830185.2012.750132.

Innate immune signals in autoimmune and autoinflammatory uveitis.

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Although traditionally the adaptive immune system has been viewed as the essential contributor to autoimmune diseases, the evidence implicating the innate immune system has grown considerably in recent years. Several multisystem inflammatory diseases affect the uvea and occur as a result of a mutation in a gene coding for a component of the innate immune system. Diseases associated with uveitis such as ankylosing spondylitis, sarcoidosis, Behcet's disease and inflammatory bowel disease can best be conceptually understood by hypotheses that consider microbial infection and innate immunity as contributing factors.

DOI: 10.3109/08830185.2012.750132

PMID: 23360159 [Indexed for MEDLINE]

2482. Rheumatol Int. 2013 Aug;33(8):1967-72. doi: 10.1007/s00296-013-2681-8. Epub 2013

Jan 29.

Evaluation of circulating endothelial biomarkers in familial Mediterranean fever.

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The aim of this was to evaluate some of the vascular biomarkers and cytokines related with atherosclerosis in regularly treated and attack-free familial Mediterranean fever (FMF) patients. Forty (21 males [M] and 19 females [F], 31 [15-58] years) FMF patients and eighteen healthy controls (11 M and 7 F, 35.5 [19-46] years) with no known cardiovascular (CV) risk factors were included. All patients were receiving regular colchicine treatment, and examinations were performed during attack-free periods. Serum samples were used for the determination of high-sensitive C-reactive protein (hs-CRP), tissue factor (TF), tissue plasminogen activator (t-PA), osteoprotegerin (OPG), interleukin-6 (IL-6), IL-17, and IL-23. Plasma samples were used for the determination of asymmetric dimethylarginine (ADMA) and thrombomodulin (TM). Age, sex distribution, waist circumference, body mass index, smoking status, and serum lipids were similar between the patients and controls ( $P > 0.05$ ). The concentrations of (hs-CRP) and IL-17 were significantly higher in FMF patients compared with controls ( $P < 0.05$ ). On the other hand, IL-6 and IL-23 levels were not different between the groups ( $P > 0.05$ ). ADMA, OPG, and TM concentrations were significantly lower in the patients' group compared to those of controls ( $P < 0.05$ ). However, vWF, TF, and t-PA levels were similar between the groups ( $P > 0.05$ ). FMF patients receiving regular colchicine therapy during inactive disease state had significantly lower levels of vascular injury parameters.

DOI: 10.1007/s00296-013-2681-8

PMID: 23358733 [Indexed for MEDLINE]

2483. Arthritis Res Ther. 2013 Jan 28;15(1):R21. doi: 10.1186/ar4154.

High prevalence of spondyloarthritis and ankylosing spondylitis among familial Mediterranean fever patients and their first-degree relatives: further evidence

for the connection.

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**INTRODUCTION:** Familial Mediterranean fever (FMF) is an auto-inflammatory disease characterized by recurrent attacks of fever and serositis. Limited data suggest that the prevalence of sacroiliitis is increased in patients with FMF. In our present study, we assessed the prevalence of spondyloarthritis (SpA), including ankylosing spondylitis (AS), among a cohort of FMF patients and their unaffected first-degree relatives (FDRs).

**METHODS:** The current study cohort comprised a consecutive group of 201 unrelated patients with FMF and 319 FDRs ( $\geq 16$  years old). These subjects were examined according to a standard protocol.

**RESULTS:** A total of 157 FMF patients (78.1%) and 233 (73%) unaffected FDRs reported back pain. Fifteen FMF patients (7.5%) and nine unaffected FDRs fulfilled the modified New York (mNY) criteria for AS. One additional FDR with AS was identified after review of the medical records. None of the FMF patients with AS was HLA-B27 positive. The allele frequency of M694V among the FMF patients with radiographic sacroiliitis was significantly higher in comparison with those without sacroiliitis (OR 4.3). When compared with the general population, the risk ratios for SpA and AS among the FDRs of our FMF patients were 3.3 (95% CI; 2.0 to 5.5) and for AS 2.9 (95% CI; 1.3 to 6.4), respectively.

**CONCLUSIONS:** Our study suggests that a) factors other than HLA-B27 play a role in the association of FMF and SpA/AS; b) MEFV gene variations may be one of the geographic/region-specific potential pathogenetic links between these two disorders in the Turkish population.

DOI: 10.1186/ar4154

PMCID: PMC3672706

PMID: 23356447 [Indexed for MEDLINE]

2484. Semin Arthritis Rheum. 2013 Aug;43(1):125-30. doi: 10.1016/j.semarthrit.2012.12.005. Epub 2013 Jan 24.

Nucleotide-binding oligomerization domain containing 2: structure, function, and diseases.

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**OBJECTIVES:** To systematically review literature about the structure and function of nucleotide-binding oligomerization domain containing 2 (NOD2) and its disease association.

**METHODS:** The English literature was searched using keywords "NOD2" and "disease". Relevant original and review articles were reviewed.

**RESULTS:** NOD2 is an intracellular protein and shares similar molecular structure with NOD1, pyrin, and cryopyrin. There are more than 100 NOD2 gene mutations, some of which have been linked to diseases such as Crohn disease, Blau syndrome, and NOD2-associated autoinflammatory disease (NAID). The NOD2 variants located in the leucine-rich repeat (LRR) region are susceptible to Crohn disease, and the variants in the nucleotide-binding domain (NBD) and in between the NBD and LRR are associated with Blau syndrome and NAID, respectively. No disease association with the gene variants has been found in rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, psoriasis/psoriatic arthritis, adult sarcoidosis, granulomatous polyangiitis, or multiple sclerosis. The potential association of the NOD2 variants with graft-versus-host-disease remains controversial. NOD2 functions mainly through RICK or RIP2 to activate p38 mitogen-activated protein kinases and NF- $\kappa$ B, resulting in inflammatory response, and enhanced autophagic activity. Biologic therapy may be beneficial for NOD2-associated diseases, and new drug development may be realized based upon the signaling pathways.

**CONCLUSIONS:** NOD2 gene mutations are associated with several diseases, and some of the mutations are of diagnostic value in Blau disease and NAID. To understand the NOD2 function, disease association, and its pathogenesis is important given the ever increasing clinical significance of NOD2.

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DOI: 10.1016/j.semarthrit.2012.12.005

PMID: 23352252 [Indexed for MEDLINE]



Increased enthesopathy in patients with familial Mediterranean fever: evaluation with a new sonographic enthesitis index.

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**OBJECTIVES:** The aim of this study was to determine the frequency of enthesopathy in familial Mediterranean fever by using a newly developed sonographic method, the Madrid Sonographic Enthesitis Index (MASEI).

**METHODS:** The study included 50 consecutive patients with familial Mediterranean fever and 57 healthy sex- and age-matched control participants. Six enthesal sites (olecranon tuberosity, superior and inferior poles of the patella, tibial tuberosity, and superior and inferior poles of the calcaneus) on both lower limbs were evaluated. All sonographic findings were identified according to MASEI. Validity was analyzed by receiver operating characteristic curves.  $P < .05$  was considered significant.

**RESULTS:** Mean total enthesitis scores  $\pm$  SD were  $7.54 \pm 4.99$  for patients and  $3.63 \pm 3.03$  for controls ( $P < .001$ ). No statistically significant correlation was found between the MASEI score and familial Mediterranean fever duration or colchicine treatment duration. There was no difference between the MASEI score and the presence or absence of arthritic involvement among the patients. The area under the receiver operating characteristic curve was 0.74 (95% confidence interval, 0.649-0.839). When analyzed by sex, men with familial Mediterranean fever had significantly higher MASEI scores than women ( $P < .05$ ).

**CONCLUSIONS:** This study showed significant enthesopathy in patients with familial Mediterranean fever. The findings support the hypothesis that familial Mediterranean fever and spondyloarthropathy may have common inflammatory mechanisms and suggest that the MASEI scoring system can be incorporated into clinical protocols for studying patients with familial Mediterranean fever in daily practice.

PMID: 23341390 [Indexed for MEDLINE]

Autoinflammatory skin disorders in inflammatory bowel diseases, pyoderma gangrenosum and Sweet's syndrome: a comprehensive review and disease classification criteria.

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Comment in

Am J Gastroenterol. 2015 Dec;110(12):1739-40.

Pyoderma gangrenosum (PG) and Sweet's syndrome (SS) are skin diseases usually presenting with recurrent ulcers and erythematous plaques, respectively. The accumulation of neutrophils in the skin, characteristic of these conditions, led to coin the term of neutrophilic dermatoses to define them. Recently, neutrophilic dermatoses have been included in the group of autoinflammatory diseases, which classically comprises genetically determined forms due to mutations of genes regulating the innate immune response. Both PG and SS are frequently associated with inflammatory bowel diseases (IBDs); however, IBD patients develop PG in 1-3 % of cases, whereas SS is rarer. Clinically, PG presents with deep erythematous-to-violaceous painful ulcers with well-defined borders; bullous, pustular, and vegetative variants can also occur. SS is characterized by the abrupt onset of fever, peripheral neutrophilia, tender erythematous skin lesions, and a diffuse neutrophilic dermal infiltrate. It is also known as acute febrile neutrophilic dermatosis. Treatment of PG involves a combination of wound care, topical medications, antibiotics for secondary infections, and treatment of the underlying IBD. Topical therapies include corticosteroids and the calcineurin inhibitor tacrolimus. The most frequently used systemic medications are corticosteroids and cyclosporine, in monotherapy or in combination. Dapsone, azathioprine, cyclophosphamide, methotrexate, intravenous immunoglobulins, mycophenolate mofetil, and plasmapheresis are considered second-line agents. Hyperbaric oxygen, as supportive therapy, can be added. Anti-TNF- $\alpha$  agents such as etanercept, infliximab, and adalimumab are used in refractory cases. SS is usually responsive to oral corticosteroids, and the above-mentioned immunosuppressants should be considered in resistant or highly

relapsing cases.

DOI: 10.1007/s12016-012-8351-x

PMID: 23334898 [Indexed for MEDLINE]

2487. Rheumatol Int. 2013 Aug;33(8):1933-7. doi: 10.1007/s00296-013-2669-4. Epub 2013 Jan 20.

Enthesopathy in patients with familial Mediterranean fever: increased prevalence in M694 V variant.

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Enthesopathy is pathology of bony insertions of tendons, ligaments or joint capsules. It is a frequent finding in rheumatic diseases, like ankylosing spondylitis (AS) and Behçet's disease. Musculoskeletal complaints are common in patients with familial Mediterranean fever (FMF), and these could be a clinical manifestation of enthesopathy. Hence, we investigated the possible association between FMF and enthesopathy. Fifty-six patients with FMF and 11 patients with FMF-associated spondyloarthropathy (FMFS) were enrolled. Forty-seven healthy individuals and 36 patients with AS formed the healthy and diseased control groups. Musculoskeletal complaints were meticulously questioned, and all patients underwent a detailed physical and ultrasonographic (US) examination of the lower limbs. US scorings of enthesopathy was performed according to the Glasgow Ultrasound Enthesitis Scoring System (GUESS). Demographic data, disease characteristics, MEFV genotypes and HLA B27 results were retrieved from the medical records. Patient-reported pain and physical examination findings consistent with enthesopathy were frequent in all groups with the highest prevalence in the FMFS group. Heel was the most common region affected in all patient groups. FMF patients harboring M694 V variant had higher GUESS scores compared to patients with other variants ( $2.78 \pm 2.43$  vs.  $1.37 \pm 1.67$ ,  $p = 0.026$ ). There was no statistically significant difference in the mean  $\pm$  SD GUESS scores between healthy subjects and those FMF patients with genetic variants

other than M694 V ( $1.38 \pm 1.42$  vs.  $1.37 \pm 1.67$ ,  $p > 0.05$ ). Enthesopathy may not be a feature of general FMF population; rather, it might be specifically associated with the presence of M694 V variant. Our results further support the previous evidence regarding M694 V mutation and spondyloarthropathy association.

DOI: 10.1007/s00296-013-2669-4

PMID: 23334425 [Indexed for MEDLINE]

2488. Peptides. 2013 Apr;42:97-100. doi: 10.1016/j.peptides.2012.12.013. Epub 2013 Jan 16.

Thr21Met (T21M) but not Ser89Asn (S89N) polymorphisms of the urotensin-II (UTS-II) gene are associated with Behcet's disease (BD).

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Behcet's disease (BD) is multisystemic vasculitis or chronic inflammation that may lead to various autoimmune and autoinflammatory syndromes. Exact etiopathogenesis of BD has not been clarified yet. Urotensin II (UTS-II) is predominantly a vasoactive peptide and Thr21Met polymorphism in UTS-II gene was proved to be increasing in some autoimmune diseases. Considering these, our objective was to evaluate whether two UTS-II gene polymorphisms (Thr21Met and Ser89Asn) were responsible in genetic susceptibility to BD in a Turkish population. A total of 198 patients with BD and 275 healthy controls were enrolled. We analyzed the genotype and allele frequencies of two UTS-II gene polymorphisms, Thr21Met and Ser89Asn, in BD patients and in controls. We found that Thr21Met but not Ser89Asn polymorphisms of the UTS-II gene were markedly associated with the risk of developing BD ( $p < 0.0001$ ). The Met21Met genotype was less common among BD patients (6.1% in patients vs. 17.1% in controls;  $p < 0.0001$ ). There was also an increase in the 21Thr allele (54.8% in BD patients vs. 43.8% in controls) and a decrease in 21Met allele frequencies (45.2% in controls vs. 56.2% in patients) in the BD groups ( $p < 0.0044$ ). To the best of our knowledge, for the first time in the literature, our study claims that there is an association between Thr21Met, and

not between Ser89Asn polymorphisms in the UTS-II gene and BD. These results put a new player to the field of undiscovered pathogenesis of BD and hopefully provide new insights to the treatment options.

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DOI: 10.1016/j.peptides.2012.12.013

PMID: 23333481 [Indexed for MEDLINE]

2489. Allergy. 2013 Mar;68(3):285-96. doi: 10.1111/all.12084. Epub 2013 Jan 18.

Unexplained recurrent fever: when is autoinflammation the explanation?

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Recurrent fever can be the sole or leading manifestation of a variety of diseases including malignancies, autoimmune diseases and infections. Because the differential diagnoses are manifold, no formal guidelines for the approach of patients with recurrent fever exists. The newly recognized group of autoinflammatory diseases are often accompanied by repetitive fever attacks. As these episodes are frequently associated by a variety of divergent presentations, the differentiation of other causes for febrile illnesses can be difficult. In this article, we first review disease entities, which frequently present with the symptom of recurrent fever. In a next step, we summarize their characteristic pattern of disease presentation. Finally, we analyse key features of autoinflammatory diseases, which are helpful to distinguish this group of diseases from the other causes of recurrent fever. Recognizing these symptom patterns can provide the crucial clues and, thus, lead to the initiation of targeted specific diagnostic tests and therapies.

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DOI: 10.1111/all.12084

2490. Mult Scler. 2013 Aug;19(9):1132-6. doi: 10.1177/1352458512472749. Epub 2013 Jan 16.

Rare MEFV variants are not associated with risk to develop multiple sclerosis and severity of disease.

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**BACKGROUND:** Recent studies suggest an association between rare variants in Mediterranean fever (MEFV), the gene underlying the auto-inflammatory disorder Familial Mediterranean Fever (FMF), the risk to develop multiple sclerosis (MS) and severity of MS.

**OBJECTIVE:** The objective of this study is to investigate these findings in a Belgian MS population and to test for association with additional clinical parameters such as treatment response.

**METHODS:** MEFV was sequenced in a cohort of MS patients (N=94) suffering from auto-inflammatory symptoms, systemic side-effects upon interferon-beta (IFN- $\beta$ ) treatment, or patients in whom glatiramer acetate was started as first choice due to severe fatigue. Five rare non-synonymous variants were detected in this cohort and subsequently genotyped in 915 MS patients and 763 healthy controls.

**RESULTS:** We observed no association between these alleles and susceptibility to MS (p-value=0.99) or disease severity (p-value=0.78). However, we did observe a correlation between carrying an MEFV variant and the development of systemic side-effects upon IFN- $\beta$  treatment (p-value=0.022).

**CONCLUSION:** In contrast to recent smaller studies, we did not find an association between carrying a rare variant in the MEFV gene and the risk to develop MS or disease severity. However, carrying rare variants in MEFV was associated with the development of severe systemic side-effects upon IFN- $\beta$  treatment.

DOI: 10.1177/1352458512472749

PMID: 23325590 [Indexed for MEDLINE]

2491. Rheumatol Int. 2013 Jun;33(6):1387-95. doi: 10.1007/s00296-012-2661-4. Epub 2013 Jan 17.

The genetics of Henoch-Schönlein purpura: a systematic review and meta-analysis.

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Henoch-Schönlein purpura (HSP) is the most common form of systemic vasculitis of unknown etiology. This study aimed at reviewing published studies investigating the association of genetic polymorphisms with HSP and its severity. We systematically reviewed all published data on genetic risk factors for HSP by searching MEDLINE. We also performed a meta-analysis of association studies of HLA-DRB1-01, 07, and 11, angiotensin I-converting enzyme (ACE) insertion/deletion (I/D) polymorphism. We identified 45 studies investigating polymorphisms in 39 genes in association with HSP and/or its severity. Most of these genes are involved in immunological and/or inflammatory responses or vasomotor regulation. Most results were negative. The most convincing finding is the association of HLA-DRB1 01, 07, and 11 with HSP susceptibility. The overall odds ratios (ORs) for the three loci were significant for HSP: HLA-DRB1 01 (OR = 1.805, 95 % CI 1.259-2.588,  $p = 0.0012$ ); HLA-DRB1 07 (OR = 0.671, 95 % CI 0.469-0.961,  $p = 0.058$ ); HLA-DRB1 11 (OR = 2.001, 95 % CI 1.50-2.67,  $p = 0.027$ ). Genetic regulation of endothelial function, such as polymorphisms in genes coding rennin-angiotensin system (RAS) components, endothelial nitric oxide synthases, Inter-Cellular Adhesion Molecule 1, and vascular endothelial growth factor, could also confer effect on HSP. In addition, MEFV, whose mutations cause familial Mediterranean fever, could be an important candidate gene for HSP. Further large studies are required to investigate the association between genetic polymorphisms and HSP. Alternative approaches, such as genome-wide association study, are necessary to help to identify genetic risks for HSP.

DOI: 10.1007/s00296-012-2661-4

PMID: 23325094 [Indexed for MEDLINE]

2492. J Rheumatol. 2013 Mar;40(3):261-4. doi: 10.3899/jrheum.120729. Epub 2013 Jan 15.

Symptoms related to tumor necrosis factor receptor 1-associated periodic syndrome, multiple sclerosis, and severe rheumatoid arthritis in patients carrying the TNF receptor superfamily 1A D12E/p.Asp41Glu mutation.

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**OBJECTIVE:** Tumor necrosis factor (TNF) receptor 1-associated periodic syndrome (TRAPS) is an autoinflammatory disorder caused by autosomal dominantly inherited mutations in the TNF receptor superfamily 1A (TNFRSF1A) gene. The D12E substitution has been described only once to date, in a 4-year-old boy with fever.

**METHODS:** For DNA sequence analysis of the TNFRSF1A gene, genomic DNA was isolated, amplified by PCR, purified, and sequenced.

**RESULTS:** We describe 3 families (8 subjects) with the TNFRSF1A D12E substitution and TRAPS-related symptoms, in 4 cases associated with the autoimmune diseases multiple sclerosis and rheumatoid arthritis.

**CONCLUSION:** The clinical phenotype might be associated with the TNFRSF1A D12E mutation. There is a close pathophysiological relationship between TNF signaling and autoimmune disorders.

DOI: 10.3899/jrheum.120729

PMID: 23322460 [Indexed for MEDLINE]

2493. Clin Rev Allergy Immunol. 2013 Aug;45(1):117-30. doi: 10.1007/s12016-013-8358-y.

IL-1 $\beta$  biological treatment of familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is a recessive, autosomal, auto-inflammatory disorder characterised by brief, recurring, self-limited episodes of fever and serositis resulting in abdominal, chest, joint and muscular pain; it is the most common of the periodic hereditary fevers and mostly affects Mediterranean populations. Daily administration of colchicine, a tricyclic alkaloid with anti-microtubule and anti-inflammatory properties, prevents the recurrence of FMF attacks and the development of secondary (AA) amyloidosis, the major long-term complication of FMF. Colchicine is generally safe and well-tolerated; nevertheless, 5-10 % of FMF patients do not respond to conventional treatment, while another 2-5 % of patients are colchicine-intolerant because of toxicity issues, leading physicians to search for alternative therapeutic strategies. Recent new insights into the mechanisms of auto-inflammation add further proof to the efficacy of IL-1 targeting drugs in colchicine non-responder/intolerant FMF patients. A systematic study of relevant literature through PubMed/Medline was performed in order to identify publications reporting IL-1 $\beta$  biological treatment of FMF. Treatment methods, comorbidities, clinical response and side effects in literature case reports were analysed, as well as recent advances in the pathogenesis of auto-inflammation mechanisms in FMF and the causes of colchicine resistance or toxicity in common clinical practice. The paradigmatic experience of an FMF patient with severe FMF mutations (M694V/M694V) suffering from colchicine toxicity and successfully treated with anakinra is also reported. The present data show that anti-IL-1 $\beta$  biological treatment is actually a therapeutic option for FMF patients unresponsive or intolerant to colchicine or in FMF patients with concomitant vasculitis.

DOI: 10.1007/s12016-013-8358-y

PMID: 23322405 [Indexed for MEDLINE]

2494. Clin Rev Allergy Immunol. 2013 Oct;45(2):227-35. doi: 10.1007/s12016-013-8355-1.

Clinical guidelines and definitions of autoinflammatory diseases: contrasts and comparisons with autoimmunity-a comprehensive review.

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Autoinflammatory diseases (AIDs) and autoimmune diseases (ADs) are characterized by an aberrant chronic activation of the immune system which causes tissue inflammation and damage in genetically predisposed individuals. Pathogenetic mechanisms underlying this damage differ between these two types of diseases; in AIDs, the innate immune system is directly responsible for tissue inflammation, while in ADs it works by activating the adaptive immune system, which becomes the main effector of the inflammatory process. Despite the fact that AIDs have only been recently defined, they are older than ADs. The innate immune system is found in plants and animals, and it developed earlier than the adaptive immune system, which first appeared in jawed vertebrates. According to genetic background and clinical, serological, and radiological findings, AIDs and ADs might be considered as a single spectrum of disorders, with a wide range of manifestations. Indeed, autoinflammatory-like diseases have been reported in simple organisms such as *Drosophila melanogaster* and *Caenorhabditis elegans*. We analyzed here the main pathogenetic and clinical features of these two groups of diseases mostly dealing with their similarities and differences.

DOI: 10.1007/s12016-013-8355-1

PMID: 23322404 [Indexed for MEDLINE]

2495. J Am Acad Dermatol. 2013 Feb;68(2):e61-3. doi: 10.1016/j.jaad.2012.09.038.

Erysipelas-like erythema as a cutaneous sign of familial Mediterranean fever: a case report and review of the histopathologic findings.

Radakovic S, Holzer G, Tanew A.

DOI: 10.1016/j.jaad.2012.09.038

PMID: 23317997 [Indexed for MEDLINE]

2496. Harefuah. 2012 Oct;151(10):570-2, 605.

[Nosology of inflammatory diseases: lessons learned from the auto-inflammatory syndromes--a focus on skin manifestations].

[Article in Hebrew]

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Auto-inflammatory diseases were first described more than 10 years ago as inherited disorders, characterized by recurrent flares of inflammation due to an abnormality in the innate immune system. The understanding of the underlying pathogenic mechanisms of these disorders, and especially the fact that they are mediated by IL-1 secretion by stimulated monocytes/macrophages, facilitated significant progress in patient management. IL-1 inhibitors are especially effective, and indeed, a brief and complete response to IL-1 inhibition is probably one of the best signs of auto-inflammation. Cutaneous manifestations are frequent in the monogenic auto-inflammatory syndromes, and a careful analysis of those findings reveals that they are almost always the consequence of neutrophilic skin infiltration. The neutrophilic dermatoses are, therefore, the cutaneous manifestations of those disorders. Even when the neutrophilic dermatoses occur outside the setting of genetically determined auto-inflammatory disorders, they probably also result from auto-inflammatory mechanisms. The distinction between auto-inflammation and autoimmunity is essential for the proper treatment of the patients. Auto-inflammation will almost always respond to IL-1 inhibition, while immunosuppressors will not be beneficial. The aim of the current paper is to review these two sub-groups of inflammatory diseases, focusing on their cutaneous manifestations, and highlighting the connection between these syndromes and inflammation in general.

PMID: 23316663 [Indexed for MEDLINE]

2497. Harefuah. 2012 Oct;151(10):553-4, 606.

[What's new in dermatology?].

[Article in Hebrew]

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Skin diseases have been the focus of many innovations in the last decade. These innovations are mainly in the classification of skin diseases (primarily due to the dramatic development of research into the genetics of skin diseases, but not only because of this element), a new understanding of the processes underlying various diseases, improvements in diagnosis and innovations in drug treatment. In the current issue of "Harefuah", we review some advances in the field of skin diseases discovered in recent years. We review psoriasis as a multi-system disease, describe new insights into polyarteritis nodosa, parapsoriasis, autoinflammatory syndromes, and pustular psoriasis of pregnancy (impetigo herpetiformis). We also describe the new immunotherapy for metastatic melanoma. Dermatology also has new technological developments, especially the in vivo reflected mode confocal laser microscopy. We describe in detail the use of this technique in dermatology.

PMID: 23316658 [Indexed for MEDLINE]

2498. Eur Arch Otorhinolaryngol. 2013 Nov;270(11):2871-4. doi: 10.1007/s00405-013-2347-x. Epub 2013 Jan 11.

Evaluation of hearing in patients with familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is a common and well-understood hereditary periodic fever syndrome. Hereditary periodic fever syndromes include a group of

multisystem diseases characterized by recurrent fever attacks with inflammation affecting skin, joints, and some other tissues. These are FMF, tumor necrosis factor receptor, tumor necrosis factor receptor associated periodic syndrome, hyperimmunoglobulinemia D syndrome, Muckle-Wells syndrome, and familial cold urticaria. In literature, it is determined that some of these diseases cause hearing loss. In light of the foregoing, we thought that FMF patients may have the same type of subclinical hearing loss and, therefore, the hearing ability of these patients was evaluated with otoacoustic emission and high frequency audiometry tests.

DOI: 10.1007/s00405-013-2347-x

PMID: 23306349 [Indexed for MEDLINE]

2499. Rheumatology (Oxford). 2013 Jul;52(7):1338-40. doi: 10.1093/rheumatology/kes377. Epub 2013 Jan 8.

Sarcoid-like granulomatosis in a patient treated by interleukin-1 receptor antagonist for TNF-receptor-associated periodic syndrome.

Sacre K, Pasqualoni E, Descamps V, Choudat L, Debray MP, Papo T.

DOI: 10.1093/rheumatology/kes377

PMID: 23302761 [Indexed for MEDLINE]

2500. PLoS One. 2012;7(12):e52252. doi: 10.1371/journal.pone.0052252. Epub 2012 Dec 27.

Disordered IL-33/ST2 activation in decidualizing stromal cells prolongs uterine receptivity in women with recurrent pregnancy loss.

Salker MS(1), Nautiyal J, Steel JH, Webster Z, Sućurović S, Nicou M, Singh Y, Lucas ES, Murakami K, Chan YW, James S, Abdallah Y, Christian M, Croy BA, Mulac-Jericevic B, Quenby S, Brosens JJ.

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Decidualization renders the endometrium transiently receptive to an implanting blastocyst although the underlying mechanisms remain incompletely understood. Here we show that human endometrial stromal cells (HESCs) rapidly release IL-33, a key regulator of innate immune responses, upon decidualization. In parallel, differentiating HESCs upregulate the IL-33 transmembrane receptor ST2L and other pro-inflammatory mediators before mounting a profound anti-inflammatory response that includes downregulation of ST2L and increased expression of the soluble decoy receptor sST2. We demonstrate that HESCs secrete factors permissive of embryo implantation in mice only during the pro-inflammatory phase of the decidual process. IL-33 knockdown in undifferentiated HESCs was sufficient to abrogate this pro-inflammatory decidual response. Further, sequential activation of the IL-33/ST2L/sST2 axis was disordered in decidualizing HESCs from women with recurrent pregnancy loss. Signals from these cultures prolonged the implantation window but also caused subsequent pregnancy failure in mice. Thus, IL-33/ST2 activation in HESCs drives an autoinflammatory response that controls the temporal expression of receptivity genes. Failure to constrain this response predisposes to miscarriage by allowing out-of-phase implantation in an unsupportive uterine environment.

DOI: 10.1371/journal.pone.0052252

PMCID: PMC3531406

PMID: 23300625 [Indexed for MEDLINE]

2501. Int J Immunopathol Pharmacol. 2012 Oct-Dec;25(4):1121-30.

Pharmacokinetics of colchicine in pediatric and adult patients with familial Mediterranean fever.

Berkun Y, Wason S, Brik R, Butbul Y, Ben-Chetrit E, Hashkes PJ, Livneh A, Ozen S, Ozdogan H, Faulkner R, Davis MW.

This study sought to determine the appropriate starting dose of colchicine in children aged 2 to 4 years with familial Mediterranean fever (FMF) based on steady-state pharmacokinetics in pediatric patients with FMF from 2 to less than 16 years and adult patients with FMF from 16 to 65 years. Outpatients received colchicine for 90 days starting with a fixed dose for 14 days (blood sampling days 14 and 15). After starting doses of colchicine (0.6 mg/day [2 to less than 4 years], 0.9 mg/day [from 4 to less than 6 years], 0.9 mg/day [from 6 to less than

12 years], 1.2 mg/day [from 12 to less than 16 years], and 1.2 mg/day [from 16 to less than 65 years]), the observed steady-state pharmacokinetic parameters were comparable across age groups, despite the higher doses of colchicine on a mg/kg/day basis in the younger age groups. An exception occurred with once-daily colchicine, whereby mean C<sub>max</sub> for colchicine was higher in patients 4 to less than 6 years (9.4 ng/mL) compared with the younger and older age groups (6.1-6.7 ng/mL). Mean AUC<sub>0-24h</sub> values in children 2 to less than 4, 6 to less than 12, and 12 to less than 16 years were similar to those in adults. However, mean AUC<sub>0-24h</sub> values in children 4 to less than 6 years were 25 percent higher than those observed in adults. The results show that the recommended starting dose for children 2-4 years and 4-6 years should be 0.6 mg/day (half the US adult dose). Children aged 6 to less than 12 years should receive 0.9 mg/day (i.e. three-quarters of the US adult dose). The safety of colchicine in children 2 to less than 4 years was comparable to that in older children and adults.

DOI: 10.1177/039463201202500429

PMID: 23298502 [Indexed for MEDLINE]

2502. Int J Immunopathol Pharmacol. 2012 Oct-Dec;25(4):823-33.

Gut microbiota and the immune system: an intimate partnership in health and disease.

Iebba V, Nicoletti M, Schippa S.

In recent years there have been increased rates of autoimmune diseases, possibly associated to altered intestinal microflora. In this brief review article, after a description of the structure and function of the gut microbiota organ and its cross-talk with the human host, we give a report on findings indicating how the host immune system responds to bacterial colonization of the gastrointestinal tract. The disturbances in the bacterial microbiota will result in the deregulation of adaptive immune cells, which may underlie autoimmune disorders. The mammalian immune system, which seems to be designed to control microorganisms, could be instead influenced by microorganisms, as suggested in recent literature. Alterations in both the structure and function of intestinal microbiota could be one of the common causative triggers of autoimmune and/or autoinflammatory disorders.

DOI: 10.1177/039463201202500401  
PMID: 23298474 [Indexed for MEDLINE]

2503. J Mol Neurosci. 2013 Jun;50(2):275-9. doi: 10.1007/s12031-012-9947-6. Epub 2013 Jan 8.

Association of missense mutations of Mediterranean fever (MEFV) gene with multiple sclerosis in Turkish population.

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Genetic risk factors are known to contribute to the etiology of multiple sclerosis (MS). Patients with familial Mediterranean fever (FMF) have susceptibility to develop MS. Mediterranean fever (MEFV) gene has already been identified as being responsible for FMF. The aim of this study was to explore the frequency of missense mutations of MEFV gene in a cohort of Turkish patients with MS. The study included 100 patients with MS and 160 healthy controls. Genomic DNA was isolated and genotyped using polymerase chain reaction and restriction fragment length polymorphism analyses for the five MEFV gene mutations (M694V, M680I, V726A, E148Q, and P369S). There were statistically significant differences of the MEFV gene mutation carrier rates and allele frequencies between MS patients and healthy controls ( $p = 0.0008$ , odds ratio (OR) 2.6, 95 % confidence interval (CI) 1.47-4.77 and  $p = 0.0002$ , OR 2.6, 95 % CI 1.55-4.48, respectively). The results of this study suggest that MEFV gene mutations are positively associated with predisposition to develop MS.

DOI: 10.1007/s12031-012-9947-6  
PMID: 23297013 [Indexed for MEDLINE]

2504. J Biol Chem. 2013 Feb 15;288(7):4594-601. doi: 10.1074/jbc.M112.443077. Epub 2013 Jan 4.

Inflammation in mice ectopically expressing human Pyogenic Arthritis, Pyoderma



Gangrenosum, and Acne (PAPA) Syndrome-associated PSTPIP1 A230T mutant proteins.

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Pyogenic Arthritis, Pyoderma Gangrenosum, and Acne Syndrome (PAPA syndrome) is an autoinflammatory disease caused by aberrant production of the proinflammatory cytokine interleukin-1. Mutations in the gene encoding proline serine threonine phosphatase-interacting protein-1 (PSTPIP1) have been linked to PAPA syndrome. PSTPIP1 is an adaptor protein that interacts with PYRIN, the protein encoded by the Mediterranean Fever (MEFV) gene whose mutations cause Familial Mediterranean Fever (FMF). However, the pathophysiological function of PSTPIP1 remains to be elucidated. We have generated mouse strains that either are PSTPIP1 deficient or ectopically express mutant PSTPIP1. Results from analyzing these mice suggested that PSTPIP1 is not an essential regulator of the Nlrp3, Aim2, or Nlrp4 inflammasomes. Although common features of human PAPA syndrome such as pyogenic arthritis and skin inflammation were not recapitulated in the mouse model, ectopic expression of the mutant but not the wild type PSTPIP1 in mice lead to partial embryonic lethality, growth retardation, and elevated level of circulating proinflammatory cytokines.

DOI: 10.1074/jbc.M112.443077

PMCID: PMC3576065

PMID: 23293022 [Indexed for MEDLINE]

2505. Nihon Rinsho Meneki Gakkai Kaishi. 2012;35(6):511-9.

[Febrile responses in patients with pediatric rheumatic diseases].

[Article in Japanese]

Yokota S(1), Kikuchi M, Nozawa T, Kizawa T, Kanetaka T, Kadota K, Miyamae T, Mori M.

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Fever is one of the critical symptoms of patients in pediatrics field. It indicates inflammatory focus somewhere in the body, and the major causes of fever are infectious diseases. Recent progresses of our knowledge about autoinflammatory syndrome promoted the investigation of the mechanism of fever, and suggested that the pro-inflammatory cytokines are the direct causative agents of fever. The basic science revealed that cooperation of IL-6 and IL-1 $\beta$  induces febrile response. Fever of unknown origin (FUO) remains a challenging problem. Rheumatic diseases, rare infectious diseases, and benign tumors and malignancies are diagnoses to be differentiated. FDG-PET is recently proved a valuable tool for the identification of the etiology in patients with FUO. Since the introduction of biological response modifiers into the treatment of patients with pediatric rheumatic diseases has shifted the therapeutic paradigm, a new concept that the blockade of a unique pro-inflammatory cytokine brings cessation of whole inflammatory responses affected tremendously the clinical medicine. A more investigation of inflammation and its pathophysiology will be needed in pediatric rheumatology.

PMID: 23291486 [Indexed for MEDLINE]

2506. Tuberk Toraks. 2012;60(4):380-4.

[Familial Mediterranean fever with pulmonary manifestations alone; early diagnosis with genetic analysis].

[Article in Turkish]

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Painful pleural effusion and fever are the only presenting clinical features in 5-10% of patients with familial Mediterranean fever (FMF). We report the results of genetic analysis that have confirmed the diagnosis of FMF in six patients who presented with fever and pleuritic pain alone. At time of presentation, all six patients received antibiotic treatment for suspected infectious etiology following routine laboratory and microbiologic evaluation. Gene analysis was performed when other diagnostic studies had failed to uncover the etiology and patients did not respond to conventional treatment. Mutation analysis for MEFV gene performed from genomic DNA by the direct DNA sequence method. Half of the patients were male. Five were older than 50, one was 33 years old. All of the patients had fever and pleuritic pain; none had the typical abdominal symptoms. Erythrocyte sedimentation rates and C-reactive protein levels were high. Pericardial effusion was discovered in three patients. Genetic analysis confirmed; R202Q/R202R, E148V/E148E, R314R, E474E, Q476Q, D510D, E148Q/E148E heterozygote polymorphisms with and M694V/M694V mutations were determined on the MEFV gene. In five patients an improvement has been observed with colchicine therapy. In one patient steroid treatment was needed because of no response to colchicine and clinical deterioration. Rapid improvement was observed in this case with steroid therapy. But after cessation of steroid therapy new flare developed that responded to new colchicine therapy. In patients who present with pleuritic chest pain and fever without an identifiable etiology, genetic analysis help making the diagnosis of FMF, especially in certain ethnic populations where FMF is relevant. This should help patients receive specific treatment without unnecessary delay. Thus, by making early diagnosis and timely delivery of treatment, disease progression is delayed and development of secondary amyloidosis avoided.

PMID: 23289470 [Indexed for MEDLINE]

2507. Srp Arh Celok Lek. 2012 Sep-Oct;140(9-10):589-94.

Nonalcoholic fatty liver disease and familial Mediterranean fever: are they related?

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**INTRODUCTION:** Familial Mediterranean fever (FMF) is a periodic febrile disease characterized by acute recurrent episodes of serositis. Liver disease is not considered a part of the spectrum of clinical manifestations of FMF.

**OBJECTIVE:** The purpose of this study was to characterize the nonalcoholic fatty liver disease (NAFLD) that could be associated with familial Mediterranean fever (FMF).

**METHODS:** Clinical findings and treatment information of the patients with FMF were obtained from outpatient files. Weight, height, hip and waist circumference, blood pressure, blood C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, glucose, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), creatinine, alanine aminotransferase (ALT), and insulin levels were determined in all subjects, and additionally liver ultrasonography was performed for signs of hepatosteatosi.

**RESULTS:** Fifty-two age and gender matched patients with FMF, and 30 healthy controls were included in the study. The prevalence of metabolic syndrome in the patient group was determined to be significantly higher in the patient group compared to the healthy group. When FMF patients with and without hepatosteatosi were compared, the prevalence of metabolic syndrome was determined to be 6 vs. 3, respectively ( $p < 0.001$ ). Eleven patients with FMF were found to have grade 1-2 hepatosteatosi, and only 6 of healthy subjects had grade 1 hepatosteatosi ( $p = 0.901$ ).

**CONCLUSION:** When compared with healthy controls, we found the prevalence of NAFLD was not increased in patients with FMF.

PMID: 23289274 [Indexed for MEDLINE]

2508. Yao Xue Xue Bao. 2012 Oct;47(10):1306-16.

[Therapeutic antibody: new opportunity for immunity and inflammatory diseases].

[Article in Chinese]

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With the development of therapeutic antibodies over the past decade, they have become the treatment options for immunity and inflammation diseases. Major limitations of mouse antibodies as therapeutic agents - immunogenicity, lack of effectors' functions and short serum half-life -- were subsequently identified and largely overcome by the advent of humanized and fully human antibody technologies. The therapeutic antibodies for immunity and inflammatory diseases are primarily utilized in the treatment of allograft rejection, autoimmune disease, autoinflammatory syndromes, allergies and other chronic inflammation. The action mechanisms of therapeutic antibody include blocking ligands or receptors, regulating receptor activity, clearing the target cells or activating receptor. Strategies for generating the antibody drugs with high efficacy and low side effects can be realized by modulation of Fc-mediated activities and optimization of antigen-binding domains.

PMID: 23289142 [Indexed for MEDLINE]

2509. Antiinflamm Antiallergy Agents Med Chem. 2013;12(1):14-23.

Colchicine: an old wine in a new bottle?

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Although colchicine, a natural product, is one of the oldest drugs still currently available, its possible functions seem to be surprisingly not well-known. Beyond its present medicinal use (gout, familial Mediterranean fever, Behcet's disease, chondrocalcinosis and other crystal arthritis), numerous other conditions have been recently proposed for the use of this drug, including pericardial diseases. However, colchicine appears as a double-edged sword, with

underestimated toxicity and frequent side effects. In this review, we present the main pharmacologic features of this drug, with an emphasis on toxicity and highlight its possible applications in the cardiovascular field.

PMID: 23286287 [Indexed for MEDLINE]

2510. *Pediatr Emerg Care*. 2013 Jan;29(1):89-92. doi: 10.1097/PEC.0b013e31827b5747.

Long-term outcome after suicidal colchicine intoxication in a 14-year-old girl: case report and review of literature.

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**BACKGROUND:** Colchicine is used as an anti-inflammatory drug in the treatment of gout, familial Mediterranean fever, and Behçet disease. However, because of its potent inhibition of mitosis, adverse effects and symptoms of intoxication are frequent. Clinical manifestations of colchicine intoxication include abdominal cramps, diarrhea, and multiorgan failure including cardiovascular collapse with fatal outcome.

**OBJECTIVE:** We report here the case of a 14-year-old girl who ingested 12.5 mg (0.23 mg/kg body weight) colchicine in a suicide attempt.

**CASE REPORT:** Major complaints of this fully conscious patient at the time of presentation ~2 hours after ingestion of colchicine were nausea and impaired vision. Apart from a colchicine serum concentration of 16.2 ng/mL, no abnormalities were seen in the physical examination and blood tests.

Gastrointestinal decontamination by activated charcoal, repeated administrations of sodium sulfate (Glauber salt) and substitution of volume and electrolytes led to complete recovery.

DOI: 10.1097/PEC.0b013e31827b5747

PMID: 23283275 [Indexed for MEDLINE]

2511. Arthritis Rheum. 2013 Apr;65(4):1116-21. doi: 10.1002/art.37827.

AA amyloidosis complicating the hereditary periodic fever syndromes.

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**OBJECTIVE:** AA amyloidosis is a life-threatening complication of the hereditary periodic fever syndromes (HPFS), which are otherwise often compatible with normal life expectancy. This study was undertaken to determine the characteristics, presentation, natural history, and response to treatment in 46 patients who had been referred for evaluation at the UK National Amyloidosis Centre.

**METHODS:** Disease activity was monitored by serial measurement of serum amyloid A. Renal function was assessed by measurement of serum creatinine and albumin levels, the estimated glomerular filtration rate, and proteinuria from 24-hour urine collections. The amyloid load was measured by serum amyloid P scintigraphy.

**RESULTS:** Twenty-four patients had familial Mediterranean fever, 12 patients had tumor necrosis factor receptor-associated periodic syndrome, 6 patients had cryopyrin-associated periodic syndromes, and 4 patients had mevalonate kinase deficiency. The median age at onset of HPFS was 5 years; median age at presentation with AA amyloidosis was 38 years. Diagnosis of an HPFS had not been considered prior to presentation with AA amyloidosis in 23 patients (50%). Eleven patients (24%) had end-stage renal failure (ESRF) at presentation; of these, 3 had received transplants prior to referral. A further 13 patients developed ESRF over the followup period, with 10 undergoing renal transplantation. The median time to progression to ESRF from onset of AA amyloidosis was 3.3 years (interquartile range [IQR] 2-8), with a median time to transplant of 4 years (IQR 3-6). Eleven patients (24%) died. The median survival in the entire cohort was 19 years from diagnosis of AA amyloidosis. Of the 37 patients who were treated successfully, or in whom at least partial suppression of the underlying HPFS was achieved, 17 (46%) showed amyloid regression, 14 (38%) showed a stable amyloid load, and 2 (5%) showed increased amyloid deposition over the followup period.

**CONCLUSION:** AA amyloidosis remains a challenging and serious late complication of HPFS; however, outcomes are excellent when HPFS is diagnosed early enough to allow effective treatment, thus preventing or retarding further amyloid

deposition and organ damage.

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DOI: 10.1002/art.37827

PMID: 23280696 [Indexed for MEDLINE]

2512. Br J Dermatol. 2013 Jun;168(6):1195-204. doi: 10.1111/bjd.12177.

The angiotensin-converting enzyme gene insertion/deletion polymorphism in Indian patients with vitiligo: a case-control study and meta-analysis.

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**BACKGROUND:** Vitiligo is a common, acquired, idiopathic depigmenting skin disorder. Although the exact pathogenesis remains unknown, genetic susceptibility and autoimmune responses play a role in vitiligo development. Previous studies have suggested that the D allele of the insertion/deletion (I/D) polymorphism of the angiotensin-converting enzyme (ACE) gene is associated with vitiligo in Indians and Koreans. Furthermore, significantly higher serum ACE levels have been demonstrated in patients with some autoimmune and autoinflammatory disorders.

**OBJECTIVES:** The objectives were to investigate any association between the ACE I/D polymorphism and vitiligo susceptibility in an Indian population, and to compare serum ACE levels in patients with vitiligo and healthy subjects.

**METHODS:** The ACE I/D genotypes of 79 patients with vitiligo and 100 normal individuals were determined by polymerase chain reaction amplification. A meta-analysis was done to compare the distribution of the ACE I/D alleles and genotypes in the current and three previous studies. Serum ACE levels were evaluated by enzyme-linked immunosorbent assay.

**RESULTS:** A significant increase in the frequency of the ACE I/D D allele was evident in patients with vitiligo in both the case-control study [ $P=0.005$ ; odds ratio (OR) 1.87; 95% confidence intervals (CI) 1.22-2.85] and the meta-analysis ( $P=0.044$ ; OR 1.44; 95% CI 1.01-2.06). Serum ACE levels were significantly



increased in patients with vitiligo compared with healthy subjects ( $P<0.0001$ ).

**CONCLUSIONS:** In agreement with earlier reports, the ACE I/D D allele is associated with vitiligo susceptibility in the Indian population. The significantly elevated serum ACE levels in our cohort of patients with vitiligo concur with those previously found in patients with some other autoimmune diseases.

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DOI: 10.1111/bjd.12177

PMID: 23278772 [Indexed for MEDLINE]

2513. Am J Med Sci. 2013 Aug;346(2):137-41. doi: 10.1097/MAJ.0b013e318277083b.

Efficacy and safety of biologic treatments in Familial Mediterranean Fever.

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**OBJECTIVE:** Colchicine is the mainstay treatment for Familial Mediterranean Fever (FMF). However 5% to 10% of the patients with FMF are unresponsive or intolerant to colchicine. Biologics are efficient in many rheumatic diseases, including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, cryopyrin-associated periodic syndromes. We performed a systematic review to analyze patients with FMF, including juvenile patients who received treatment with biologics.

**METHODS:** A MEDLINE search, including articles published in English language between 1990 and May 2012, was performed. Patients who had Mediterranean fever variants but could not be classified as FMF according to Tel-Hashomer criteria were excluded.

**RESULTS:** There is no controlled trial on the efficacy and safety of biologics in FMF. Fifty-nine (32 female and 27 male) patients with FMF who had been treated with biologics (infliximab, etanercept, adalimumab, anakinra, and canakinumab) were reported in 24 single reports and 7 case series. There were 16 children and

43 adults (7- to 68-year olds). Five patients were reported to have colchicine intolerance or had adverse events related to colchicine use, and the rest 54 were unresponsive to colchicine treatment.

**CONCLUSIONS:** The current data are limited to case reports, and it is difficult to obtain a quantitative evaluation of response to biologic treatments. However, on the basis of reported cases, biologic agents seem to be an alternative treatment for patients with FMF who are unresponsive or intolerant to colchicine therapy and seem to be safe. Controlled studies are needed to better evaluate the safety and efficacy of biologics in the treatment of patients with FMF.

DOI: 10.1097/MAJ.0b013e318277083b

PMID: 23276893 [Indexed for MEDLINE]

2514. *Mod Rheumatol.* 2013 Nov;23(6):1166-71. doi: 10.1007/s10165-012-0815-6. Epub 2012 Dec 29.

P-wave duration and dispersion in children with uncomplicated familial Mediterranean fever.

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**OBJECTIVES:** This was a prospective controlled study to determine the P-wave duration (Pdu) and P-wave dispersion (Pd) in patients with familial Mediterranean fever (FMF).

**METHODS:** The study group consisted of 26 children with uncomplicated FMF and 25 age- and sex-matched healthy controls. We performed electrocardiography (ECG) with Doppler echocardiography on patients and controls. All participants underwent 12-lead electrocardiography under strict standards. Pdu and Pd were computed from a randomly selected beat and from an averaged beat constructed from 12 beats, included in a 10-s ECG.

**RESULTS:** The left ventricle (LV) dimensions, LV ejection fraction (LVEF), and LV fractional shortening (LVFS) values, left atrium dimension, and aortic dimension were in normal range in both groups. There were significant differences between the groups regarding LV-isovolumic relaxation time (IRT), LV-isovolumic

contraction time (ICT), right ventricle (RV)-ICT, RV-IRT, and Pd (all  $p < 0.0001$ ). However, highly significant positive correlation was detected between LV-ICT, LV-IRT, RV-ICT, RV-IVT, C-reactive protein (CRP), and Pd ( $r = 0.505$ ,  $p < 0.0001$ ;  $r = 0.483$ ,  $p < 0.0001$ ;  $r = 0.433$ ,  $p = 0.001$ ;  $r = 0.421$ ,  $p = 0.001$ ;  $r = 0.452$ ,  $p = 0.001$ ;  $r = 0.478$ ,  $p < 0.0001$ , respectively).

**CONCLUSIONS:** Uncomplicated FMF children who are continuously treated with colchicine and do not develop amyloidosis have abnormal atrial dispersion and therefore seemingly have an increased electrocardiographic risk of atrial fibrillation.

DOI: 10.1007/s10165-012-0815-6

PMID: 23274952 [Indexed for MEDLINE]

2515. Rheumatol Int. 2013 Jul;33(7):1713-9. doi: 10.1007/s00296-012-2622-y. Epub 2012 Dec 29.

Quality of life in adult patients with Familial Mediterranean fever living in Germany or Turkey compared to healthy subjects: a study evaluating the effect of disease severity and country of residence.

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We assessed quality of life (QOL) and disease activity in patients with Familial Mediterranean fever (FMF) of Turkish ancestry living in Germany or Turkey and conducted a correlation with FMF disease activity. 40 FMF patients in Turkey (TR), 40 FMF patients in Germany (G) and 40 healthy controls in Germany (C) were included. QOL was evaluated with the short form of the World Health Organisation Quality of Life scale (WHOQOL-BREF). FMF disease activity was examined with the Pras score. Mean age was TR  $30.5 \pm 10.6$ , G  $35.2 \pm 10.2$ , C  $34.6 \pm 10.7$ . Of the 120 participants, 77 were female. FMF patients in TR and G had a significantly decreased QOL physical health domain compared to controls (TR  $59.7 \pm 18.8$ , G  $60.4 \pm 19.4$ , C  $76.5 \pm 14.6$ ). Turkish FMF patients had a lower QOL environment domain compared to controls (TR  $62.3 \pm 17.5$ , G  $69.7 \pm 16.5$ , C  $72.3 \pm 13.5$ ). In the other

QOL domains, no significant differences were found. The differences in QOL were robust to a regression analysis. No significant correlation between QOL and FMF disease activity was found. German FMF patients had longer duration of disease, younger age at onset and longer delay from disease onset to colchicine treatment. A total of 5 of 40 German FMF patients were not taking colchicine (TR:0). Erythrocyte sedimentation rate was lowest in TR with significant difference between TR and G as well as G and C (TR  $13.2 \pm 10.3$ , G  $27.8 \pm 19.4$ , C  $16.3 \pm 12.8$  mm/h). C-reactive protein did not differ between TR and G. FMF has an important impact on QOL physical health domain. No correlation between FMF disease activity and the WHOQOL-BREF could be found.

DOI: 10.1007/s00296-012-2622-y

PMID: 23274441 [Indexed for MEDLINE]

2516. J Clin Med. 2013 Aug 19;2(3):45-8. doi: 10.3390/jcm2030045.

Recurrent Fever of Unknown Origin (FUO) Due to Periodic Fever, Aphthous Stomatitis, Pharyngitis and Adenitis (FAPA) Syndrome in an Adult.

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FAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis and adenitis) is a relatively new entity described in pediatric patients. In adults, reports of FAPA are limited to rare case reports. The differential diagnosis of FAPA in adults includes Behcet's syndrome, familial Mediterranean fever (FMF), Hyper IgD syndrome and juvenile rheumatoid arthritis (JRA), i.e., adult Still's disease. With FAPA syndrome, between episodes patients are completely asymptomatic and serologic inflammatory markers such as erythrocyte sedimentation rate (ESR),

C-reactive protein (CRP) and white blood cell (WBC) count are normal. The etiology of FAFA is unknown, but lack of secondary cases or clustering in close contacts, lack of seasonality, and the lack of progression for years argue against an infectious etiology. We describe an extremely rare case of an adult with a recurrent FUO with profuse night sweats and prominent chills due to FAPA syndrome.

DOI: 10.3390/jcm2030045

PMCID: PMC4470227

PMID: 26237061

2517. Curr Rheumatol Rev. 2013;9(1):8-10.

The SAPHO syndrome and genetics - discoveries in need of replication.

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SAPHO and its relative CMRO are uncommon but not rare chronic conditions with unknown etiology. Environmental factors, perhaps related to microorganisms, may be important triggers, but there is no support for a septic nature. The monogenic animal models called cmo and Lupo with autosomal recessive transmission have not been replicated in human disease. Interesting but unconfirmed studies indicate impaired p53 formation, increased IL-10 production and decreased capacity to mount ROS responses in different patients with SAPHO. There is more evidence supporting an autoinflammatory than an autoimmune pathogenesis of SAPHO. Susceptibility genes on chromosomes 1 and 18 need to be confirmed. More studies in larger numbers of patients are needed to confirm the often anecdotal observations reviewed here. It is hoped that this review may stimulate such work.

PMID: 25198360

2518. Cold Spring Harb Symp Quant Biol. 2013;78:141-7. doi: 10.1101/sqb.2013.78.020107.

Dissection of signaling in inflammation: three novel inflammatory regulators.

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Uncontrolled inflammation is a feature of autoimmune diseases and autoinflammatory syndromes and may promote tumorigenesis. Thus, identifying molecules that regulate the signaling pathways triggering, mediating, and suppressing inflammation could be helpful in developing new therapeutic approaches for these debilitating diseases. In this review, we present new information on three molecules with important roles in controlling inflammation: MALT1, Ariadne-2, and acetylcholine. We summarize our current state of knowledge of how these molecules function, and how they are involved in pathways of NF- $\kappa$ B activation or vagal nerve stimulation associated with inflammation.

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DOI: 10.1101/sqb.2013.78.020107

PMID: 25028400 [Indexed for MEDLINE]

2519. J Leukoc Biol. 2013 Apr;93(4):489-97. doi: 10.1189/jlb.1012543. Epub 2012 Dec 27.

The role of inflammasome-derived IL-1 in driving IL-17 responses.

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NLRs are members of the PRR family that sense microbial pathogens and mediate

host innate immune responses to infection. Certain NLRs can assemble into a multiprotein complex called the inflammasome, which activates caspase-1 required for the cleavage of immature forms of IL-1 $\beta$  and IL-18 into active, mature cytokines. The inflammasome is activated by conserved, exogenous molecules from microbes and nonmicrobial molecules, such as asbestos, alum, or silica, as well as by endogenous danger signals, such as ATP, amyloid- $\beta$ , and sodium urate crystals. Activation of the inflammasome is a critical event triggering IL-1-driven inflammation and is central to the pathology of autoinflammatory diseases, such as gout and MWS. Recent studies have also shown IL-1 or IL-18, in synergy with IL-23, can promote IL-17-production from Th17 cells and  $\gamma\delta$  T cells, and this process can be regulated by autophagy. IL-1-driven IL-17 production plays a critical role in host protective immunity to infection with fungi, bacteria, and certain viruses. However, Th17 cells and IL-17-secreting  $\gamma\delta$  T cells, activated by inflammasome-derived IL-1 or IL-18, have major pathogenic roles in many autoimmune diseases. Consequently, inflammasomes are now major drug targets for many autoimmune and chronic inflammatory diseases, as well as autoinflammatory diseases.

DOI: 10.1189/jlb.1012543

PMID: 23271701 [Indexed for MEDLINE]

2520. Rheumatol Int. 2013 Jul;33(7):1675-80. doi: 10.1007/s00296-012-2609-8. Epub 2012 Dec 27.

The association of TNFRSF1A gene and MEFV gene mutations with adult onset Still's disease.

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Adult onset Still's disease (ASD) is a systemic inflammatory disorder of unknown etiology. ASD is characterized by fever with unknown etiology, rash, arthritis, and involvement of several organ systems. FMF and TRAPS are two important autoinflammatory diseases which characterized with recurrent inflammatory

attacks. We aimed in this study to investigate the MEFV gene and TNFRSF1A gene variations in ASD. Twenty consecutive Turkish ASD patients (14 female and 6 male; mean age  $38.45 \pm 14$ ; mean disease duration  $3.3 \pm 2.3$ ; mean age of the disease onset  $35.1 \pm 14.4$ ) and 103 healthy controls of Turkish origin were analyzed. All ASD patients were genotyped for the 4 MEFV mutations (M694V, E148Q, V726A, M680I) and TNFRSF1A gene exon 2-3 and exon 4-5 by using sequence analysis. The healthy controls are genotyped using PCR-RFLP method for intron 4 variation. The results of MEFV gene mutations screening show an increase in the MEFV mutation rate in ASD group, but it was not significantly different ( $p = 0.442$ , OR 1.64, 95 % CI 0.409-6.589). T-C polymorphism (rs1800692) was the only variation in the intron 4 of TNFRSF1A gene that we observed at the ASD patients. The frequency of TT genotype was 15 %, TC: 45 %, and CC: 40 % in ASD patients and the frequencies were 22, 41, and 37 % in healthy controls, respectively. When we analyzed the allele difference between both groups, there was no difference ( $p = 0.54$ , OR 1.24, 0.619-2.496-2.654). The variations in MEFV may have role in ASD pathogenesis. Our findings suggest that there is no significant association between ASD and TNFRSF1A variations.

DOI: 10.1007/s00296-012-2609-8

PMID: 23269568 [Indexed for MEDLINE]

2521. Clin Immunol. 2013 Jun;147(3):229-41. doi: 10.1016/j.clim.2012.11.008. Epub 2012 Dec 7.

Phagocyte-derived S100 proteins in autoinflammation: putative role in pathogenesis and usefulness as biomarkers.

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The cytoplasmic S100 proteins derived from cells of myeloid origin are promising new markers of (auto-)inflammation. S100A8/A9 and S100A12 are released from monocytes and granulocytes during activation of the innate immune system. Tissue and serum concentrations correlate to disease activity, both during local and systemic inflammation. In autoinflammatory diseases such as Familial



Mediterranean Fever (FMF) and Systemic onset Juvenile Idiopathic Arthritis (SJIA), a dysregulation of alternative secretory pathways may be involved in pathogenesis and lead to hypersecretion of S100 proteins. Since autoinflammatory diseases can be difficult to diagnose, phagocyte-derived S100 proteins are valid tools in the diagnosis of autoinflammatory diseases. In addition, they may help achieve a better understanding of the pathophysiology of autoinflammatory disorders including SJIA and FMF, and even provide novel therapeutic targets in the future.

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DOI: 10.1016/j.clim.2012.11.008

PMID: 23269200 [Indexed for MEDLINE]

2522. *Pediatr Radiol*. 2013 Mar;43(3):355-75. doi: 10.1007/s00247-012-2544-6. Epub 2012 Dec 22.

Chronic recurrent multifocal osteomyelitis (CRMO): a longitudinal case series review.

Falip C(1), Alison M, Boutry N, Job-Deslandre C, Cotten A, Azoulay R, Adamsbaum C.

Author information:

(1)AP-HP, Pediatric Imaging Department, St. Vincent de Paul Hospital, Paris, France.

**BACKGROUND:** Chronic recurrent multifocal osteomyelitis (CRMO) is an autoinflammatory disorder that is currently diagnosed based on clinical, radiologic, pathological and longitudinal findings.

**OBJECTIVE:** To provide detailed descriptions of CRMO lesion patterns seen on radiographs and MRI and to suggest clinical use of whole-body MRI and propose noninvasive diagnostic strategy.

**MATERIALS AND METHODS:** Retrospective longitudinal study (1989-2010) of 31 children (22 girls, 9 boys) diagnosed with CRMO. Imaging data were evaluated by two pediatric radiologists.

**RESULTS:** Mean age at diagnosis was 11 years (3-17). A total of 108 lesions were investigated. The most common sites were the long bone metaphyses (56 lesions in

24 children) especially femoral and tibial (20/24); pelvis (10/31); spine (9/31); clavicle (6/31) and mandible (3/31). In long bones, the radiologic appearance was normal (22/56), mixed lytic and sclerotic (20/56), sclerotic (8/56) or lytic (6/56) often juxtaphyseal (36/56), with hyperostosis or periosteal thickening (10/56). Vertebral involvement was often multifocal (6/9). Medullary edema was seen on MRI (42) with epiphyseal (23/42) or soft-tissue (22/42) inflammation and juxtaphyseal nodule-like appearance (7/42). Whole-body MRI (15/31) was key in detecting subclinical lesions.

CONCLUSION: CRMO is a polymorphous disorder in which whole-body MRI is extremely useful for showing subclinical edema. Vertebral collapse requires long-term monitoring.

DOI: 10.1007/s00247-012-2544-6

PMID: 23263195 [Indexed for MEDLINE]

2523. J Paediatr Child Health. 2013 Mar;49(3):E243-5. doi: 10.1111/jpc.12042. Epub 2012 Dec 18.

Recurrent fevers.

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Author information:

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An 11-year-old girl had four episodes of fever in a year, lasting 7-10 days and associated with headache and neck stiffness. She had a long history of recurrent urticaria, usually preceding the fevers. There was also a history of vague pains in her knees and in the small joints of her hands. Her serum C-reactive protein was moderately raised at 41 g/L (normal <8). Her rheumatologist felt the association of recurrent fevers that lasted 7 or more days with headaches, arthralgia and recurrent urticaria suggested one of the periodic fever syndromes. Genetic testing confirmed she had a gene mutation consistent with one of tumour necrosis factor receptor-associated periodic syndrome.

DOI: 10.1111/jpc.12042

PMID: 23252425 [Indexed for MEDLINE]

2524. *Pediatr Infect Dis J*. 2013 Jan;32(1):94. doi: 10.1097/INF.0b013e3182700cc1.

Chronic recurrent multifocal osteomyelitis and deficiency of interleukin-1-receptor antagonist.

Sakran W, Shalev SA, Sakran W, Shalev SA, El-Shanti H, Uziel Y, Uziel Y.

DOI: 10.1097/INF.0b013e3182700cc1

PMID: 23241992 [Indexed for MEDLINE]

2525. *Rheumatol Int*. 2013 Dec;33(12):3039-42. doi: 10.1007/s00296-012-2577-z. Epub 2012 Dec 13.

Mevalonate kinase genotype in children with recurrent fevers and high serum IgD level.

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Comment in

*Rheumatol Int*. 2014 Mar;34(3):423-4.

In selected cases, childhood's recurrent fevers of unknown origin can be referred to systemic autoinflammatory diseases as mevalonate kinase deficiency (MKD), caused by mutations in the mevalonate kinase gene (MVK), previously named "hyper-IgD syndrome" due to its characteristic increase in serum IgD level. There is no clear evidence for studying MVK genotype in these patients. From a cohort of 305 children evaluated for recurrent fevers in our outpatient clinic during the decade 2001-2011, we have retrospectively selected 10 unrelated Italian children displaying febrile episodes, associated with recurrent inflammatory

signs (variably involving gastrointestinal tube, joints, lymph nodes, and skin) and persistently increased serum IgD levels. All these patients were examined for MVK genotype: only 2 presented bonafide MVK mutations, 5 showed the same S52N MVK polymorphism, while the remaining 3 had a wild-type MVK sequence. Clinical details of these patients have been reviewed through the critical analysis of their medical charts. Our report underscores the pitfalls of MKD diagnosis based on clinical grounds and IgD levels, emphasizing the uncertain contribution of MVK polymorphisms in the diagnostic assessment of the syndrome.

DOI: 10.1007/s00296-012-2577-z

PMID: 23239036 [Indexed for MEDLINE]

2526. Fukushima J Med Sci. 2012;58(2):127-35.

Association of the toll-like receptor 9 gene polymorphisms with Behcet's disease in a Japanese population.

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Bacterial infection (i.e., *Streptococcus sanguinis*) has been suggested to be related to pathogenesis and/or symptom of Behcet's disease (BD). Toll-like receptor 9 (TLR9) plays an important role in both the innate and adaptive immune systems by recognizing a component of bacterial DNA (i.e., CpG-DNA). Previous studies have demonstrated that single nucleotide polymorphisms (SNPs) in TLR9 were associated with infectious and autoimmune/autoinflammatory diseases. In this study, we detected five SNPs with BD patients in a Japanese population. Allele frequency analysis of the three common SNPs (-1486: T/C (promoter region), 1174: A/G (intron 1), 2848: G/A (exon 2; Pro545Pro)) showed no statistically significant difference between the BD patients and the healthy controls. However, genotyping analysis revealed that the homozygous genotypes -1486CC and 1174GG were significantly more frequent in the BD patients compared to the healthy controls ( $P = 0.048$  and  $P = 0.027$ , respectively). The homozygous diplotype distribution C-G-A/C-G-A was significantly more frequent in the BD patients compared to the healthy controls ( $P = 0.041$ ). For reporter gene assay, the

plasmid construct carrying diplotype distribution C-G/C-G of the -1486T/C and 1174A/G SNPs showed significantly higher luciferase activity compared to the plasmid construct carrying diplotype distribution T-A/T-A ( $P = 0.019$ ). These results suggested an association of the homozygous genotypes and homozygous diplotype configuration of the TLR9 SNPs with susceptibility to BD in the Japanese population.

PMID: 23237868 [Indexed for MEDLINE]

2527. Amyloid. 2013 Mar;20(1):56-7. doi: 10.3109/13506129.2012.746655. Epub 2012 Dec 14.

How nature preserves fetuses.

Adami F, Fedrigo M, Gervasi MT, Verga L, Coccato M, Lessi F, Angelini A, Daliento L.

We report on a young pregnant woman developing distal leg edema and hypoalbuminemia, who was lately diagnosed with AL amyloidosis. Fetal growth retardation led to a caesarian section in the 27th week of gestation. A live birth healthy female, 710 g weight, was admitted to the neonatal intensive care unit and survived. Thereafter the mother underwent specific chemotherapy achieving only a partial and transient response, and eventually died due to sepsis. Interestingly, amyloidotic material was found on the maternal but not on the fetal side of the placenta. Experimental data show suppression of AA amyloid formation during pregnancy and suggest a protective role of the placenta on the offspring. However, most reported cases deal with pregnant women diagnosed with AA amyloidosis associated with Familial Mediterranean Fever and describe growth retardation of the fetus, worsening renal function and preeclampsia. To the best of our knowledge, this is the first report of AL amyloidosis diagnosed in a pregnant woman. In our patient, as well as in the other reported cases, amyloidosis during pregnancy has been confirmed to be an ominous condition. Therefore mild leg edema and proteinuria during pregnancy, though a common finding, may not be innocent.

DOI: 10.3109/13506129.2012.746655

PMID: 23237236 [Indexed for MEDLINE]

2528. Nat Rev Rheumatol. 2013 Jun;9(6):375-9. doi: 10.1038/nrrheum.2012.205. Epub 2012 Dec 11.

The role of IL-17-secreting mast cells in inflammatory joint disease.

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The proinflammatory cytokine IL-17 has an important role in pathogenesis of several inflammatory diseases. In immune-mediated joint diseases, IL-17 can induce secretion of other proinflammatory cytokines such as IL-1, IL-6 and TNF, as well as matrix metalloproteinase enzymes, leading to inflammation, cartilage breakdown, osteoclastogenesis and bone erosion. In animal models of inflammatory arthritis, mice deficient in IL-17 are less susceptible to development of disease. The list of IL-17-secreting cells is rapidly growing, and mast cells have been suggested to be a dominant source of IL-17 in inflammatory joint disease. However, many other innate sources of IL-17 have been described in both inflammatory and autoinflammatory conditions, raising questions as to the role of mast cells in orchestrating joint inflammation. This article will critically assess the contribution of mast cells and other cell types to IL-17 production in the inflammatory milieu associated with inflammatory arthritis, understanding of which could facilitate targeted therapeutic approaches.

DOI: 10.1038/nrrheum.2012.205

PMID: 23229447 [Indexed for MEDLINE]

2529. Ren Fail. 2013;35(2):226-30. doi: 10.3109/0886022X.2012.745115. Epub 2012 Dec 11.

Phenotype 2 familial mediterranean fever: evaluation of 22 case series and review of the literature on phenotype 2 FMF.

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Familial Mediterranean fever (FMF) is an autosomal recessive autoimmune disorder characterized by recurrent bouts of fever and serosal inflammation. FMF may be complicated by AA-type amyloidosis, worsening the prognosis, with associated renal failure in some patients. Complication rate varies with race, being as high as 60% in Turks and as low as 2% in Armenians. In a few cases of patients with FMF (phenotype 2), amyloid nephropathy may be the presenting manifestation. This study included 420 patients who were admitted to the Nephrology and Rheumatology Departments of Atatürk Education and Research Hospital with unexplained proteinuria/nephrotic syndrome. The initial screening test for amyloidosis was the presence of significant proteinuria (300 mg/24 h). All MEFV gene exons were screened for causative mutations by direct DNA sequencing to check for any mutations. There were 22 phenotype 2 FMF patients with 27 allelic variants. The most prevalent allelic variants were M694V (10/27, 37%) and E148Q (7/27, 26%). Phenotype 2 FMF is not as rare as it was thought before; this should be kept in mind for all patients with unexplained proteinuria and/or acute phase response in high-risk ethnic groups for FMF.

DOI: 10.3109/0886022X.2012.745115

PMID: 23228227 [Indexed for MEDLINE]

2530. PLoS One. 2012;7(11):e51105. doi: 10.1371/journal.pone.0051105. Epub 2012 Nov 30.

Genetic loss of murine pyrin, the Familial Mediterranean Fever protein, increases interleukin-1 $\beta$  levels.

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Familial Mediterranean Fever (FMF) is an inherited autoinflammatory disorder characterized by unprovoked episodes of fever and inflammation. The associated gene, MEFV (Mediterranean Fever), is expressed primarily by cells of myeloid

lineage and encodes the protein pyrin/TRIM20/Marenostrin. The mechanism by which mutations in pyrin alter protein function to cause episodic inflammation is controversial. To address this question, we have generated a mouse line lacking the *Mefv* gene by removing a 21 kb fragment containing the entire *Mefv* locus. While the development of immune cell populations appears normal in these animals, we show enhanced interleukin (IL) 1 $\beta$  release by *Mefv*(-/-) macrophages in response to a spectrum of inflammatory stimuli, including stimuli dependent on IL-1 $\beta$  processing by the NLRP1b, NLRP3 and NLRC4 inflammasomes. Caspase-1 activity, however, did not change under identical conditions. These results are consistent with a model in which pyrin acts to limit the release of IL-1 $\beta$  generated by activation and assembly of inflammasomes in response to subclinical immune challenges.

DOI: 10.1371/journal.pone.0051105

PMCID: PMC3511413

PMID: 23226472 [Indexed for MEDLINE]

2531. PLoS One. 2012;7(11):e49408. doi: 10.1371/journal.pone.0049408. Epub 2012 Nov 30.

Homeostatic tissue responses in skin biopsies from NOMID patients with constitutive overproduction of IL-1 $\beta$ .

Aubert P(1), Suárez-Fariñas M, Mitsui H, Johnson-Huang LM, Harden JL, Pierson KC, Dolan JG, Novitskaya I, Coats I, Estes J, Cowen EW, Plass N, Lee CC, Sun HW, Lowes MA, Goldbach-Mansky R.

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The autoinflammatory disorder, Neonatal-onset Multisystem Inflammatory Disease (NOMID) is the most severe phenotype of disorders caused by mutations in *CIAS1* that result in increased production and secretion of active IL-1 $\beta$ . NOMID patients present with systemic and organ-specific inflammation of the skin, central nervous system and bone, and respond dramatically to treatment with IL-1 blocking agents. We compared the cellular infiltrates and transcriptome of skin biopsies from patients with NOMID (n = 14) before treatment (lesional (LS) and non-lesional (pre-NL) skin) and after treatment (post-NL) with the IL-1 blocker anakinra (recombinant IL-1 receptor antagonist, Kineret<sup>®</sup>, Swedish Orphan



Biovitrum AB, SOBI), to normal skin (n = 5) to assess tissue responses in the context of untreated and treated disease. Abundant neutrophils distinguish LS skin from pre-NL and post-NL skin. CD11c(+) dermal dendritic cells and CD163(+) macrophages expressed activated caspase-1 and are a likely source of cutaneous IL-1 production. Treatment with anakinra led to the disappearance of neutrophils, but CD3(+) T cells and HLA-DR(+) cells remained elevated. Among the upregulated genes IL-6, IL-8, TNF, IL-17A, CCL20, and the neutrophil defensins DEFA1 and DEFA3 were differentially regulated in LS tissues (compared to normal skin). Important significantly downregulated pathways in LS skin included IL-1R/TLR signaling, type I and II cytokine receptor signaling, mitochondrial dysfunction, and antigen presentation. The differential expression and regulation of microRNAs and pathways involved in post-transcriptional modification were suggestive of epigenetic modification in the chronically inflamed tissue. Overall, the dysregulated genes and pathways suggest extensive "adaptive" mechanisms to control inflammation and maintain tissue homeostasis, likely triggered by chronic IL-1 release in the skin of patients with NOMID.

DOI: 10.1371/journal.pone.0049408

PMCID: PMC3511496

PMID: 23226210 [Indexed for MEDLINE]

2532. Ann Rheum Dis. 2013 Jun;72(6):1064-70. doi: 10.1136/annrheumdis-2012-202082. Epub 2012 Dec 5.

Microarray-based gene expression profiling in patients with cryopyrin-associated periodic syndromes defines a disease-related signature and IL-1-responsive transcripts.

Balow JE Jr(1), Ryan JG, Chae JJ, Booty MG, Bulua A, Stone D, Sun HW, Greene J, Barham B, Goldbach-Mansky R, Kastner DL, Aksentijevich I.

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OBJECTIVE: To analyse gene expression patterns and to define a specific gene expression signature in patients with the severe end of the spectrum of cryopyrin-associated periodic syndromes (CAPS). The molecular consequences of

interleukin 1 inhibition were examined by comparing gene expression patterns in 16 CAPS patients before and after treatment with anakinra.

**METHODS:** We collected peripheral blood mononuclear cells from 22 CAPS patients with active disease and from 14 healthy children. Transcripts that passed stringent filtering criteria ( $p$  values  $\leq$  false discovery rate 1%) were considered as differentially expressed genes (DEG). A set of DEG was validated by quantitative reverse transcription PCR and functional studies with primary cells from CAPS patients and healthy controls. We used 17 CAPS and 66 non-CAPS patient samples to create a set of gene expression models that differentiates CAPS patients from controls and from patients with other autoinflammatory conditions.

**RESULTS:** Many DEG include transcripts related to the regulation of innate and adaptive immune responses, oxidative stress, cell death, cell adhesion and motility. A set of gene expression-based models comprising the CAPS-specific gene expression signature correctly classified all 17 samples from an independent dataset. This classifier also correctly identified 15 of 16 post-anakinra CAPS samples despite the fact that these CAPS patients were in clinical remission.

**CONCLUSIONS:** We identified a gene expression signature that clearly distinguished CAPS patients from controls. A number of DEG were in common with other systemic inflammatory diseases such as systemic onset juvenile idiopathic arthritis. The CAPS-specific gene expression classifiers also suggest incomplete suppression of inflammation at low doses of anakinra.

DOI: 10.1136/annrheumdis-2012-202082

PMCID: PMC4174357

PMID: 23223423 [Indexed for MEDLINE]

2533. Lancet. 2012 Dec 8;380(9858):2052. doi: 10.1016/S0140-6736(12)61377-4.

Mediterranean mimicker.

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DOI: 10.1016/S0140-6736(12)61377-4

PMID: 23217869 [Indexed for MEDLINE]

2534. Biochem Biophys Res Commun. 2013 Jan 4;430(1):425-8. doi: 10.1016/j.bbrc.2012.11.070. Epub 2012 Dec 1.

Reduced expression of NLRP3 and MEFV in human ischemic heart tissue.

Hermansson C(1), Lundqvist A, Wasslavik C, Palmqvist L, Jeppsson A, Hultén LM.

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The innate immune system and, in particular, activation of the multi-protein complex known as the inflammasome complex are involved in ischemic injury in myocardial cells. The nucleotide-binding leucine-rich repeat-containing pyrin receptor 3 (NLRP3) inflammasome has been linked to inflammation and NLRP3 is especially important for increased inflammation in atherosclerosis, which may lead to myocardial infarction. Here we investigated how inflammasome molecules are affected in human ischemic heart tissue. Surprisingly the important member of the inflammasome complex, NLRP3, displayed markedly decreased levels in human ischemic heart tissue compared with non ischemic control heart tissue. However, subsequent gene analysis revealed mutations in NLRP3 in human ischemic heart tissues but not in non-ischemic control tissue. Gene polymorphisms in the NLRP3 inflammasome have been shown to be associated with increased IL-1 $\beta$  and IL-18 production and severe inflammation. The autoinflammatory disorder familial Mediterranean fever (FMF) is associated with decreased expression of the Mediterranean fever gene (MEFV) and increased inflammation. We also observed reduced expression of MEFV in ischemic versus non-ischemic heart tissue. Further analyses showed a mutation in MEFV in human ischemic heart tissue but not in non-ischemic control tissue. Our data show that defects in the inflammasome and associated proteins may be involved in promoting ischemic heart disease.

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DOI: 10.1016/j.bbrc.2012.11.070

PMID: 23206693 [Indexed for MEDLINE]

2535. Ital J Pediatr. 2012 Dec 4;38:66. doi: 10.1186/1824-7288-38-66.

The expanded clinical profile and the efficacy of colchicine therapy in Egyptian children suffering from familial Mediterranean fever: a descriptive study.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by self-limiting recurrent attacks of fever and serosal inflammation, leading to abdominal, thoracic or articular pain.

**OBJECTIVE:** To detect variable clinical presentations and genotypic distribution of different groups of FMF patients and the efficacy of colchicine therapy in treatment of these groups of FMF after one year.

**METHODS:** A cross-sectional study was conducted on 70 patients already diagnosed with FMF and following-up at the Rheumatology Clinic, Children's Hospital - Cairo University. Diagnosis of FMF was determined according to Tel Hashomer criteria for FMF. All patients were subjected to a questionnaire including detailed history with emphasis on clinical manifestations and colchicine dose to control attacks. Mutational analysis was performed for all study subjects covering 12 mutations in the MEFV gene: E148Q, P369S, F479L, M680I (G/C), M680I (G/A), I692del, M694V, M694I, K695R, V726A, A744S and R761H. Response to colchicine treatment was evaluated as complete, incomplete and unresponsive.

**RESULTS:** Out of the 70 patients- 40 males and 30 females- fever was the most common presenting feature, followed by abdominal pain, and arthritis; documented in 95.7%, 94.3%, and 77.1% of cases respectively. Mutational analysis detected gene mutation on both alleles in 20 patients (homozygotes), on only 1 allele in 40 patients (heterozygotes), and on none of the alleles (uncharacterized cases). Mild to moderate disease severity score (according to Tel Hashomer key to severity score) was detected in a significant proportion of heterozygotes and the uncharacterized group than the homozygotes. All patients received colchicine therapy; 22.9% of them showed complete response, 74.3% showed incomplete response and 2.9% showed no response to therapy. The colchicine dose needed to control attacks was significantly lower in heterozygotes than the homozygotes( $P=0.04$ ). Also patients' response to colchicine therapy was significantly better in the

heterozygous group( $P=0.023$ ).

CONCLUSION: Fever, abdominal pain and arthritis are the most common presenting features for homozygous, Heterozygous and uncharacterized patients. E148Q, V726A, and M680I were the most common mutations detected in the heterozygous group. Homozygosity were found for M680I, M694V, and M694I mutations in 13 patients (65% of homozygotes). Heterozygotes presenting with severe phenotype should be further analyzed for less common second MEFV mutation using gene sequencing. The colchicine dose required to control the attacks was significantly lower and patients' response to colchicine therapy was significantly better in the heterozygous group than homozygous group.

DOI: 10.1186/1824-7288-38-66

PMCID: PMC3541094

PMID: 23206577 [Indexed for MEDLINE]

2536. Nihon Naika Gakkai Zasshi. 2012 Sep 10;101(9):2733-9.

[109th Scientific Meeting of the Japanese Society of Internal Medicine: educational lecture: 14. Autoinflammatory syndrome].

[Article in Japanese]

Kawakami A(1), Migita K, Ida H, Yoshiura K, Arima K, Eguchi K.

Author information:

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PMID: 23205462 [Indexed for MEDLINE]

2537. Arthritis Rheum. 2013 Mar;65(3):671-80. doi: 10.1002/art.37786.

Therapeutic efficacy of Tyro3, Axl, and Mer tyrosine kinase agonists in collagen-induced arthritis.

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Rothlin CV, van den Berg WB, van de Loo FA.

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**OBJECTIVE:** Hyperactivation of innate immunity by Toll-like receptors (TLRs) can contribute to the development of autoinflammatory or autoimmune diseases. This study evaluated the activation of Tyro3, Axl, Mer (TAM) receptors, physiologic negative regulators of TLRs, by their agonists, growth arrest-specific protein 6 (GAS-6) and protein S, in the prevention of collagen-induced arthritis (CIA).

**METHODS:** Adenoviruses overexpressing GAS-6 and protein S were injected intravenously or intraarticularly into mice during CIA. Splenic T helper cell subsets from intravenously injected mice were studied by flow cytometry, and the knee joints of mice injected intravenously and intraarticularly were assessed histologically. Synovium from mice injected intraarticularly was evaluated for cytokine and suppressor of cytokine signaling (SOCS) expression.

**RESULTS:** Protein S significantly reduced ankle joint swelling when overexpressed systemically. Further analysis of knee joints revealed a moderate reduction in pathologic changes in the joint and a significant reduction in the number of splenic Th1 cells when protein S was overexpressed systemically. Local overexpression of GAS-6 decreased joint inflammation and joint pathology. Protein S treatment showed a similar trend of protection. Consistently, GAS-6 and protein S reduced cytokine production in the synovium. Moreover, levels of messenger RNA for interleukin-12 (IL-12) and IL-23 were reduced by GAS-6 and protein S treatment, with a corresponding decrease in the production of interferon- $\gamma$  and IL-17. TAM ligand overexpression was associated with an increase in SOCS-3 levels, which likely contributed to the amelioration of arthritis.

**CONCLUSION:** This study provides the first evidence that TAM receptor stimulation by GAS-6 and protein S can be used to ameliorate arthritis when applied systemically or locally. TAM receptor stimulation limits proinflammatory signaling and adaptive immunity. This pathway provides a novel strategy by which to combat rheumatoid arthritis.

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DOI: 10.1002/art.37786

PMCID: PMC3582862

PMID: 23203851 [Indexed for MEDLINE]

2538. Case Rep Nephrol Urol. 2012 Jan;2(1):20-4. doi: 10.1159/000338269. Epub 2012 Apr 11.

Massive colchicine overdose with recovery.

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Colchicine is an active alkaloid that is commonly used for treatment of multiple diseases including gout, primary biliary cirrhosis and familial Mediterranean fever. Less commonly, it has been implicated in several fatal overdoses. Deaths from colchicine overdoses are usually due to multi-organ failure, whether directly from colchicine toxicity or due to ensuing sepsis. We report an extreme case of colchicine ingestion (1.38 mg/kg), which is the largest reported non-fatal colchicine overdose. The patient was a 47-year-old First Nations woman with a history of depression and no other comorbidities. Ingestion was intentional and initial presentation was within 2 h of ingestion, at which point she had normal clinical and laboratory parameters. Early implementation of a targeted therapeutic strategy directed at the predicted multi-organ failure which included aggressive use of a GI decontamination protocol, timely supportive measures including ventilator support and renal replacement therapy, as well as the utilization of broad-spectrum antibiotics and G-CSF for sepsis and leucopenia management, resulted in successful support and discharge of this patient off dialysis.

DOI: 10.1159/000338269

PMCID: PMC3482071

PMID: 23197951

2539. Acta Paediatr. 2013 Feb;102(2):193-8. doi: 10.1111/apa.12075. Epub 2012 Dec 7.

Familial Mediterranean Fever -- an increasingly important childhood disease in Sweden.

Wekell P(1), Friman V, Balci-Peynircioglu B, Yilmaz E, Fasth A, Berg S.

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**AIM:** To characterize Familial Mediterranean Fever (FMF) in western Sweden, focusing on genotype, clinical picture, prevalence and age of onset as well as time to diagnosis.

**METHODS:** Patients with autoinflammatory diseases are continuously registered at the five main hospitals in Western Sweden. Case records of patients with FMF were analysed retrospectively. Population data on immigration was retrieved from Statistics Sweden.

**RESULTS:** Until 2008, 37 patients with FMF were identified. The prevalence among inhabitants of Turkish, Lebanese, Syrian and Iranian origin was 173, 124, 86 and 17/100 000, respectively. Median age at first symptoms was 4 years (range 3 month-37 years) and at diagnosis 10 years (range 2-44 years). Median time from first symptoms to diagnosis was 4 years (range <1 year-34 years). Among 32 patients screened for twelve common mutations, 75% were homozygotes or compound heterozygotes, 16% were heterozygotes and in 9% no mutation was found. In our cohort the frequencies of symptoms were fever 100%, peritonitis 92%, pleuritis 22% and arthritis 11%.

**CONCLUSIONS:** The majority of patients with FMF present during childhood. The prevalence among immigrants in western Sweden is in the same range as in their country of origin. Time to diagnosis needs to be shortened by means of increased awareness of the disease.

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DOI: 10.1111/apa.12075

PMID: 23194659 [Indexed for MEDLINE]

2540. Eurasian J Med. 2012 Dec;44(3):131-4. doi: 10.5152/eajm.2012.31.

Anti-cyclic citrullinated Peptide frequency in patients with chronic hepatitis C virus infection and effect of presence of systemic disease.

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**OBJECTIVE:** Patients with chronic hepatitis C virus (HCV) infection may show a variety of rheumatic symptoms and signs. Anti-cyclic citrullinated peptide (anti-CCP) is widely used as a marker, particularly for rheumatoid arthritis (RA), and may be positive in some diseases that also cause arthritis, such as systemic lupus erythematosus, familial Mediterranean fever, Behçet's disease, and psoriatic arthritis.

**MATERIALS AND METHODS:** Blood samples were obtained (in routine protocols) from 57 patients with chronic HCV infection from the Gastroenterology Clinic of Ataturk University and Infectious Disease Clinic of Erzurum Region Research and Education Hospital. Normal sera were obtained from volunteer blood donors at Ataturk University.

**RESULTS:** Anti-CCP antibodies were found in 5 chronic HCV patients with RA. The patient with the highest anti-CCP antibody level had RA. No patient in the control group was positive for anti-CCP antibodies.

**CONCLUSION:** Anti-cyclic citrullinated peptide (anti-CCP) antibodies should be measured frequently in patients with HCV and an additional systemic disease, such as end-stage chronic renal failure, chronic obstructive airway disease, and decompensated liver cirrhosis, to differentiate RA from non-RA arthropathy.

**Publisher:** Kronik hepatit C virüs (HCV) enfeksiyonu çeşitli romatolojik belirti ve semptomlarla seyredebilir. Anti-siklik sitrüllenmiş peptid (Anti-CCP) özellikle romatoid artrit (RA) tanısında yaygın şekilde kullanılan, ayrıca sistemik lupus eritematozus, ailevi akdeniz ateşi ve psöriatik artrit gibi artritlerle birlikte seyreden bazı hastalıklarda da pozitif olduğu gösterilmiş bir antikordur. Çalışmada Atatürk Üniversitesi Gastroenteroloji Kliniği ve Erzurum Bölge Eğitim ve Araştırma Hastanesi Enfeksiyon Hastalıkları Kliniği'nden 57 kronik HCV enfeksiyonlu hastadan rutin tetkikleri sırasında alınmış olan kanlar kullanıldı. Kontrol kanları Atatürk Üniversitesi kan vericilerinden alınan kanlardan toplandı. Kronik HCV enfeksiyonuna ilaveten RA tanısı da almış olan 5 hastanın tamamında Anti-CCP pozitif bulundu. Anti-CCP seviyesi en yüksek olan hasta da RA'li olan bir hasta idi. Kontrol grubundaki hastalardan hiçbirinde

Anti-CCP pozitif değildi. Kronik HCV'li hastalarda kronik böbrek yetmezliği, kronik obstruktif akciğer hastalığı veya dekompanse karaciğer sirozu gibi sistemik hastalıkların varlığında, Anti-CCP daha sık olarak görülebilmektedir. Ayrıca Anti-CCP pozitifliğinin, bu hasta grubunda RA ile non-RA artropati ayrımında da kullanılabileceği düşünülmektedir.

DOI: 10.5152/eajm.2012.31

PMCID: PMC4261378

PMID: 25610226

2541. Immunobiology. 2013 Jun;218(6):892-8. doi: 10.1016/j.imbio.2012.10.007. Epub 2012 Oct 26.

Activated phenotype of circulating neutrophils in familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is autoinflammatory disorder, characterized by MEFV gene mutations and recurrent episodes of fever and serosal or synovial inflammation. Neutrophils are the predominant effector cells of acute inflammatory attacks in FMF; however pathogenic role and molecular phenotype of these cells remain largely unknown. To gain insight into the processes that contribute to the self-directed autoinflammation we characterized expression of a spectrum of genes involved in regulation of inflammation in unstimulated and LPS-activated neutrophils from FMF patients. Expression of 12 candidate immune genes encoding for inflammation-related molecules was assessed by quantitative RT-PCR in freshly isolated and LPS-stimulated peripheral polymorphonuclear neutrophils from fifteen FMF patients in attack-free period and ten healthy volunteers as controls. The relative expression was calculated using the second derivative method; the target gene expression was normalized to the expression of RPL32 gene. FMF neutrophils were characterized by up-regulated baseline gene expression of c-FOS (9.5-fold,  $p < 0.05$ ), IL-8 (12-fold,  $p < 0.05$ ), MMP9 (8-fold,  $p < 0.01$ ), TLR2 (7-fold,  $p < 0.05$ ) compared to the neutrophils from control subjects, a trend was also evident towards increased caspase-1 expression

(3-fold,  $p = 0.09$ ). Discriminant analysis clustered the patient and control subjects into two distinct groups (Wilks's  $\lambda = 0.165$ ,  $p = 0.042$ ). Further, LPS-induced alterations of expression profiles were shared between FMF and healthy neutrophils, the profile consisting namely of up-regulated IL-1 $\beta$ , TLR4, IL-8, and TNFAIP6 transcripts. Present study demonstrates distinct expression patterns of pre-activated neutrophils during attack-free period of FMF when compared to neutrophils from healthy controls. Furthermore, our data emphasize the importance of host-derived ligands in activation of FMF neutrophils.

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DOI: 10.1016/j.imbio.2012.10.007

PMID: 23182715 [Indexed for MEDLINE]

2542. *Dermatology*. 2012;225(3):215-9. doi: 10.1159/000343602. Epub 2012 Nov 16.

Pyoderma gangrenosum, acne and suppurative hidradenitis syndrome following bowel bypass surgery.

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The clinical triad of pyoderma gangrenosum (PG), acne and suppurative hidradenitis (PASH) has recently been described as a new disease entity within the spectrum of autoinflammatory syndromes, which are an emerging group of inflammatory diseases distinct from autoimmune, allergic and infectious disorders. PASH syndrome is similar to PAPA (pyogenic arthritis, acne and PG), but it differs in lacking the associated arthritis and on a genetic basis. PAPA syndrome is caused by mutations in a gene involved in the regulation of innate immune responses, the PSTPIP1, while no mutations have been detected to date in patients with PASH syndrome. We report a young male patient who developed coexisting disseminated PG, typical suppurative hidradenitis and acneiform eruption on the face, after he had undergone bowel bypass surgery for obesity. The cutaneous manifestations associated with bowel bypass syndrome often mimic PG

or other neutrophilic dermatoses, suggesting a pathogenesis related to neutrophil-mediated inflammation for this condition. This is the first report describing PASH syndrome after bariatric surgery, and we propose to include such neutrophilic dermatoses in the list of complications occurring after bowel bypass surgery. Extensive genetic studies may help to clarify the etiopathogenesis of PASH as well as of autoinflammatory diseases in general.

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DOI: 10.1159/000343602

PMID: 23171584 [Indexed for MEDLINE]

2543. Exp Dermatol. 2012 Dec;21(12):961-4. doi: 10.1111/exd.12037.

Strong induction of AIM2 expression in human epidermis in acute and chronic inflammatory skin conditions.

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Absent in melanoma 2 (AIM2) is a double-stranded DNA receptor, and its activation initiates an interleukin-1 beta processing inflammasome. AIM2 is implicated in host defense against several pathogens, but could hypothetically also contribute to autoinflammatory or autoimmune diseases, such as is the case for NLRP3. Using thoroughly characterised antibodies, we analysed AIM2 expression in human tissues and primary cells. A strong epidermal upregulation of AIM2 protein expression was observed in several acute and chronic inflammatory skin disorders, such as psoriasis, atopic dermatitis, venous ulcers, contact dermatitis, and experimental wounds. We also found AIM2 induction by interferon-gamma in submerged and three-dimensional in vitro models of human epidermis. Our data highlight the dynamics of epidermal AIM2 expression, showing Langerhans cell and melanocyte-restricted expression in normal epidermis but a pronounced induction in subpopulations of epidermal keratinocytes under inflammatory conditions.

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DOI: 10.1111/exd.12037

PMID: 23171461 [Indexed for MEDLINE]

2544. J Korean Med Sci. 2012 Nov;27(11):1424-7. doi: 10.3346/jkms.2012.27.11.1424. Epub 2012 Oct 30.

Familial Mediterranean fever: the first adult case in Korea.

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Familial Mediterranean fever (FMF) is known to be a genetic disorder that prevalent among populations surrounding the Mediterranean Sea. Since Mediterranean fever gene (MEFV) was discovered at 1997, some cases have been reported in countries not related or close to this area like Japan. In addition it has been generally accepted that the clinical onset of FMF begins before 20 yr of age in most patients. Onset of the disease at an older age may occur but is rare. Adult-onset FMF may be a form of disease with distinct clinical, demographic and molecular characteristics. We describe a case of adult-onset FMF confirmed by DNA analysis of the MEFV gene in a Korean patient. A 32-yr-old man, who has no family history of FMF, presented with periodic fever, abdominal pain and vomiting. Though several various tests were thoroughly performed to evaluate the cause of his symptoms, there was no evidence of infectious, autoimmune or neoplastic diseases. Several gene analysis of periodic fever syndrome was finally performed and two point mutations (p.Leu110Pro, p.Glu148Gln) were identified. We confirmed the first adult case of FMF through detection of MEFV gene mutations in Korea and describe his clinical characteristics.

DOI: 10.3346/jkms.2012.27.11.1424

PMCID: PMC3492681

PMID: 23166428 [Indexed for MEDLINE]

2545. J Pediatr Gastroenterol Nutr. 2013 May;56(5):498-502. doi: 10.1097/MPG.0b013e31827dd763.

Association of inflammatory bowel disease with familial Mediterranean fever in

Turkish children.

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**BACKGROUND AND AIMS:** Inflammatory bowel disease (IBD) and familial Mediterranean fever (FMF) share common clinical and biological features. The prevalence of other inflammatory diseases, including IBD, is increased in FMF. We investigated the presence of IBD accompanying FMF in patients who were being followed up with a diagnosis of FMF and the relation of IBD with the MEFV gene mutation.

**METHODS:** A total of 78 children with FMF were enrolled in the study. The patients were included in the study independent of the presence of complaints. Colonoscopy for IBD was performed if any of the following was present: blood mixed with mucus in the stool; chronic diarrhea (loose and frequent stools lasting >4 weeks); abdominal pain incompatible with FMF (localized in a certain part of the abdomen, not occurring during attacks, >3 days); and positive IgA and IgG anti-Saccharomyces cerevisiae antibodies and perinuclear antineutrophil cytoplasmic antibodies. MEFV gene mutations were analyzed in patients diagnosed as having IBD and FMF.

**RESULTS:** Of the 78 patients with a diagnosis of FMF, colonoscopy was performed and biopsy samples were taken in 20 patients (25.6%) who had abdominal pain incompatible with FMF, chronic diarrhea, bloody stools, and/or positive perinuclear anti-neutrophil cytoplasmic antibody or anti-Saccharomyces cerevisiae antibody. Histopathological examination resulted in a diagnosis of IBD in 12 of the 78 patients (15.4%). MEFV gene mutations were present in all 12 patients diagnosed as having IBD. We observed M694 V mutations in 5 of 12 patients (41.7%), M680I mutations in 3 (25%), K695R mutations in 3 (25%), and E148Q mutations in 1 (8.3%).

**CONCLUSIONS:** We found that the number of patients with FMF was higher than the number with IBD in the general population. When IBD accompanied FMF, the most common mutation was M694 V; however, the high rate (25%) of K695R mutation in our patients with FMF and IBD was not observed in previous studies.

DOI: 10.1097/MPG.0b013e31827dd763

PMID: 23164758 [Indexed for MEDLINE]

2546. Nat Immunol. 2012 Dec;13(12):1133-5. doi: 10.1038/ni.2471.

HOIL and water: the two faces of HOIL-1 deficiency.

Ombrello MJ, Kastner DL, Milner JD.

Comment on

Nat Immunol. 2012 Dec;13(12):1178-86.

DOI: 10.1038/ni.2471

PMID: 23160206 [Indexed for MEDLINE]

2547. Hum Exp Toxicol. 2013 Apr;32(4):337-43. doi: 10.1177/0960327112464797. Epub 2012 Nov 15.

The scintigraphic evaluation and genetic correlation of joint involvements in pediatric patients with familial Mediterranean fever.

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**PURPOSE:** We aimed to evaluate the articular involvements in pediatric patients with familial Mediterranean fever (FMF) with joint symptoms by bone scintigraphy and to correlate the involved joints with the gene mutations.

**MATERIALS AND METHODS:** A total of 41 newly diagnosed patients in pediatric age group (28 girls and 13 boys; mean age  $9.14 \pm 2.91$  years) with joint involvement symptoms were included in this study. Scintigraphic images were obtained at 5th min (blood pool or early phase) and starting at 3 h (late phase) after (after tracer injection) intravenous administration of technetium-99m ( $^{99m}\text{Tc}$ )-methylenediphosphonate (MDP). Genomic DNA was isolated from leukocytes using standard salting out procedure. The sequencing data were analyzed.

**RESULTS:** Of the 41 patients, arthritis was found in 21 (51.2%) patients. Of the 21 patients, there was single joint involvement in 15 (71.4%) patients and

multiple joint involvement in six (28.6%) patients. The mean age of patients with joint involvement ( $8 \pm 2.3$  years) were considerably lower than the patients without joint involvement ( $10.35 \pm 3.04$  years), and this was statistically significant ( $p = 0.008$ ). The most commonly involved joints were ankles and knees. Multiple joint involvements were most frequently observed in the M694V and M694I gene mutations (16.7%).

**CONCLUSIONS:** We use and recommend the bone scintigraphy in patients with FMF to determine the presence and distribution of arthritis, since bone scintigraphy is inexpensive, noninvasive, easy-to-use, and also is more sensitive in the diagnosis and distribution of arthritis than conventional radiological methods and clinical examination.

DOI: 10.1177/0960327112464797

PMID: 23155201 [Indexed for MEDLINE]

2548. Pathol Res Pract. 2012 Dec 15;208(12):713-8. doi: 10.1016/j.prp.2012.07.011. Epub 2012 Nov 13.

Hepatic amyloidosis: morphologic spectrum of histopathological changes in AA and nonAA amyloidosis.

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In hepatic amyloidosis (HA), the relationships between the pattern and extent of amyloid deposition, morphologic changes, associated diseases and clinical data have not yet been demonstrated. In this study, we sought the correlation between the above mentioned parameters in HA. Liver biopsies of 34 HA were retrospectively analyzed for the type, distribution, and intensity of amyloid deposition and associated morphologic changes. AA and nonAA types were classified on the basis of immunohistochemistry. Follow-up clinical and laboratory findings were reviewed. Twenty-three out of 34 patients (67.6%) had AA, and 11 out of 34 patients (32.4%) had nonAA amyloidosis. The predominant localization pattern in AA amyloidosis was vascular (91.3%), and in nonAA amyloidosis it was mixed with other patterns (72.7%). We confirmed that nonAA amyloid involves the hepatic



artery, as well as the portal and central vein, but deposition occurred more frequently in the sinusoidal areas. We detected a portal stromal pattern only in cases of nonAA amyloidosis with a mixed pattern of amyloid deposition. The pattern of amyloid deposition in liver differs between the AA and nonAA type amyloidosis. The distribution of amyloid within the liver is not a reliable method for distinguishing AA from nonAA amyloidosis. However, the histological pattern provides strong clues as to the etiology of the amyloid deposits, and could provide information on the clinical status and prognosis of these patients.

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DOI: 10.1016/j.prp.2012.07.011

PMID: 23154038 [Indexed for MEDLINE]

2549. Rheumatol Int. 2013 Nov;33(11):2937-41. doi: 10.1007/s00296-012-2547-5. Epub 2012 Nov 15.

No evidence for involvement of the toll-like receptor (TLR) 4 gene Asp299Gly and Thr399Ile polymorphisms in susceptibility to primary gouty arthritis.

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Previous studies demonstrated that toll-like receptor (TLR) 4 was involved in the development of autoinflammatory disease including gouty arthritis (GA). TLR4 functional gene Asp299Gly and Thr399Ile polymorphisms play a role in some autoinflammatory disease susceptibility. We undertook this study to analyze the association between the genetic polymorphisms within TLR4 gene and the susceptibility to GA in Chinese Han people. Two functional variants, Asp299Gly and Thr399Ile, in the TLR4 gene were genotyped using 5' exonuclease TaqMan technology from 218 male GA patients and 226 ethnically matched controls. None polymorphisms of Asp299Gly and Thr399Ile were detected in all GA cases and controls, which indicates that there is no evidence for involvement of the TLR4 gene Asp299Gly and Thr399Ile polymorphisms in susceptibility to primary GA in the

Chinese Han population. Further studies with extended single nucleotide polymorphisms should be performed.

DOI: 10.1007/s00296-012-2547-5

PMID: 23152086 [Indexed for MEDLINE]

2550. Acta Reumatol Port. 2012 Apr-Jun;37(2):144-8.

Autoantibodies are not associated with familial mediterranean fever.

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**OBJECTIVE:** It has been suggested that Mediterranean fever (MEFV) gene mutations are also seen in certain autoimmune diseases and are related to severity of the disease activity. As most of the clinical symptoms of these inflammatory diseases are related to autoantibody positivity, we assessed autoantibody prevalence in patients with Familial Mediterranean fever (FMF) and investigated the relationship between clinical involvement of FMF and the autoantibodies. There are a few studies on this subject with conflicting results.

**PATIENTS AND METHODS:** Fifty patients with FMF without attack and 27 healthy controls were enrolled to the study. Clinical characteristics of the patient group were questioned. Rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) values, Fluorescent antinuclear antibody (ANA), extractable nuclear antigen (ENA) profile was studied in both groups.

**RESULTS:** No statistically significant difference was found in ANA, ENA profile, anti-CCP, and RF positivity between the groups ( $p>0.05$ ). There was no relationship between the autoantibodies and the clinical status in patients with FMF. MEFV gene mutations were identified in 98% of the FMF patients.

**CONCLUSION:** In conclusion, autoantibody positivity is similar to the healthy population in FMF. Although MEFV mutations affect clinical course in other autoantibody mediated diseases, it is not related to autoantibody formation in FMF.

PMID: 23149636 [Indexed for MEDLINE]

2551. J Coll Physicians Surg Pak. 2012 Nov;22(11):737-9. doi: 11.2012/JCPSP.737739.

Colchicine and NSAID combination causing acute kidney injury.

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Colchicine is used mainly for the treatment of gout and familial mediterranean fever. The use of colchicine is limited by its toxicity, and colchicine overdose is associated with a high mortality rate. Herein, we are reporting a young man who presented to the emergency department after ingesting 13.5 mg of colchicine and 1200 mg of aceclofenac (non-steroid anti-inflammatory drug) for deliberate self harm. He developed acute kidney injury, metabolic acidosis, and bradycardia after admission. A combination effect of non-steroid anti-inflammatory drug and colchicines was responsible for this event.

DOI: 11.2012/JCPSP.737739

PMID: 23146861 [Indexed for MEDLINE]

2552. Clin Radiol. 2013 Apr;68(4):371-5. doi: 10.1016/j.crad.2012.08.030. Epub 2012 Nov 10.

Exertional muscle pain in familial Mediterranean fever patients evaluated by MRI and 31P magnetic resonance spectroscopy.

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AIM: To evaluate the effect of physical activity on the structural, morphological, and metabolic characteristics of the gastrocnemius muscle in

familial Mediterranean fever (FMF) patients, utilizing quantitative (31)P magnetic resonance spectroscopy (MRS), in order to elucidate the mechanism of their exertional leg pain.

**MATERIALS AND METHODS:** Eleven FMF patients suffering from exertional leg pain (eight male, three female; mean age 33 years) and six healthy individuals (three male, three female; mean age 39 years) constituted the control group. All of the participants underwent magnetic resonance imaging (MRI) and non-selective (31)P MRS (3 T) of the leg muscles before and after graded exercise on a treadmill.

Phosphocreatine (PCr):inorganic phosphate (Pi), PCr:adenosine triphosphate (ATP) ratios and the intracellular pH of the leg muscles were measured using (31)P MRS.

**RESULTS:** For both groups, normal muscle mass with no signal alterations was observed on the MRI images after exercise. The normal range of pre- and post-exercise MRS muscle parameters was observed in both groups. However, the intracellular pH post-exercise, was significantly higher (less acidic) in the FMF group compared to the control group [pH (FMF) =  $7.03 \pm 0.02$ ; pH (control)  $7.00 \pm 0.02$ ;  $p < 0.0006$ ].

**CONCLUSIONS:** The finding of a less prominent, post-exercise acidification of the gastrocnemius muscle in this FMF patient group suggests a forme fruste of glycogenosis. This preliminary observation should be further investigated in a future, larger-scale study.

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DOI: 10.1016/j.crad.2012.08.030

PMID: 23146552 [Indexed for MEDLINE]

2553. Nature. 2012 Dec 6;492(7427):123-7. doi: 10.1038/nature11588. Epub 2012 Nov 11.

The calcium-sensing receptor regulates the NLRP3 inflammasome through Ca<sup>2+</sup> and cAMP.

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Comment in

Nat Rev Immunol. 2013 Jan;13(1):1.

Mutations in the gene encoding NLRP3 cause a spectrum of autoinflammatory diseases known as cryopyrin-associated periodic syndromes (CAPS). NLRP3 is a key component of one of several distinct cytoplasmic multiprotein complexes (inflammasomes) that mediate the maturation of the proinflammatory cytokine interleukin-1 $\beta$  (IL-1 $\beta$ ) by activating caspase-1. Although several models for inflammasome activation, such as K(+) efflux, generation of reactive oxygen species and lysosomal destabilization, have been proposed, the precise molecular mechanism of NLRP3 inflammasome activation, as well as the mechanism by which CAPS-associated mutations activate NLRP3, remain to be elucidated. Here we show that the murine calcium-sensing receptor (CASR) activates the NLRP3 inflammasome, mediated by increased intracellular Ca(2+) and decreased cellular cyclic AMP (cAMP). Ca(2+) or other CASR agonists activate the NLRP3 inflammasome in the absence of exogenous ATP, whereas knockdown of CASR reduces inflammasome activation in response to known NLRP3 activators. CASR activates the NLRP3 inflammasome through phospholipase C, which catalyses inositol-1,4,5-trisphosphate production and thereby induces release of Ca(2+) from endoplasmic reticulum stores. The increased cytoplasmic Ca(2+) promotes the assembly of inflammasome components, and intracellular Ca(2+) is required for spontaneous inflammasome activity in cells from patients with CAPS. CASR stimulation also results in reduced intracellular cAMP, which independently activates the NLRP3 inflammasome. cAMP binds to NLRP3 directly to inhibit inflammasome assembly, and downregulation of cAMP relieves this inhibition. The binding affinity of cAMP for CAPS-associated mutant NLRP3 is substantially lower than for wild-type NLRP3, and the uncontrolled mature IL-1 $\beta$  production from CAPS patients' peripheral blood mononuclear cells is attenuated by increasing cAMP. Taken together, these findings indicate that Ca(2+) and cAMP are two key molecular regulators of the NLRP3 inflammasome that have critical roles in the molecular pathogenesis of CAPS.

DOI: 10.1038/nature11588

PMCID: PMC4175565

PMID: 23143333 [Indexed for MEDLINE]

[Update: Behçet's disease].

[Article in German]

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Behçet's disease (BD) is now mentioned in the latest Chapel Hill nomenclature of vasculitides and is classified under the variable vessel vasculitides (VVV).

Pathogenetically, a new classification among the so-called mixed-pattern diseases between classical polygenic autoinflammatory disorders and autoimmune diseases is being discussed. The genetic association with HLA-B51 is undisputed and an association with HLA-A26 as well as with polymorphisms in the IL-10 and IL23R-IL12RB2 genes have recently been described. Increasingly, a participation of IL-17 in the pathogenesis of BD is assumed. Therapeutically, the EULAR recommendations are still applicable. Interferon-alpha can be discontinued for severe ocular BD in remission without further relapses. Infliximab can be switched to adalimumab effectively and recent case series show an efficacy of IL-1 antagonists, tocilizumab and rituximab for BD.

DOI: 10.1007/s00393-012-0984-x

PMID: 23138553 [Indexed for MEDLINE]

2555. Gut Microbes. 2013 Jan-Feb;4(1):84-8. doi: 10.4161/gmic.22822. Epub 2012 Nov 8.

Targeting aberrant colon cancer-specific DNA methylation with lipoteichoic acid-deficient *Lactobacillus acidophilus*.

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Pathogenic autoinflammatory responses triggered by dysregulated microbial interactions may lead to intestinal disorders and malignancies. Previously, we demonstrated that a lipoteichoic acid (LTA)-deficient *Lactobacillus acidophilus* strain, NCK2025, ameliorated inflammation-induced colitis, significantly reduced the number of polyps in a colonic polyposis cancer model and restored physiological homeostasis in both cases. Nonetheless, the regulatory signals delivered by NCK2025 to reprogram the gastrointestinal microenvironment, and thus resist colonic cancer progression, remain unknown. Accumulating evidence suggest that epigenetic changes, in the presence and absence of pathogenic inflammation, can result in colorectal cancer (CRC). To test possible epigenetic modifications induced by NCK2025, the expression of epigenetically regulated, CRC-associated genes was measured with and without bacterial treatment. In vivo and in vitro, NCK2025 enhanced the expression of tumor suppressor genes that may regulate CRC development. Therefore, differential epigenetic regulation of CRC-related genes by NCK2025 represents a potential therapy against colitis-associated and sporadic CRC.

DOI: 10.4161/gmic.22822

PMCID: PMC3555892

PMID: 23137966 [Indexed for MEDLINE]

2556. Scand J Rheumatol. 2013;42(1):52-8. doi: 10.3109/03009742.2012.714796. Epub 2012 Nov 8.

Familial Mediterranean fever in Germany: clinical presentation and amyloidosis risk.

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OBJECTIVE: To characterize patients with familial Mediterranean fever (FMF) with and without AA amyloidosis living in Germany.

**METHOD:** Clinical and genetic data from 64 FMF patients were analysed for amyloidosis risk factors.

**RESULTS:** Fifty-five patients (85%) were of Turkish or Armenian origin. Thirty-one patients (48%) developed FMF symptoms before the age of 16 years. Sixteen patients (26%) became symptomatic after age 20. Symptoms reported were peritonitis (95%), fever (78%), pleuritis (59%), arthralgia (60%), arthritis (32%), erysipelas-like erythema (23%), and vasculitis (8%). FMF diagnosis was delayed for a median of 8.0 years. Genetic analysis confirmed M694V as the most prevalent Mediterranean fever (MEFV) gene mutation in 46 out of 59 patients (78%). M694V homozygosity was associated with an earlier FMF onset (median age 5.5 years,  $p = 0.0001$ ) and a higher prevalence of peritonitis ( $p = 0.007$ ) and pleuritis ( $p = 0.0007$ ) compared to patients without an M694V mutation. AA amyloidosis was detected in 16 patients (25%) at a median age of 36.5 years and tended to be associated with a higher age at disease onset ( $p = 0.062$ ) and a higher FMF activity score ( $p = 0.093$ ). AA amyloidosis was significantly associated with a higher age at FMF diagnosis ( $p = 0.0022$ ).

**CONCLUSIONS:** Clinical symptoms of FMF-affected migrants living in Germany resemble those observed in their home country. In particular, patients with an onset of FMF symptoms after age 20 and a later FMF diagnosis have a high risk of AA amyloidosis. Symptomatic patients who originate from countries with a higher FMF prevalence should be screened for FMF and proteinuria.

DOI: 10.3109/03009742.2012.714796

PMID: 23137073 [Indexed for MEDLINE]

2557. Ann Rheum Dis. 2013 Jun;72(6):1044-52. doi: 10.1136/annrheumdis-2012-201952. Epub 2012 Oct 31.

Autophagy contributes to inflammation in patients with TNFR-associated periodic syndrome (TRAPS).

Bachetti T(1), Chiesa S, Castagnola P, Bani D, Di Zanni E, Omenetti A, D'Ossualdo A, Fraldi A, Ballabio A, Ravazzolo R, Martini A, Gattorno M, Ceccherini I.

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Comment in



**OBJECTIVES:** Tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is caused by TNFRSF1A mutations, known to induce intracellular retention of the TNF $\alpha$  receptor 1 (TNFR1) protein, defective TNF $\alpha$ -induced apoptosis, and production of reactive oxygen species. As downregulation of autophagy, the main cellular pathway involved in insoluble aggregate elimination, has been observed to increase the inflammatory response, we investigated whether it plays a role in TRAPS pathogenesis.

**METHODS:** The possible link between TNFRSF1A mutations and inflammation in TRAPS was studied in HEK-293T cells, transfected with expression constructs for wild-type and mutant TNFR1 proteins, and in monocytes derived from patients with TRAPS, by investigating autophagy function, NF- $\kappa$ B activation and interleukin (IL)-1 $\beta$  secretion.

**RESULTS:** We found that autophagy is responsible for clearance of wild-type TNFR1, but when TNFR1 is mutated, the autophagy process is defective, probably accounting for mutant TNFR1 accumulation as well as TRAPS-associated induction of NF- $\kappa$ B activity and excessive IL-1 $\beta$  secretion, leading to chronic inflammation. Autophagy inhibition due to TNFR1 mutant proteins can be reversed, as demonstrated by the effects of the antibiotic geldanamycin, which was found to rescue the membrane localisation of mutant TNFR1 proteins, reduce their accumulation and counteract the increased inflammation by decreasing IL-1 $\beta$  secretion.

**CONCLUSIONS:** Autophagy appears to be an important mechanism in the pathogenesis of TRAPS, an observation that provides a rationale for the most effective therapy in this autoinflammatory disorder. Our findings also suggest that autophagy could be proposed as a novel therapeutic target for TRAPS and possibly other similar diseases.

DOI: 10.1136/annrheumdis-2012-201952

PMID: 23117241 [Indexed for MEDLINE]

2558. Medicine (Baltimore). 2012 Nov;91(6):337-43. doi: 10.1097/MD.0b013e318277cf75.

Familial Mediterranean fever in Japan.

Migita K(1), Uehara R, Nakamura Y, Yasunami M, Tsuchiya-Suzuki A, Yazaki M, Nakamura A, Masumoto J, Yachie A, Furukawa H, Ishibashi H, Ida H, Yamazaki K,

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Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease that is prevalent in Mediterranean populations. While it is considered a rare disease in the rest of world, a significant number of FMF patients have been reported in East Asia, including Japan. Our aim was to determine the prevalence of FMF in Japan and elucidate the clinical and genetic features of Japanese patients. A primary nationwide survey of FMF was conducted between January and December 2009. Hospitals specializing in pediatrics and hospitals with pediatric, internal medicine, and rheumatology/allergy departments were asked to report all patients with FMF during the survey year. The estimated total number of Japanese FMF patients was 292 (95% confidence interval, 187-398 people). We evaluated the clinical and genetic profiles of Japanese patients from the data obtained in a secondary survey of 134 FMF patients. High-grade fever was observed in 95.5%, chest pain (pleuritis symptoms) in 36.9%, abdominal pain (peritonitis symptoms) in 62.7%, and arthritis in 31.3%. Of the patients profiled, 25.4% of patients experienced their first attack before 10 years of age, 37.3% in their teens, and 37.3% after age 20 years. Colchicine was effective in 91.8% of patients at a relatively low dose (mean dose,  $0.89 \pm 0.45$  mg/d). AA amyloidosis was confirmed in 5 patients (3.7%). Of the 126 patients studied, 109 (86.5%) were positive for 1 or more genetic mutations and 17 (13.5%) had no mutation detected. Common Mediterranean fever gene (MEFV) mutations were E148Q/M694I (19.8%) and M694I/normal (12.7%). The differences in the prevalence of peritonitis, pleuritis, and a family history of FMF were statistically significant between FMF patients with MEFV exon 10 mutations compared with those without exon 10 mutations. In conclusion, a significant number of patients with FMF exist in Japan. Although Japanese patients with FMF are clinically or genetically different from Mediterranean patients, the delay in diagnosis is an issue that should be resolved.

DOI: 10.1097/MD.0b013e318277cf75

PMID: 23111802 [Indexed for MEDLINE]

Oct 4.

Mevalonate kinase deficiency, a metabolic autoinflammatory disease.

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Mevalonate kinase deficiency is a rare autosomal recessive inborn error of metabolism with an autoinflammatory phenotype. In this review we discuss its pathogenesis, clinical presentation and treatment. Mutations in both copies of the MVK-gene lead to a block in the mevalonate pathway. Interleukin-1 $\beta$  mediates the inflammatory phenotype. Shortage of a non-sterol isoprenoid product of the mevalonate pathway, Geranylgeranylpyrophosphate leads to aberrant activation of the small GTPase Rac1, and inflammasome activation. The clinical phenotype ranges widely, depending on the severity of the enzyme defect. All patients show recurrent fevers, lymphadenopathy and high acute phase proteins. Severely affected patients have antenatal disease onset, dysmorphic features, growth retardation, cognitive impairment and progressive ataxia. Diagnosis relies on mutation analysis of the MVK-gene. There is no evidence based therapy. IL-1 blockade is usually effective. Severe cases require allogeneic stem cell transplantation. Targeted therapies are needed.

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DOI: 10.1016/j.clim.2012.09.011

PMID: 23110805 [Indexed for MEDLINE]

2560. QJM. 2015 Jun;108(6):497-501. doi: 10.1093/qjmed/hcs208. Epub 2012 Oct 29.

Mullins' syndrome: a new gammopathy-related autoinflammatory syndrome resistant to anakinra.

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DOI: 10.1093/qjmed/hcs208

PMCID: PMC4446788

PMID: 23108029 [Indexed for MEDLINE]

2561. Exp Biol Med (Maywood). 2012 Oct;237(10):1117-22. doi: 10.1258/ebm.2012.012151. Epub 2012 Oct 26.

The periprosthetic capsule and connective tissue diseases: a piece in the puzzle of autoimmune/autoinflammatory syndrome induced by adjuvants.

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Breast prostheses have been criticized for being responsible for triggering systemic autoimmune disease. The presence of breast implants causes a natural foreign body reaction characterized by the infiltration of macrophages and T-cells. Using PubMed, Medline and eMedicine, we performed a systematic literature review on the stages of periprosthetic capsule formation and cells involved in order to understand which immunological pathways could be responsible for giving rise to, and the development of, connective tissue disease such as systemic sclerosis. We focused on the relationship between tissue growth factor- $\beta$ , interleukin (IL)-1, IL-6 and T helper 17 or T regulatory cells, as well as on their effects on the different steps of capsular tissue formation. A disturbance in the modulation of these key cytokines may be responsible, in susceptible individuals, for a perpetuation of the inflammatory reaction which can locally lead to capsular contracture and at the systemic level may contribute to triggering autoimmune diseases.

DOI: 10.1258/ebm.2012.012151

PMID: 23104503 [Indexed for MEDLINE]

2562. Nat Immunol. 2012 Dec;13(12):1178-86. doi: 10.1038/ni.2457. Epub 2012 Oct 28.

Immunodeficiency, autoinflammation and amylopectinosis in humans with inherited HOIL-1 and LUBAC deficiency.

Boisson B(1), Laplantine E, Prando C, Giliani S, Israelsson E, Xu Z, Abhyankar A, Israël L, Trevejo-Nunez G, Bogunovic D, Cepika AM, MacDuff D, Chrabieh M, Hubeau M, Bajolle F, Debré M, Mazzolari E, Vairo D, Agou F, Virgin HW, Bossuyt X, Rambaud C, Facchetti F, Bonnet D, Quartier P, Fournet JC, Pascual V, Chaussabel D, Notarangelo LD, Puel A, Israël A, Casanova JL, Picard C.

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Comment in

Nat Immunol. 2012 Dec;13(12):1133-5.

We report the clinical description and molecular dissection of a new fatal human inherited disorder characterized by chronic autoinflammation, invasive bacterial infections and muscular amylopectinosis. Patients from two kindreds carried biallelic loss-of-expression and loss-of-function mutations in HOIL1 (RBCK1), a component of the linear ubiquitination chain assembly complex (LUBAC). These mutations resulted in impairment of LUBAC stability. NF- $\kappa$ B activation in response to interleukin 1 $\beta$  (IL-1 $\beta$ ) was compromised in the patients' fibroblasts. By contrast, the patients' mononuclear leukocytes, particularly monocytes, were hyper-responsive to IL-1 $\beta$ . The consequences of human HOIL-1 and LUBAC deficiencies for IL-1 $\beta$  responses thus differed between cell types, consistent with the unique association of autoinflammation and immunodeficiency in these patients. These data suggest that LUBAC regulates NF- $\kappa$ B-dependent IL-1 $\beta$  responses differently in different cell types.

DOI: 10.1038/ni.2457

PMCID: PMC3514453

PMID: 23104095 [Indexed for MEDLINE]

2563. J Am Acad Dermatol. 2013 Apr;68(4):624-631. doi: 10.1016/j.jaad.2012.09.025. Epub

2012 Oct 24.

Dermatitis as a characteristic phenotype of a new autoinflammatory disease associated with NOD2 mutations.

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**OBJECTIVES:** We sought to characterize a new category of autoinflammatory disease associated with nucleotide-binding oligomerization domain 2 (NOD2) gene mutations.

**METHODS:** A total of 22 patients were identified, inclusive of those reported previously. All had autoinflammatory phenotypes and NOD2 gene mutations that were prospectively studied between January 2009 and February 2012.

**RESULTS:** All 22 patients were non-Jewish whites (13 women and 9 men). The mean age at diagnosis was 40.1 years (range 17-72), with a mean disease duration of 4.7 years (range 1-13). Three female patients were siblings. Common clinical features were weight loss (13/22), episodic self-limiting fever (13/22), dermatitis (19/22), and inflammatory polyarthritis/polyarthralgia (20/22).

Gastrointestinal symptoms occurred in 13 patients, sicca-like symptoms in 9, and recurrent chest pain in 5. All patients carried the NOD2 gene mutations, with the intervening sequence 8(+158) variant in 21 and the R702W variant in 8.

**LIMITATIONS:** The NOD2 allelic frequency may need to be examined in a larger population with systemic autoimmune diseases.

**CONCLUSIONS:** The characteristic clinical phenotype, notably dermatitis, coupled with certain NOD2 variants constitutes a new autoinflammatory disease entity, which we have named as NOD2-associated autoinflammatory disease.

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DOI: 10.1016/j.jaad.2012.09.025

PMID: 23102769 [Indexed for MEDLINE]

2564. Insights Imaging. 2011 Oct;2(5):501-13. doi: 10.1007/s13244-011-0115-2. Epub 2011 Jul 13.

Small bowel MRI in adult patients: not just Crohn's disease-a tutorial.

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**OBJECTIVES:** To provide an overview of less well-known small bowel and mesenteric diseases found at small bowel magnetic resonance (MR) enterography/enteroclysis and to review the imaging findings. MR enterography and enteroclysis are important techniques for evaluation of small bowel diseases. In most centres these techniques are primarily used in Crohn's disease, and most radiologists are familiar with these MRI findings. However, the knowledge of findings in other diseases is often sparse, including diseases that may cause similar clinical symptoms to those of Crohn's disease.

**METHODS:** We present a spectrum of less common and less well-known bowel and mesenteric diseases (e.g. internal hernia, intussusception, neuroendocrine tumour) from our small bowel MR database of over 2,000 cases.

**RESULTS:** These diseases can be found in patients referred for bowel obstruction, abdominal pain or rectal blood loss. Further, in patients with (or suspected to have) Crohn's disease, some of these diseases (e.g. neuroendocrine tumour, familial Mediterranean fever) may mislead radiologists to erroneously diagnose active Crohn's disease.

**CONCLUSION:** Radiologists should be familiar with diseases affecting the small bowel other than Crohn's disease, including diseases that may mimic Crohn's disease.

DOI: 10.1007/s13244-011-0115-2

PMCID: PMC3289029

PMID: 23100018

2565. Dig Dis. 2012;30 Suppl 1:74-7. doi: 10.1159/000341129. Epub 2012 Oct 11.

Toll-like receptors in gastrointestinal diseases.

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Innate immune cells - and many other cells - express evolutionarily conserved, germline-encoded receptors that recognize seemingly pathogen-derived ligands (also termed pathogen-associated molecular patterns), thereby allowing the host to perceive infection. Although they were the first to be discovered, Toll-like receptors (TLRs) are not the only pattern recognition receptors. TLRs are unlikely to discriminate between commensals and pathogens in the gut microbiota. There is, however, increasing evidence that TLRs shape intestinal function. In addition, certain bacteria appear to drive either Th1/Th17 proinflammatory immune responses, or T regulatory responses. Furthermore, TLRs appear to trigger 'sterile' autoinflammatory responses by sensing metabolically altered host (self) components.

Copyright © 2012 S. Karger AG, Basel.

DOI: 10.1159/000341129

PMID: 23075872 [Indexed for MEDLINE]

2566. Front Immunol. 2012 Oct 9;3:315. doi: 10.3389/fimmu.2012.00315. eCollection 2012.

IL-1 family cytokines trigger sterile inflammatory disease.

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Inflammation plays vital roles in protective responses against pathogens and tissue repair, however, improper resolution of inflammatory networks is centrally involved in the pathogenesis of many acute and chronic diseases. Extensive advances have been made in recent years to define the inflammatory processes that are required for pathogen clearance, however, in comparison, less is known about the regulation of inflammation in sterile settings. Over the past decade non-communicable chronic diseases that are potentiated by sterile inflammation have replaced infectious diseases as the major threat to global human health. Thus, improved understanding of the sterile inflammatory process has emerged as one of the most important areas of biomedical investigation during our time. In this review we highlight the central role that interleukin-1 family cytokines play in sterile inflammatory diseases.

DOI: 10.3389/fimmu.2012.00315

PMCID: PMC3466588

PMID: 23087690

2567. Ann Rheum Dis. 2013 Mar;72(3):410-3. doi: 10.1136/annrheumdis-2012-201818. Epub 2012 Oct 20.

Efficacy of anti-IL-1 treatment in Majeed syndrome.

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**BACKGROUND AND OBJECTIVE:** Majeed syndrome is an autosomal recessive disorder characterised by the triad of chronic recurrent multifocal osteomyelitis, congenital dyserythropoietic anaemia and a neutrophilic dermatosis that is caused by mutations in LPIN2. Long-term outcome is poor. This is the first report detailing the treatment of Majeed syndrome with biological agents and demonstrates clinical improvement with IL-1blockade.

**METHODS:** We describe the clinical presentation, genetic analysis, cytokine profiles and response to biological therapy in two brothers with Majeed syndrome.

**RESULTS:** Both boys were homozygous for a novel 2-base pair deletion in LPIN2 (c.1312\_1313delCT; p.Leu438fs+16X), confirming the diagnosis. Their bone disease and anaemia were refractory to treatment with corticosteroids. Both siblings had

elevated proinflammatory cytokines in their serum, including tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ), however a trial of the TNF inhibitor etanercept resulted in no improvement. IL-1 inhibition with either a recombinant IL-1 receptor antagonist (anakinra) or an anti-IL-1 $\beta$  antibody (canakinumab) resulted in dramatic clinical and laboratory improvement.

**CONCLUSIONS:** The differential response to treatment with TNF- $\alpha$  or IL-1 blocking agents sheds light into disease pathogenesis; it supports the hypothesis that Majeed syndrome is an IL-1 $\beta$  dependent autoinflammatory disorder, and further underscores the importance of IL-1 in sterile bone inflammation.

DOI: 10.1136/annrheumdis-2012-201818

PMCID: PMC3660147

PMID: 23087183 [Indexed for MEDLINE]

2568. Ann Rheum Dis. 2013 Oct;72(10):1634-8. doi: 10.1136/annrheumdis-2012-202192. Epub 2012 Oct 19.

Sustained efficacy of the monoclonal anti-interleukin-1 beta antibody canakinumab in a 9-month trial in Schnitzler's syndrome.

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**OBJECTIVES:** Schnitzler's syndrome is a chronic disabling autoinflammatory disorder, characterised by chronic urticaria, paraproteinemia and systemic inflammation. The interleukin (IL) 1 receptor antagonist anakinra is a very effective treatment, but requires daily injection and blocks both IL-1 $\alpha$  and IL-1 $\beta$ . Canakinumab is a selective human monoclonal anti-IL-1 $\beta$  antibody with a long half-life. We investigated the long-term efficacy and safety of canakinumab in Schnitzler's syndrome.

**METHODS:** In an open-label, single-treatment arm trial, eight patients with Schnitzler's syndrome received monthly injections with 150 mg canakinumab subcutaneously for 6 months, followed by a 3-month observation period. Primary outcome was complete or clinical remission at day 14. Secondary outcome measures

included inflammatory markers, quality of life, time to relapse, safety and tolerability.

**RESULTS:** After stopping anakinra, patients developed moderate to severe clinical symptoms. Canakinumab induced complete or clinical remission at day 14 in all eight patients. Median C-reactive protein concentrations decreased from 169 mg/l at baseline to less than 10 mg/l on day 14 and remained low or undetectable. One patient discontinued participation on day 39 because of return of symptoms while all others remained in complete or clinical remission during the 6-month treatment period. Relapse after last canakinumab dose occurred within 3 months in four patients. For two patients, remission continued several months post-study. Five patients reported at least one adverse event, predominantly mild upper respiratory tract infections. One patient died in a traffic accident.

**CONCLUSIONS:** In this 9-month study, monthly 150 mg canakinumab injection was an effective and well-tolerated treatment for Schnitzler's syndrome. Our data demonstrate that IL-1 $\beta$  plays a pivotal role in this disease. CLINICALTRIALS.GOV: NCT01276522.

DOI: 10.1136/annrheumdis-2012-202192

PMID: 23087179 [Indexed for MEDLINE]

2569. Mod Rheumatol. 2013 May;23(3):425-9. doi: 10.1007/s10165-012-0769-8. Epub 2012 Oct 20.

Guidance on the use of canakinumab in patients with cryopyrin-associated periodic syndrome in Japan.

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Cryopyrin-associated periodic syndrome (CAPS) is an orphan disease with incidence of about one in 1,000,000 persons. This autoinflammatory disease develops in the neonatal period or early childhood, with various inflammatory symptoms occurring repeatedly throughout the patient's lifetime. It is caused by abnormality of the NLRP3 protein which mediates the intracellular signal transduction mechanism of

inflammatory processes, resulting in continuous overproduction of interleukin (IL)-1 $\beta$ , which induces chronic inflammation and progressive tissue damage. Definitive diagnosis of CAPS is difficult, and treatment has also been difficult because of a lack of effective medications in Japan. Clinical studies of human anti-human IL-1 $\beta$  monoclonal antibody (canakinumab) treatment were conducted in Japan, and approval was granted for therapeutic use of canakinumab for CAPS in September 2011. Similar to other biological drugs, canakinumab is clinically highly effective. However, sufficient attention to the method of use and adverse drug reactions is necessary. This guidance describes the use of canakinumab in Japan for CAPS in relation to exclusion criteria, method of use, evaluation criteria, and adverse drug reactions.

DOI: 10.1007/s10165-012-0769-8

PMID: 23085882 [Indexed for MEDLINE]

2570. J Med Case Rep. 2012 Oct 18;6:354. doi: 10.1186/1752-1947-6-354.

Suppurative necrotizing granulomatous lymphadenitis in adult-onset Still's disease: a case report.

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**INTRODUCTION:** Lymphadenopathy is found in about 65% of patients with adult-onset Still's disease and is histologically characterized by an intense, paracortical immunoblastic hyperplasia. Adult-onset Still's disease has not been previously described as an etiology of suppurative necrotizing granulomatous lymphadenitis.

**CASE PRESENTATION:** We describe a 27-year-old Greek man who manifested prolonged fever, abdominal pain, increased inflammatory markers, episodic skin rash and mesenteric lymphadenopathy histologically characterized by necrotizing granulomatous adenitis with central suppuration. Disease flares were characterized by systemic inflammatory response syndrome with immediate clinico-laboratory response to corticosteroids but the patient required prolonged administration of methylprednisolone at a dose of above 12mg/day for disease

control. After an extensive diagnostic work-up, which ruled out any infectious, malignant, rheumatic or autoinflammatory disease the patient was diagnosed as having adult-onset Still's disease. The patient is currently treated with 4mg of methylprednisolone, 100mg of anakinra daily and methotrexate 7.5mg for two consecutive days per week and exerts full disease remission for six months.

**CONCLUSION:** To the best of our knowledge this is the first report of suppurative necrotizing granulomatous lymphadenitis attributed to adult-onset Still's disease. This case indicates that the finding of a suppurative necrotizing granulomatous lymphadenitis should not deter the consideration of adult-onset Still's disease as a potential diagnosis in a compatible clinical context; however, the exclusion of other diagnoses is a prerequisite.

DOI: 10.1186/1752-1947-6-354

PMCID: PMC3492103

PMID: 23078628

2571. J Obstet Gynaecol. 2012 Nov;32(8):756-9. doi: 10.3109/01443615.2012.698667.

Pregnancy outcome in women with familial Mediterranean fever.

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Author information:

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This study comprised 74 infertile patients with familial Mediterranean fever (FMF), among which 26 women became pregnant. Pregnancies were followed according to the standard antenatal follow-up protocol of high-risk pregnancies. The principal outcome measures were the termination of pregnancy and its upshot. This study comprised 74 infertile patients with FMF. Of the cases, 12 (16.22%) had antiphospholipid syndrome (APS); 16 patients (21.62%) had a history of previous abdominal/pelvic surgery, which might have been contributing to delay of conception; 66 patients (89.18%) were on drug therapy by corticosteroids, colchicines and other agents. A total of 10/22 patients were delivered by caesarean section for complicated pregnancies. Six of the newborns were positive for the MEFV gene. Favourable pregnancy outcome occurs in patients with FMF treated with colchicine before and after pregnancy. Neonatal outcome was similar to that expected in the general population.

DOI: 10.3109/01443615.2012.698667  
PMID: 23075349 [Indexed for MEDLINE]

2572. Ann Intern Med. 2012 Oct 16;157(8):l-44. doi:  
10.7326/0003-4819-157-8-201210160-00001.

Summaries for patients. Therapy for patients with familial Mediterranean fever when colchicine is not enough or is not tolerated.

[No authors listed]

DOI: 10.7326/0003-4819-157-8-201210160-00001  
PMID: 23070503 [Indexed for MEDLINE]

2573. Ann Intern Med. 2012 Oct 16;157(8):533-41. doi:  
10.7326/0003-4819-157-8-201210160-00003.

Riloncept for colchicine-resistant or -intolerant familial Mediterranean fever: a randomized trial.

Hashkes PJ(1), Spalding SJ, Giannini EH, Huang B, Johnson A, Park G, Barron KS, Weisman MH, Pashinian N, Reiff AO, Samuels J, Wright DA, Kastner DL, Lovell DJ.

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Erratum in

Ann Intern Med. 2014 Feb 18;160(4):291-2.

**BACKGROUND:** Currently, there is no proven alternative therapy for patients with familial Mediterranean fever (FMF) that is resistant to or intolerant of colchicine. Interleukin-1 is a key proinflammatory cytokine in FMF.

**OBJECTIVE:** To assess the efficacy and safety of riloncept, an interleukin-1 decoy receptor, in treating patients with colchicine-resistant or -intolerant FMF.

DESIGN: Randomized, double-blind, single-participant alternating treatment study. (ClinicalTrials.gov number: NCT00582907).

SETTING: 6 U.S. sites.

PATIENTS: Patients with FMF aged 4 years or older with 1 or more attacks per month.

INTERVENTION: One of 4 treatment sequences that each included two 3-month courses of rilonacept, 2.2 mg/kg (maximum, 160 mg) by weekly subcutaneous injection, and two 3-month courses of placebo.

MEASUREMENTS: Differences in the frequency of FMF attacks and adverse events between rilonacept and placebo.

RESULTS: 8 males and 6 females with a mean age of 24.4 years (SD, 11.8) were randomly assigned. Among 12 participants who completed 2 or more treatment courses, the rilonacept-placebo attack risk ratio was 0.59 (SD, 0.12) (equal-tail 95% credible interval, 0.39 to 0.85). The median number of attacks per month was 0.77 (0.18 and 1.20 attacks in the first and third quartiles, respectively) with rilonacept versus 2.00 (0.90 and 2.40, respectively) with placebo (median difference, -1.74 [95% CI, -3.4 to -0.1];  $P = 0.027$ ). There were more treatment courses of rilonacept without attacks (29% vs. 0%;  $P = 0.004$ ) and with a decrease in attacks of greater than 50% compared with the baseline rate during screening (75% vs. 35%;  $P = 0.006$ ) than with placebo. However, the duration of attacks did not differ between placebo and rilonacept (median difference, 1.2 days [-0.5 and 2.4 days in the first and third quartiles, respectively];  $P = 0.32$ ). Injection site reactions were more frequent with rilonacept (median difference, 0 events per patient treatment month [medians of -4 and 0 in the first and third quartiles, respectively];  $P = 0.047$ ), but no differences were seen in other adverse events.

LIMITATION: Small sample size, heterogeneity of FMF mutations, age, and participant indication (colchicine resistance or intolerance) were study limitations.

CONCLUSION: Rilonacept reduces the frequency of FMF attacks and seems to be a treatment option for patients with colchicine-resistant or -intolerant FMF.

PRIMARY FUNDING SOURCE: U.S. Food and Drug Administration, Office of Orphan Products Development.

DOI: 10.7326/0003-4819-157-8-201210160-00003

PMID: 23070486 [Indexed for MEDLINE]

## Oral manifestations of systemic autoimmune and inflammatory diseases: diagnosis and clinical management.

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**CONTEXT:** Systemic autoimmune and inflammatory diseases often manifest oral lesions in their earliest stages, and early diagnosis, which may be spurred by a dental examination, is key for improved outcomes. After systemic diagnosis, oral lesions benefit from specialized care by dentists in collaboration with the medical team. This review aims to educate dental clinicians about the most relevant systemic autoimmune and inflammatory conditions with accompanying oral lesions, their implications for health, and management strategies supported by the biomedical literature and clinical experience. Ulcerative conditions including Behcet and Crohn diseases are discussed, along with rheumatic conditions including Sjögren syndrome, lupus erythematosus, and rheumatoid arthritis.

**EVIDENCE ACQUISITION:** Evidence was accumulated through PubMed searches using pertinent keywords for each subsection. References were reviewed and original publications examined to verify the accuracy of the information. We focused on evidence included in current reviews and randomized trials. Recommendations were supported by multiple studies and consensus expert opinion.

**EVIDENCE SYNTHESIS:** Disease phenotypes described and clinical recommendations were synthesized from best-quality evidence available for each disease. Efforts were made to describe evidence selection within each disease section.

**CONCLUSIONS:** Dentists play an important role in the early detection and multidisciplinary medical management of complex autoimmune diseases. It is important to recognize prevalent medical and dental issues and special needs of patients with autoimmune conditions. The management of many inflammatory conditions is similar, and often begins with the use of topical steroids, analgesics, and antimicrobial treatments, in addition to careful attention to oral hygiene and appropriate fluoride usage. In this brief review, we aim to discuss the presentation/prevalence, diagnosis, and treatment of oral manifestations encountered in autoimmune, autoinflammatory and systemic chronic



inflammatory diseases. Systemic autoimmune conditions are estimated to affect 5% to 8% of Americans.(1) Oral manifestations are encountered with high frequency, and are often the first clinical signs or symptoms of the general disease. Optimal management of complex autoimmune diseases requires a multidisciplinary medical team including dentists to care for lesions of the oral cavity. The dental practitioner may be asked to play a primary role in the diagnosis of such conditions and to participate with other health professionals working together to achieve effective clinical management. To aid in this process, we discuss in this article the current general knowledge of systemic autoimmune conditions that present with prevalent oral manifestations. The focus is on the diagnosis and management of the oral component of each disease. Importantly, whereas the etiology and pathogenesis and systemic clinical presentation may vary, presentation in the oral cavity is often similar and many conditions involve oral ulcerations. For this reason, we discuss the differential diagnosis and management of the most common oral ulcerations in a general section and subsequently address individual conditions that present with oral ulcerations. Similarly, treatment of various autoimmune/inflammatory oral conditions is often common and involves modulation or suppression of the immune response locally and/or systemically and will be therefore addressed in a common section as well as individually for each disease when unique treatment regimens are recommended. We present here our general treatment recommendations based on clinical experience and literature review; however, it is critical that good clinical judgment and specifics of an individual case should determine the appropriate dental/oral medicine intervention for a specific patient.

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DOI: 10.1016/S1532-3382(12)70051-9

PMID: 23040353 [Indexed for MEDLINE]

2575. Iran J Pediatr. 2012 Mar;22(1):23-7.

Dapsone as an alternative therapy in children with familial mediterranean Fever.

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**OBJECTIVE:** Familial Mediterranean Fever is an hereditary autoinflammatory disease that presents with recurrent febrile attacks and poly serositis. Colchicine is the only known treatment in this disease. However, nearly 5-10% of patients are resistant to colchicines. There are many different modalities in colchicine resistant patients, biologic and immunosuppressive drugs being the known ones. We studied the efficacy of Dapsone as an anti inflammatory drug in children with FMF who did not tolerate colchicine well.

**METHODS:** This is a case series study in 10 patients who had FMF on the base of Tel-Hashomer criteria and did not tolerate colchicine or did not respond to it well. Patients took 2mg/kg dapsone in single dose, during 6 months.

**FINDINGS:** In four patients episodic attacks returned after 27 days, so the drug was discontinued. One patient refused to continue the study; in five patients dapsone was taken in average for 8 months and 6 days, at least for 6 months. These five patients had no episodes of attack during the following observation.

**CONCLUSION:** Dapsone could control episodic attacks of FMF in 50% of cases. It might be considered as an alternative therapy in FMF cases not responding to colchicine.

PMCID: PMC3448211

PMID: 23056855

2576. Mod Rheumatol. 2013 Sep;23(5):959-62. doi: 10.1007/s10165-012-0779-6. Epub 2012 Oct 10.

Increased frequency of MEFV gene mutations in patients with primary dysmenorrhea.

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**OBJECTIVES:** Familial Mediterranean fever (FMF) is an autoinflammatory disease characterized by recurrent attacks of fever and polyserositis and an autosomal

recessive inheritance mode. Up to 15 % of FMF patients are reported to experience perimenstrual attacks. Primary dysmenorrhea could be an incomplete abdominal attack, or patients with dysmenorrhea may have increased frequency of MEFV gene mutation carriage. Therefore, we aimed to evaluate the frequency of MEFV gene mutations in patients with dysmenorrhea.

**METHODS:** Eighty-four patients with primary dysmenorrhea attending consecutively to our gynecology department and 73 healthy female controls selected from hospital staff were included in the study, and MEFV gene mutations were analyzed.

**RESULTS:** The prevalence of total allelic variants was significantly increased in dysmenorrhea patients ( $p = 0.015$ ); analysis of individual variant rates revealed a significant increase in the frequency of MEFV gene mutations in dysmenorrhea patients compared with the control group ( $p = 0.036$ ).

**CONCLUSION:** Gynecologists and primary care physicians must be aware of FMF in the differential diagnosis of dysmenorrhea.

DOI: 10.1007/s10165-012-0779-6

PMID: 23053724 [Indexed for MEDLINE]

2577. *Pediatr Cardiol.* 2013;34(8):1989-91. doi: 10.1007/s00246-012-0532-0. Epub 2012 Oct 7.

Efficacy of an interleukin-1 $\beta$  receptor antagonist (anakinra) in idiopathic recurrent pericarditis.

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Comment in

*Pediatr Cardiol.* 2013 Jun;34(5):1293-4.

Pericarditis may recur in up to 30 % of adult patients, but recurrent pericarditis is a rare disease in childhood. The etiology of the initial attack and the causes of recurrences often remain unknown. Recurrent pericarditis is accompanied by a high morbidity rate and may represent a challenge to the clinician due to problems in management. Therapeutic strategies are not specific

and include nonsteroidal antiinflammatory drugs, corticosteroids, immunosuppressive drugs, colchicine, and pericardiectomy. Controlled trials have demonstrated that colchicine can reduce the recurrent rate of pericarditis, whereas early corticosteroid therapy promotes recurrences. Anakinra, a recombinant human interleukin-1 $\beta$  receptor antagonist, is a promising new biologic agent for the treatment of autoinflammatory diseases such as cryopyrinopathies, tumor necrosis factor receptor-associated periodic syndrome, and hyperimmunoglobulinemia D with periodic fever syndrome. This report describes an 11-year-old boy successfully treated with anakinra for a steroid-dependent recurrent pericarditis unresponsive to conventional treatment.

DOI: 10.1007/s00246-012-0532-0

PMID: 23052671 [Indexed for MEDLINE]

2578. Eur J Pediatr. 2013 Jan;172(1):91-8. doi: 10.1007/s00431-012-1844-z. Epub 2012 Oct 5.

Plasminogen activator inhibitor-1 gene polymorphism in Iranian Azeri Turkish patients with FMF disease and its association with amyloidosis.

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Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by intermittent episodes of fever with serositis, arthritis, or erisiplemia. Plasminogen activator inhibitor 1 (PAI-1) is a key element in the inhibition of fibrinolysis by inactivating tissue-type and urokinase-type plasminogen activators. We evaluated the association of PAI-1 -675 4G/5G polymorphism with the severity of FMF disease. For this purpose, 89 FMF patients with M694V homozygous mutation and 95 healthy controls from Iranian Azeri Turks were selected. Detection of this polymorphism was performed by polymerase chain reaction using allele-specific primers. No significant association was found between patients and control group. However, these data showed that FMF patients with M694V homozygous mutation carrying 4G/4G genotype have a reduced risk for development of pleuritis (odds ratios (OR) 0.36; 95 % confidence intervals (CI)

0.5-0.85; P value = 0.007) compared with 5G/5G homozygotes who have increased risk for development of amyloidosis (OR = 2.46; 95 %CI = 1.29-4.72; P value = 0.001), pleuritis (OR = 2.55; 95 %CI = 1.31-4.99; P value = 0.001), and fever (OR = 4.68; 95 %CI = 2.04-10.96; P value = 0.000). Furthermore, the allelic frequency of the 4G among the patients with pleuritis was significantly low (OR = 0.5, 95 % CI = 0.27-0.92, P value = 0.008).CONCLUSION: Our data suggest a protective role for the 4G allele against pleuritis in FMF patients with M694V homozygous mutation in this cohort. More evaluation of this polymorphism may be important and require further studies.

DOI: 10.1007/s00431-012-1844-z

PMID: 23052617 [Indexed for MEDLINE]

2579. Z Rheumatol. 2012 Oct;71(8):685-96; quiz 697. doi: 10.1007/s00393-012-1012-x.

[Behçet's disease].

[Article in German]

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Behçet's disease is a systemic disorder with the histopathological correlate of leukocytoclastic vasculitis. Pathogenetically, besides a strong genetic component participation of the innate immune system and an autoinflammatory component are discussed. The disease is most common in countries along the former silk route but in Germany the disease is rare (prevalence approximately 0.6/100,000). Oral aphthous ulcers are the main symptom, followed by skin manifestations, genital ulcers and oligoarthritis of large joints. Severe manifestations, threatening quality of life and even life itself, are the gastrointestinal manifestations which often perforate, arterial, mainly pulmonary arterial aneurysms which cause life-threatening bleeding, CNS manifestations and ocular disease, which with occlusive retinal vasculitis often leads to blindness. For milder manifestations

low-dose steroids and colchicine are used, for moderate manifestations such as arthritis or ocular disease not immediately threatening visual acuity, azathioprin or cyclosporin A are combined with steroids. For severe manifestations, interferon-alpha, TNF-antagonists or cytotoxic drugs are recommended. Interleukin 1 (IL-1) antagonists are currently being examined in clinical studies.

DOI: 10.1007/s00393-012-1012-x

PMID: 23052559 [Indexed for MEDLINE]

2580. Best Pract Res Clin Rheumatol. 2012 Aug;26(4):505-33. doi: 10.1016/j.berh.2012.07.009.

Autoinflammatory syndromes and cellular responses to stress: pathophysiology, diagnosis and new treatment perspectives.

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The term 'autoinflammatory disease' was first proposed in 1999 to encompass some of the distinct clinicopathologic features of a group of monogenic conditions, characterised by recurrent episodes of inflammation, without high-titre autoantibodies or antigen-specific T cells. It was subsequently observed that several of these conditions were caused by mutations in proteins involved in the innate immune response, including, among others, components of the NLRP3 inflammasome, cytokine receptors (tumour necrosis factor receptor 1 (TNFR1)) and receptor antagonists (interleukin 1 receptor antagonist (IL-1RA)). More recently, additional mechanisms linking innate immune-mediated inflammation with a variety of cellular processes, including protein misfolding, oxidative stress and mitochondrial dysfunction, have been recognised to play a role in the pathogenesis of some monogenic autoinflammatory conditions, and also in more common diseases such as type 2 diabetes (T2D), previously perceived as a metabolic disorder, but reclassified as a chronic inflammatory condition. NLRP3 inflammasome activation is induced by islet amyloid polypeptides (IAPPs) in T2D and this condition may, in future, be more commonly treated with targeted

anti-cytokine therapies. Caspase 1 activation and release of IL-1 $\beta$ /IL-1 family members is central to the pathogenesis of many autoinflammatory syndromes, as evidenced by the effectiveness of anti-IL-1 biologics in treating these disorders. However, many patients continue to experience symptoms of chronic inflammation, and it will be necessary to translate discoveries on the immunopathology of these conditions into more effective therapies. For example, in tumour necrosis factor receptor-associated periodic fever syndrome (TRAPS), the pathogenesis may vary with each mutation and therefore future approaches to treatment of individual patients will require a more tailored approach based on genetic and functional studies.

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DOI: 10.1016/j.berh.2012.07.009

PMID: 23040364 [Indexed for MEDLINE]

2581. Clin Genet. 2013 Jul;84(1):55-9. doi: 10.1111/cge.12029. Epub 2012 Nov 7.

The M694V mutation in Armenian-Americans: a 10-year retrospective study of MEFV mutation testing for familial Mediterranean fever at UCLA.

Ong FS(1), Vakil H, Xue Y, Kuo JZ, Shah KH, Lee RB, Bernstein KE, Rimoin DL, Getzug T, Das K, Deignan JL, Rotter JI, Grody WW.

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Familial Mediterranean fever (FMF), inherited in an autosomal recessive manner, is a systemic auto-inflammatory disorder characterized by recurrent attacks of fever with peritonitis, pleuritis, synovitis and erysipeloid rash. The marenostin-encoding fever (MEFV) gene, located on chromosome 16p13.3, is the only gene in which mutations are currently known to cause FMF. To correlate specific genotypes with adverse phenotypes of affected populations residing in the Western United States, a retrospective case series review was conducted of all MEFV gene mutation testing completed at UCLA Clinical Molecular Diagnostic Laboratory between February 2002 and February 2012, followed by clinical chart review of all subjects who either have a single or double mutation. All 12 common

mutations in the MEFV gene were analyzed and the M694V variant was found to be associated with an adverse FMF clinical outcome in the Armenian-American population, manifested by earlier onset of disease, increased severity of disease, and renal amyloidosis.

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DOI: 10.1111/cge.12029

PMCID: PMC3570680

PMID: 23038988 [Indexed for MEDLINE]

2582. Gene. 2012 Dec 15;511(2):371-4. doi: 10.1016/j.gene.2012.09.073. Epub 2012 Sep 29.

Prevalence of known mutations and a novel missense mutation (M694K) in the MEFV gene in a population from the Eastern Anatolia Region of Turkey.

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Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent attacks of fever and serositis. Mutations in the Mediterranean fever gene (MEFV) localized on the short arm of chromosome 16 cause FMF. Over 90 MEFV missense/nonsense mutations have been identified so far in FMF patients, mostly in the 10th exon of the gene. In this study, the molecular test results of 891 patients identified as having FMF clinical symptoms referred to Molecular Genetics Laboratory of the Department of Medical Biology and Genetics, Faculty of Medicine, Inonu University, Malatya/Turkey were retrospectively evaluated. Patients were referred by their physicians for MEFV mutation detection. The DNA fragments including hot spots within the coding sequences of the MEFV gene were amplified by PCR using genomic DNA and analyzed by pyrosequencing technique. Of the 891 patients investigated, 420 (47.13%) had at least one mutation. The most frequent mutation was E148Q, followed by M694V, M680I (G/C), P369S, V726A, R761H, A744S, M694I, K695R and F479L mutations. In addition, a novel missense mutation (M694K) was reported in seven members of a



family in the course of mutation screening of patients.

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DOI: 10.1016/j.gene.2012.09.073

PMID: 23031807 [Indexed for MEDLINE]

2583. Clin Ther. 2012 Oct;34(10):2091-103. doi: 10.1016/j.clinthera.2012.09.009. Epub 2012 Sep 29.

Long-term efficacy and safety profile of rilonacept in the treatment of cryopyrin-associated periodic syndromes: results of a 72-week open-label extension study.

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**BACKGROUND:** Cryopyrin-associated periodic syndromes (CAPS) are rare, inherited autoinflammatory disorders associated with considerable hardship to patients. The interleukin-1 inhibitor rilonacept has been shown to be well-tolerated and effective in preventing CAPS symptoms in 2 pivotal studies.

**OBJECTIVE:** In this study, the long-term effects of rilonacept for improvement in CAPS symptoms and its safety and tolerability were evaluated during extended treatment.

**METHODS:** Patients with CAPS entered a 72-week open-label extension (OLE) following 2 sequential placebo-controlled Phase III studies (n = 44), or entered directly into the OLE (n = 57). Adults received weekly subcutaneous rilonacept 160 mg, and pediatric patients received subcutaneous rilonacept 2.2 mg/kg, up to 160 mg/week. Safety was evaluated in all patients, and efficacy was evaluated using a validated composite key symptom score in 56 patients.

**RESULTS:** After rilonacept treatment for 72 to 96 weeks mean key symptom score at OLE Week 72 was reduced from 2.6 to 0, and the mean number of multisymptom flare days was reduced from 7.3 (34.8% of days) at baseline to 0.6 (2.9% of days) at end point. Elevated levels of inflammatory markers (eg, high sensitivity-C reactive protein and serum amyloid A, were normalized. Adverse events were generally mild to moderate, the most common being injection site reactions and

upper respiratory tract infections. The incidence of these events was similar to or lower than the rate reported in the pivotal studies.

**CONCLUSIONS:** Long-term treatment with rilonacept of up to 96 weeks resulted in improvements in clinical signs and symptoms of CAPS and normalized biomarkers of inflammation. Rilonacept exhibited a generally favorable safety and tolerability profile in adult and pediatric patients with CAPS throughout the extended treatment period. ClinicalTrials.gov identifier: NCT 00288704.

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DOI: 10.1016/j.clinthera.2012.09.009

PMID: 23031624 [Indexed for MEDLINE]

2584. J Rheumatol. 2012 Nov;39(11):2170-4. doi: 10.3899/jrheum.120530. Epub 2012 Oct 1.

Familial Mediterranean fever in siblings.

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**OBJECTIVE:** Genetic and environmental factors have been implicated in disease severity and development of amyloidosis in familial Mediterranean fever (FMF). We investigated similarities in clinical characteristics, disease severity, and treatment response within siblings with FMF.

**METHODS:** The study group consisted of 2 or more siblings who were followed in our center with the diagnosis of FMF. Siblings were evaluated for demographic data, clinical and laboratory disease features, genetic analysis of MEFV mutations, and disease severity score. The intraclass correlation coefficient (ICC), which can be interpreted as the expected correlation between 2 siblings, was used to reflect within-family similarity.

**RESULTS:** The study included 67 pediatric patients from 31 different families. When we investigated the similarity of siblings after adjusting for genetic effects, we found very low ICC with  $p > 0.05$  in the majority of clinical features, disease severity, and colchicine dosages. However, age at disease onset, age at onset of therapy, attack-free acute-phase reactant levels, and

presence of amyloidosis were found to be similar within siblings (relatively high ICC with  $p < 0.05$ ).

**CONCLUSION:** Siblings with FMF had different clinical findings and disease severity. They had similar amyloidogenic potential, proven by both similar presence of amyloid and increased levels of acute-phase reactants between attacks. Our findings strongly support that genetic factors may be more dominant in the development of amyloidosis.

DOI: 10.3899/jrheum.120530

PMID: 23027888 [Indexed for MEDLINE]

2585. J Clin Immunol. 2013 Feb;33(2):325-34. doi: 10.1007/s10875-012-9805-x. Epub 2012 Sep 27.

In vitro analysis of the functional effects of an NLRP3 G809S variant with the co-existence of MEFV haplotype variants in atypical autoinflammatory syndrome.

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**PURPOSE:** Hereditary periodic fever syndromes have been considered monogenic diseases. However, some recent reports have described patients with co-existence of recurrent fever responsible genes. This study assessed whether a rare variant, found in Japanese children showing atypical autoinflammatory syndrome, located in the leucine-rich repeat domain of Nod-like receptor family, pyrin domain containing 3 (NLRP3) with co-existence of Mediterranean fever (MEFV) haplotype variants may contribute to a proinflammatory phenotype using a systematic approach.

**METHODS:** Cytokine production in serum or from peripheral blood monocytes was measured by ELISA. DNA sequence analysis of genes including NLRP3, MEFV, mevalonate kinase (MVK), and tumor necrosis factor receptor superfamily, member 1A (TNFRSF1A) were performed on patient samples. In vitro functional assays determined the effects of the NLRP3 variants and pyrin using NF- $\kappa$ B activation and speck formation assays.

**RESULTS:** A heterozygous genetic variant of NLRP3, G809S, was found in samples from both patients. Additionally the previously reported heterozygous MEFV variants (P369S-R408Q or E148Q-P369S-R408Q) were also detected in both patients. Serum IL-1ra and sTNFR1 levels increased in the attack phase of the disease in both patients. The production levels of IL-1 $\beta$  from monocytes isolated from both cases were elevated following LPS and IFN- $\gamma$  stimulation. The NLRP3 G809S variant demonstrated no increase of NF- $\kappa$ B activity following monosodium urate stimulation, whereas it significantly increased speck formation by interacting with apoptosis-associated speck-like protein with caspase recruitment domain.

**CONCLUSIONS:** The phenotype of atypical autoinflammatory disease in patients could be modified by a synergistic effect with two other variants of autoinflammatory-associated genes.

DOI: 10.1007/s10875-012-9805-x

PMID: 23015306 [Indexed for MEDLINE]

2586. Clin Exp Rheumatol. 2012 May-Jun;30(3 Suppl 72):S104-7. Epub 2012 Sep 25.

Therapeutic approach to patients with familial Mediterranean fever-related amyloidosis resistant to colchicine.

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The frequency of FMF-related amyloidosis has been decreased by colchicine use over the past few decades. However, the beneficial effect of colchicine may differ in accordance with nephropathic stages. When used in proper doses and with compliance, colchicine is very effective in preclinical and proteinuric stages of FMF-related amyloidosis. Even so, a large number of patients with nephrotic range proteinuria, despite compliance and an ideal dose of colchicine, may still progress to end-stage renal failure (ESRF). We do not know exactly what we can do with such patients. This paper discusses the therapeutic approach to patients with FMF-related amyloidosis.

2587. Clin Chim Acta. 2012 Dec 24;414:36-40. doi: 10.1016/j.cca.2012.07.019. Epub 2012 Aug 7.

Association between sequence variations of the Mediterranean fever gene and fibromyalgia syndrome in a cohort of Turkish patients.

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**OBJECTIVE:** Fibromyalgia syndrome (FMS) is a common chronic widespread pain syndrome mainly affecting women. Genetic risk factors are known to contribute to the etiology of the syndrome. Clinical features show that FMS and familial Mediterranean fever (FMF) have some overlapping symptoms. Mediterranean fever (MEFV) gene has already been identified as being responsible for FMF. The aim of this study was to explore the frequency and clinical significance of missense mutations and a common polymorphism of MEFV gene in a cohort of Turkish patients with FMS.

**METHODS:** The study included 187 patients with FMS and 190 healthy controls. Genomic DNA was isolated and genotyped using polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) analyses for the five MEFV gene mutations (M694V, M680I, V726A, E148Q and P369S) and one polymorphism (R202Q).

**RESULTS:** There were statistically significant differences of the MEFV gene mutation carrier rates and allele frequencies between FMS patients and healthy controls ( $p=0.002$ , OR: 2.3, 95% CI: 1.35-4.16 and  $p=0.003$ , OR: 2.2, 95% CI: 1.28-3.75, respectively). There was also a significant difference between MEFV mutation carriers and non-carriers with respect to the clinical characteristic of morning fatigue ( $p=0.045$ ). The genotype and allele frequencies of R202Q polymorphism of MEFV gene showed statistically significant differences between FMS patients and healthy controls ( $p<0.0001$  and  $p<0.0001$ , respectively) and especially the homozygous AA genotype was significantly higher in FMS patients than in healthy controls ( $p=0.0003$ ; OR: 7.43, 95% CI: 2.14-39.75). While 13 of the 44 FMS patients with MEFV mutation had R202Q polymorphism, none of the 22 controls with MEFV mutation had R202Q polymorphism. Stratification analysis

according to clinical features for this disease reveals that morning fatigue and irritable bowel syndrome had associations with R202Q polymorphism ( $p=0.022$  and  $p=0.031$  respectively).

**CONCLUSION:** The results of this study suggest that MEFV gene mutations and polymorphism are positively associated with predisposition to develop FMS. Further studies with larger populations will be required to confirm these findings.

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DOI: 10.1016/j.cca.2012.07.019

PMID: 23010357 [Indexed for MEDLINE]

2588. Clin Exp Rheumatol. 2012 May-Jun;30(3 Suppl 72):S90-5. Epub 2012 Sep 25.

FMF - clinical features, new treatments and the role of genetic modifiers: a critical digest of the 2010-2012 literature.

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The last two years have been marked by many studies trying to better characterize the clinical features of FMF in children and proposal of new treatment for those who are resistant to colchicine. In addition, many studies tried to address the potential effect of genetic modifiers on FMF and the potential effect of MEFV mutations on other inflammatory diseases. The main points arose from these studies include a breakthrough in the therapeutic approach for FMF and the lack of consistency regarding the reciprocal effect of MEFV mutations on other diseases and the effect of genetic modifiers on FMF. The highlights of these studies, their potential clinical implications and the unmet needs, which are still to be addressed, are summarised in this review.

PMID: 23009752 [Indexed for MEDLINE]

2589. Ren Fail. 2012;34(10):1333-4. doi: 10.3109/0886022X.2012.718950. Epub 2012 Sep 25.

Concomitance of Gitelman syndrome and familial Mediterranean fever: a rare case presentation.

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We report a case that has Gitelman syndrome (GS) and familial Mediterranean fever (FMF) presenting with recurrent arthritis of right knee and heel pain.

Investigations showed hypokalemia and hypomagnesemia with urinary magnesium wasting. Genetic analysis revealed the presence of heterozygous E148Q mutation in the MEFV gene. Management with potassium, magnesium supplements, spironolactone for GS, and colchicine for FMF resulted in a significant improvement in symptoms.

To the best of our knowledge, this is the first report of association between GS and FMF. Further studies are needed to identify if there is an association between these two diseases and the genes responsible for these diseases.

DOI: 10.3109/0886022X.2012.718950

PMID: 23009175 [Indexed for MEDLINE]

2590. Curr Neurol Neurosci Rep. 2012 Dec;12(6):675-9. doi: 10.1007/s11910-012-0316-1.

Neurological complications of Behçet's syndrome.

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Behçet's syndrome is an autoinflammatory disease of uncertain cause characterized by mucous membrane ulceration, arthritis and inflammation within most tissues.

Its prevalence differs throughout different populations, but neurological complications arise in 10 % of all those affected. The majority develop inflammation within the central nervous system which may remit but may also progressively worsen without treatment. This article reviews the epidemiology, clinical characteristics, natural history and management of the disorders, and emphasizes recent considerable advances in our understanding of the various treatments which may be beneficial across the spectrum of disease types.

DOI: 10.1007/s11910-012-0316-1

PMID: 23007835 [Indexed for MEDLINE]

2591. J Allergy Clin Immunol. 2013 Jun;131(6):1635-43. doi: 10.1016/j.jaci.2012.07.043. Epub 2012 Sep 21.

Periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis syndrome is linked to dysregulated monocyte IL-1 $\beta$  production.

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**BACKGROUND:** The exact pathogenesis of the pediatric disorder periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome is unknown.

**OBJECTIVES:** We hypothesized that PFAPA might be due to dysregulated monocyte IL-1 $\beta$  production linked to genetic variants in proinflammatory genes.

**METHODS:** Fifteen patients with PFAPA syndrome were studied during and outside a febrile episode. Hematologic profile, inflammatory markers, and cytokine levels were measured in the blood. The capacity of LPS-stimulated PBMCs and monocytes to secrete IL-1 $\beta$  was assessed by using ELISA, and active IL-1 $\beta$  secretion was visualized by means of Western blotting. Real-time quantitative PCR was performed to assess cytokine gene expression. DNA was screened for variants of the MEFV, TNFRSF1A, MVK, and NLRP3 genes in a total of 57 patients with PFAPA syndrome.

**RESULTS:** During a febrile attack, patients with PFAPA syndrome revealed significantly increased neutrophil counts, erythrocyte sedimentation rates, and C-reactive protein, serum amyloid A, myeloid-related protein 8/14, and S100A12



levels compared with those seen outside attacks. Stimulated PBMCs secreted significantly more IL-1 $\beta$  during an attack (during a febrile episode, 575  $\pm$  88 pg/mL; outside a febrile episode, 235  $\pm$  56 pg/mL;  $P < .001$ ), and this was in the mature active p17 form. IL-1 $\beta$  secretion was inhibited by ZYVAD, a caspase inhibitor. Similar results were found for stimulated monocytes (during a febrile episode, 743  $\pm$  183 pg/mL; outside a febrile episode, 227  $\pm$  92 pg/mL;  $P < .05$ ). Genotyping identified variants in 15 of 57 patients, with 12 NLRP3 variants, 1 TNFRSF1A variant, 4 MEFV variants, and 1 MVK variant.

**CONCLUSION:** Our data strongly suggest that IL-1 $\beta$  monocyte production is dysregulated in patients with PFAPA syndrome. Approximately 20% of them were found to have NLRP3 variants, suggesting that inflammasome-related genes might be involved in this autoinflammatory syndrome.

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DOI: 10.1016/j.jaci.2012.07.043

PMID: 23006543 [Indexed for MEDLINE]

2592. Am J Hum Genet. 2012 Oct 5;91(4):713-20. doi: 10.1016/j.ajhg.2012.08.006. Epub 2012 Sep 20.

A hypermorphic missense mutation in PLCG2, encoding phospholipase C $\gamma$ 2, causes a dominantly inherited autoinflammatory disease with immunodeficiency.

Zhou Q(1), Lee GS, Brady J, Datta S, Katan M, Sheikh A, Martins MS, Bunney TD, Santich BH, Moir S, Kuhns DB, Long Priel DA, Ombrello A, Stone D, Ombrello MJ, Khan J, Milner JD, Kastner DL, Aksentijevich I.

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Whole-exome sequencing was performed in a family affected by dominantly inherited inflammatory disease characterized by recurrent blistering skin lesions, bronchiolitis, arthralgia, ocular inflammation, enterocolitis, absence of autoantibodies, and mild immunodeficiency. Exome data from three samples, including the affected father and daughter and unaffected mother, were filtered

for the exclusion of reported variants, along with benign variants, as determined by PolyPhen-2. A total of eight transcripts were identified as possible candidate genes. We confirmed a variant, c.2120C>A (p.Ser707Tyr), within PLCG2 as the only de novo variant that was present in two affected family members and not present in four unaffected members. PLCG2 encodes phospholipase C $\gamma$ 2 (PLC $\gamma$ 2), an enzyme with a critical regulatory role in various immune and inflammatory pathways. The p.Ser707Tyr substitution is located in an autoinhibitory SH2 domain that is crucial for PLC $\gamma$ 2 activation. Overexpression of the altered p.Ser707Tyr protein and ex vivo experiments using affected individuals' leukocytes showed clearly enhanced PLC $\gamma$ 2 activity, suggesting increased intracellular signaling in the PLC $\gamma$ 2-mediated pathway. Recently, our laboratory identified in individuals with cold-induced urticaria and immune dysregulation PLCG2 exon-skipping mutations resulting in protein products with constitutive phospholipase activity but with reduced intracellular signaling at physiological temperatures. In contrast, the p.Ser707Tyr substitution in PLC $\gamma$ 2 causes a distinct inflammatory phenotype that is not provoked by cold temperatures and that has different end-organ involvement and increased intracellular signaling at physiological temperatures. Our results highlight the utility of exome-sequencing technology in finding causal mutations in nuclear families with dominantly inherited traits otherwise intractable by linkage analysis.

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DOI: 10.1016/j.ajhg.2012.08.006

PMCID: PMC3484656

PMID: 23000145 [Indexed for MEDLINE]

2593. Ter Arkh. 2012;84(6):53-9.

[Muckle-Wells syndrome caused by a new cryopyrin mutation: effective treatment with interleukin-1 antagonist].

[Article in Russian]

Rameev VV, Kozlovskaja LV, Bogdanova MV.

A significant progress in the field of molecular-biological investigations

resulted in definition of a new group of systemic diseases referred to as autoinflammatory. This group comprises familial periodic fevers: periodic disease (mediterranean fever), Muckle-Wells syndrome, others cryopyrinopathy, TRAPS-syndrome. As shown by case reports, Muckle-Wells syndrome is not a rare disease, its sporadic forms are encountered as well as a less severe variant of cryopyrinopathy - nonallergic cold urticaria. Awareness of the physicians in respect of this pathology is essential especially because early diagnosis enables control of this disease with use of biological preparations the spectrum of which tends to expansion. Moreover, arrest of inflammation is necessary for prevention of development and progression of such prognostically poor complication as AA-amyloidosis.

PMID: 22997920 [Indexed for MEDLINE]

2594. Ter Arkh. 2012;84(6):45-8.

[Serum levels of myeloid-related protein MRP 8/14 (calprotectin) in Armenian patients with familial mediterranean fever].

[Article in Russian]

Dzhndoian ZT.

AIM: The determination of serum myeloid-related protein MRP 8/14 (calprotectin) in Armenian patients with FMF before and after treatment with colchicine (including colchicine-resistant patients who don't respond to 2 mg of colchicine; t patients who don't respond to 1,5 mg of colchicine, and also responders to different dose of colchicine) and estimation of the response to antiinflammatory therapy.

MATERIAL AND METHODS: MRP 8/14 serum levels were measured in 80 FMF patients before and after treatment with colchicine and in healthy individuals (n = 11) and patients with rheumatoid arthritis RA (n=11) as a control group. Serum MRP 8/14 concentration was measured by ELISA (Enzyme Linked-Immuno-Sorbent-Assay) method using "Buhlmann" kit (Switzerland) in the laboratory with modern equipment.

RESULTS: Serum MRP 8/14 concentrations were within a normal ranges in healthy individuals and elevated in patients with FMF and RA. MRP 8/14 serum levels in

FMF patients were higher than in RA patients. Serum MRP 8/14 concentrations in FMF patients before colchicines therapy were higher than after treatment.

CONCLUSION: The findings of our study indicate that myeloid-related protein MRP 8/14 is a very sensitive marker of the disease activity and response to antiinflammatory therapy in FMF.

PMID: 22997918 [Indexed for MEDLINE]

2595. Intern Med. 2012;51(18):2649-53. Epub 2012 Sep 15.

Familial Mediterranean fever with onset at 66 years of age.

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The patient was a 68-year-old woman who had experienced recurrent febrile episodes since 66 years of age. Despite various examinations and treatments, the etiology remained unclear. Further examinations following another referral failed to uncover the cause. Therefore, despite her age, it was presumed that she had familial Mediterranean fever. An analysis of the familial Mediterranean fever (MEFV) gene detected heterozygous L110P, E148Q, and R202Q mutations. No further febrile episodes occurred after colchicine treatment was initiated. Familial Mediterranean fever presenting in patients in their sixties is extremely rare.

PMID: 22989844 [Indexed for MEDLINE]

2596. J Clin Immunol. 2013 Jan;33(1):74-83. doi: 10.1007/s10875-012-9763-3. Epub 2012 Sep 15.

The prevalences [correction] and patient characteristics of primary immunodeficiency diseases in Turkey--two centers study.

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**PURPOSE:** Primary immunodeficiency diseases (PIDs) are inherited disorders of the immune system resulting in increased susceptibility to unusual infections and predisposition to autoimmunity and malignancies. The European Society for Immunodeficiencies (ESID) has developed an internet-based database for clinical and research data on patients with PID. This study aimed to provide a minimum estimate of the prevalence of each disorder and to determine the clinical characteristics and outcomes of patients with PID in Turkey.

**METHODS:** Clinical features of 1435 patients with primary immunodeficiency disorders are registered in ESID Online Patient Registry by the Pediatric Immunology Departments of the Medical Faculties of Uludag University and Ege University Between 2004 and 2010. These two centers are the major contributors reporting PID patients to ESID database from Turkey.

**RESULTS:** Predominantly antibody immunodeficiency (73.5 %) was the most common category followed by autoinflammatory disorders (13.3 %), other well defined immunodeficiencies (5.5 %), congenital defects of phagocyte number, function or both 3.5 %), combined T and B cell immunodeficiencies (2 %), defects in innate immunity (1 %), and diseases of immune dysregulation (0.7 %). Patients between 0 and 18 years of age constituted 94 % of total and the mean age was  $9.2 \pm 6$  years. The consanguinity rate within the registered patients was 14.3 % (188 of 1130 patients). The prevalence of all PID cases ascertained from the registry was 30.5/100.000. The major cause of the mortality was severe infection which was seen in forty-two of seventy five deceased patients. The highest mortality was observed in patients with severe combined immunodeficiencies and ataxia-telangiectasia.

**CONCLUSION:** Promoting the awareness of PID among the medical professionals and the general public is required if premature death and serious morbidity occurs due to late diagnosis of the wider spectrum of PID are to be avoided.

DOI: 10.1007/s10875-012-9763-3

PMID: 22983506 [Indexed for MEDLINE]

2597. Brain Dev. 2013 Jun;35(6):561-8. doi: 10.1016/j.braindev.2012.08.008. Epub 2012 Sep 13.

Clinical spectrum of the pseudotumor cerebri in children: etiological, clinical features, treatment and prognosis.

Per H(1), Canpolat M, Gümüş H, Poyrazoğlu HG, Yıkılmaz A, Karaküçük S, Doğan H, Kumandaş S.

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**OBJECTIVE:** Pseudotumor cerebri (PTC) is a clinical condition characterized by signs and symptoms of increased intracranial pressure, such as headache and papilledema. Our aim was to investigate the etiological and clinical features of pseudotumor cerebri (PTC) in children.

**MATERIALS AND METHOD:** We performed a comprehensive analysis of epidemiology, diagnostic work-up, therapy, and clinical follow-up in 42 consecutive patients.

**RESULTS:** Totally 42 patients diagnosed with PTC [27 (64.3%) females and 15 (35.7%) males] were included in the study. The average age of the symptoms onset was  $10.79 \pm 3.43$  years (range from 12 months to 17 years). Obesity was found in eleven (26.2%) of them. Two of the patients had familial mediterranean fever, two of them had posttraumatic PTC. The following diseases were one patient, respectively; mycophenolate mofetil-induced PTC, hypervitaminosis A induced PTC, corticosteroid induced withdrawal due to nephritic syndrome, use of oral contraceptives, Guillain-Barre syndrome, urinary tract infection, varicella-zoster virus infection and dural venous sinus thrombosis associated with otitis media. The most common symptom was headache, recorded in 76.2% of the patients. All patients were treated medically. Three patients in our group also required a ventriculoperitoneal shunt.

**CONCLUSION:** Pseudotumor cerebri is an avoidable cause of visual loss, both in adults and children. Pre-pubertal obese girls are more common. Medical therapy appeared to be successful in treating pediatric PTC in most patients.

Nevertheless, despite adequate treatment, children can rarely experience loss of visual field and acuity; thus, prompt diagnosis and management are important.

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DOI: 10.1016/j.braindev.2012.08.008

PMID: 22981259 [Indexed for MEDLINE]

2598. Bratisl Lek Listy. 2012;113(9):561-4.

Cu/Zn-superoxide dismutase, paraoxonase and arylesterase activities and malondialdehyde levels in patients with familial mediterranean fever.

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Comment in

Bratisl Lek Listy. 2013;114(11):668.

**OBJECTIVES:** In this study, alterations in antioxidant enzyme activities and malondialdehyde (MDA) levels in the serum samples of patients with familial Mediterranean fever (FMF), an autosomal recessive disease characterized by recurrent episodes of peritonitis, pleuritis, arthritis and fever, were investigated and compared with those of age- and sex-matched healthy controls.

**METHODS:** Twenty-five patients with FMF undergoing colchicine therapy at doses of 1-1.5 mg and 25 age- and sex-matched healthy controls were included in the study. In the patients with FMF and control subjects, the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level were measured. Cu/Zn-superoxide dismutase (Cu/Zn-SOD), paraoxonase-1 (PON-1) and arylesterase (ARE) enzyme activities and MDA levels as a production of lipid peroxidation were evaluated using the appropriate methods.

**RESULTS:** No statistically significant differences in the serum levels of ESR, CRP, Cu/Zn-SOD, MDA and PON-1 between the groups were observed ( $p>0.05$ ). Serum ARE activity was significantly decreased in the patients with FMF compared with the control subjects ( $p<0.01$ ).

**CONCLUSION:** In conclusion, some abnormalities in the antioxidant defense system and lipid peroxidation may be observed in FMF patients during attack-free periods. However, further long-term studies on the subject are needed to explore altered lipid peroxidation and antioxidant defense mechanisms in patients with

FMF (Tab. 1, Fig. 1, Ref. 35).

PMID: 22979914 [Indexed for MEDLINE]

2599. Allergy. 2012 Dec;67(12):1465-74. doi: 10.1111/all.12030. Epub 2012 Sep 15.

How not to miss autoinflammatory diseases masquerading as urticaria.

Krause K(1), Grattan CE, Bindslev-Jensen C, Gattorno M, Kallinich T, de Koning HD, Lachmann HJ, Lipsker D, Navarini AA, Simon A, Traidl-Hoffmann C, Maurer M.

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Urticarial skin reactions are one of the most frequent problems seen by allergists and clinical immunologists in daily practice. The most common reason for recurrent wheals is spontaneous urticaria. There are, however, several less common diseases that present with urticarial rash, such as urticarial vasculitis and autoinflammatory disorders. The latter include cryopyrin-associated periodic syndrome and Schnitzler's syndrome, both rare and disabling conditions mediated by increased interleukin-1 secretion. Apart from the urticarial rash, patients are suffering from a variety of systemic symptoms including recurrent fever attacks, arthralgia or arthritis and fatigue. Autoinflammatory diseases are often associated with a diagnostic delay of many years and do not respond to antihistamines and other treatments of urticaria. Also, the chronic inflammation may lead to long-term complications such as amyloidosis. It is therefore important not to miss these diseases when diagnosing and treating patients with chronic recurrent urticarial rash. Here, we present clinical clues and tips that can help to identify autoinflammatory disorders in patients presenting with chronic urticarial rash and discuss their clinical picture and management.

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DOI: 10.1111/all.12030

PMID: 22978406 [Indexed for MEDLINE]



2600. Annu Rev Cell Dev Biol. 2012;28:137-61. doi:  
10.1146/annurev-cellbio-101011-155745. Epub 2012 Sep 10.

Inflammasomes and their roles in health and disease.

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Inflammasomes are a set of intracellular protein complexes that enable autocatalytic activation of inflammatory caspases, which drive host and immune responses by releasing cytokines and alarmins into circulation and by inducing pyroptosis, a proinflammatory cell death mode. The inflammasome type mediating these responses varies with the microbial pathogen or stress factor that poses a threat to the organism. Since the discovery that polymorphisms in inflammasome genes are linked to common autoimmune diseases and less frequent periodic fever syndromes, inflammasome signaling has been dissected at the molecular level. In this review, we present recently gained insight on the distinct inflammasome types, their activation and effector mechanisms, and their modulation by microbial virulence factors. In addition, we discuss recently gained knowledge on the role of deregulated inflammasome activity in human autoinflammatory, autoimmune, and infectious diseases.

DOI: 10.1146/annurev-cellbio-101011-155745

PMID: 22974247 [Indexed for MEDLINE]

2601. Nihon Naika Gakkai Zasshi. 2012 Aug 10;101(8):2304-6.

[Case report; A Japanese case of familial Mediterranean fever with onset in the thirties].

[Article in Japanese]

Sawada J(1), Asanome A, Endo H, Saito T, Katayama T, Hasebe N, Migita K, Ida H.

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PMID: 22973704 [Indexed for MEDLINE]

2602. Front Immunol. 2012 Sep 7;3:282. doi: 10.3389/fimmu.2012.00282. eCollection 2012.

Optical projection tomography reveals dynamics of HEV growth after immunization with protein plus CFA and features shared with HEVs in acute autoinflammatory lymphadenopathy.

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The vascular-stromal compartment of lymph nodes is important for lymph node function, and high endothelial venules (HEVs) play a critical role in controlling the entry of recirculating lymphocytes. In autoimmune and autoinflammatory diseases, lymph node swelling is often accompanied by apparent HEV expansion and, potentially, targeting HEV expansion could be used therapeutically to limit autoimmunity. In previous studies using mostly flow cytometry analysis, we defined three differentially regulated phases of lymph node vascular-stromal growth: initiation, expansion, and the re-establishment of vascular quiescence and stabilization. In this study, we use optical projection tomography to better understand the morphologic aspects of HEV growth upon immunization with ovalbumin/CFA (OVA/CFA). We find HEV elongation as well as modest arborization during the initiation phase, increased arborization during the expansion phase, and, finally, vessel narrowing during the re-establishment of vascular quiescence and stabilization. We also examine acutely enlarged autoinflammatory lymph nodes induced by regulatory T cell depletion and show that HEVs are expanded and morphologically similar to the expanded HEVs in OVA/CFA-stimulated lymph nodes. These results reinforce the idea of differentially regulated, distinct phases of vascular-stromal growth after immunization and suggest that insights gained from studying immunization-induced lymph node vascular growth may help to understand how the lymph node vascular-stromal compartment could be therapeutically targeted

in autoimmune and autoinflammatory diseases.

DOI: 10.3389/fimmu.2012.00282

PMCID: PMC3435517

PMID: 22973277

2603. Nat Rev Rheumatol. 2012 Oct;8(10):621. doi: 10.1038/nrrheum.2012.54-c1. Epub 2012 Sep 11.

Severity scoring system for paediatric FMF.

Kalkan G, Demirkaya E, Ozen S.

Comment on

Nat Rev Rheumatol. 2012 Jun;8(6):309-10.

DOI: 10.1038/nrrheum.2012.54-c1

PMID: 22964532 [Indexed for MEDLINE]

2604. Dis Markers. 2012;33(3):113-8.

Common Mediterranean fever (MEFV) gene mutations associated with ankylosing spondylitis in Turkish population.

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Ankylosing spondylitis (AS) is a common inflammatory rheumatic disease. Mediterranean fever (MEFV) gene, which has already been identified as being responsible for familial Mediterranean fever (FMF), is also a suspicious gene for AS because of the clinical association of these two diseases. The aim of this study was to explore the frequency and clinical significance of MEFV gene mutations (M694V, M680I, V726A, E148Q and P369S) in a cohort of Turkish patients with AS. Genomic DNAs of 103 AS patients and 120 controls were isolated and

genotyped using polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) methods. There was a statistically significant difference of the MEFV gene mutation carrier rates between AS patients and healthy controls ( $p=0.004$ , OR: 2.5, 95% CI: 1.32-4.76). This association was also observed in allele frequencies ( $p=0.005$ , OR: 2.3, 95% CI: 1.27-4.2). A relatively higher frequency was observed for M694V mutation in AS patients than controls (10.7% versus 4.2% ,  $p=0.060$ ). There were no significant differences between MEFV mutation carriers and non-carriers with respect to the clinical and demographic characteristics. The results of this study suggest that MEFV gene mutations are positively associated with a predisposition to develop AS.

DOI: 10.3233/DMA-2012-0911

PMCID: PMC3810788

PMID: 22960328 [Indexed for MEDLINE]

2605. Eur Rev Med Pharmacol Sci. 2012 Jul;16(7):983-5.

A case of psoriasis with secondary amyloidosis, associated symbrachydactyly of the hand and a transverse deficiency of the foot.

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Secondary amyloidosis is associated with a variety of chronic inflammatory diseases such as rheumatoid arthritis, ankylosing spondylitis, familial Mediterranean fever, osteomyelitis, inflammatory bowel diseases and infective or neoplastic conditions. Few cases of secondary amyloidosis complicating psoriasis have been reported. We describe a 58-year-old patient with secondary amyloidosis, psoriasis, an associated symbrachydactyly of the hand and a transverse deficiency of the foot. To the best of our knowledge, no case of this association has been previously reported.

PMID: 22953651 [Indexed for MEDLINE]

2606. Eur Rev Med Pharmacol Sci. 2012 Jul;16(7):949-51.

The frequency of MEFV gene mutation in patients admitted to hospital with preliminary diagnosis of familial mediterranean fever who undergone a prior appendectomy.

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**OBJECTIVES:** Familial mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent and self-limiting fever, peritonitis, arthritis, synovitis, pleuritis, carditis, and erysipelas-like lesions. The aim of this study was to investigate the frequency of the MEFV gene mutation in patients who admitted to hospital with preliminary diagnosis FMF and who had undergone a prior appendectomy.

**PATIENTS AND METHODS:** We retrospectively reviewed the files of 52 patients between the ages of 7-18 who admitted to hospital with preliminary diagnosis of FMF and who had undergone a prior appendectomy. Age, gender and the MEFV gene mutations were included in the data. The 12 known, common MEFV gene mutations [E148Q, P369S, F479L, M6801 (G/C), M6801 (G/A), 1692del, M694V, M694I, K695R, V726A, A744S, R761H] were investigated in the patients.

**RESULTS:** Of these 52 cases, 29 (55.8%) were female and 23 (44.2%) were male. Their mean age was 12.1 +/- 3.1 years (range 7-18 yr). MEFV gene mutation was detected in 31/52 cases (59.6%). In this study was found an high frequency of the MEFV gene mutation in patients admitted to hospital with a preliminary diagnosis FMF who had undergone a prior appendectomy. MEFV gene mutations were M694V 16/41 (39%), E148Q 13/41 (31%), M6801 6/41 (15%), V726A 4/41 (10%) and R761H 2/41 (5%). Other genes mutations were F479L, M6801 (G/A), 1692del, M694I, K695R and A744S.

**CONCLUSION:** There are too much indications of unnecessary appendectomy in MEFV gene mutation carriers. In MEFV gene mutation carriers the frequency of appendicitis can be higher than the normal population. A more detailed and extensive study should be done about it.

PMID: 22953644 [Indexed for MEDLINE]

2607. Scand J Rheumatol. 2012;41(6):482-6. doi: 10.3109/03009742.2012.698301. Epub 2012 Sep 6.

Exertional leg pain as a manifestation of occult spondyloarthropathy in familial Mediterranean fever: an MRI evaluation.

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**OBJECTIVES:** Familial Mediterranean fever (FMF) is characterized by recurrent episodes of fever, peritonitis, arthritis, and pleuritis, caused by neutrophil-induced sterile serositis. Another clinical manifestation in patients with FMF is exertional leg and ankle pain that appears after minor exercise, for which the underlying mechanism is obscure. The purpose of the current study was to feature distal leg changes in FMF patients complaining of exertional leg pain, using magnetic resonance imaging (MRI).

**METHODS:** Eleven patients with FMF who suffer from exertional leg pain (eight males, three females; mean age 33 years) and six unaffected controls (three males, three females; mean age 39 years) underwent MRI (3 T) of the ankle, including conventional T1 and T2 with fat saturation sequences, before and after graded exercise on a treadmill. Clinical and genetic data and sacroiliac radiographs were obtained.

**RESULTS:** Ten patients (91%) with FMF but none of the control group had signs compatible with enthesitis of the Achilles tendon, long plantar ligament, or the plantar fascia (including enthesophytes, erosions, and bone marrow oedema). Nine patients (80%) had radiographic signs of sacroiliitis on the pelvic radiograph.

**CONCLUSIONS:** Exertional leg pain in FMF patients, shown to be associated with signs of enthesopathy on imaging, may be included within the spectrum of spondyloarthropathy.

DOI: 10.3109/03009742.2012.698301

PMID: 22950526 [Indexed for MEDLINE]

2608. J Leukoc Biol. 2013 Jan;93(1):51-61. doi: 10.1189/jlb.0612293. Epub 2012 Sep 4.

The dual roles of inflammatory cytokines and chemokines in the regulation of autoimmune diseases and their clinical implications.

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Cytokines and chemokines are secreted, small cell-signaling protein molecules, whose receptors are expressed on immune cells. These factors play a critical role in immune cell differentiation, migration, and polarization into functional subtypes and in directing their biological functions. Much attention has been devoted to exploring the role of key inflammatory cytokines and promigratory chemokines in autoimmune, autoinflammatory, and allergic diseases, leading to development of therapeutic strategies that are based on their targeted neutralization. Recent studies, including those coming from our groups, show that several major proinflammatory cytokines and chemokines, including IFN- $\gamma$ , IL-2, CCL2, and CXCL12, may also function as anti-inflammatory mediators and therefore, may have potential as anti-inflammatory drugs. Likewise, major anti-inflammatory mediators, such as TGF- $\beta$ , may under certain conditions, in combination with other cytokines, exhibit proinflammatory function and direct the polarization of the highly inflammatory CD4(+) Th17 cells. We show here that the biological function of pro- and anti-inflammatory cytokines is dependent on three key parameters: the local concentration of a given cytokine, the stage of disease in which it is administered, and its combination with other cytokines. The therapeutic implications of these findings are discussed, including two very recent studies summarizing clinical trials, in which low-dose administration of IL-2 was used to successfully suppress HCV and GVHD.

DOI: 10.1189/jlb.0612293

PMID: 22949334 [Indexed for MEDLINE]

2609. Indian J Hematol Blood Transfus. 2011 Sep;27(3):164-8. doi: 10.1007/s12288-011-0095-x. Epub 2011 Jul 21.

## High Frequency of Inherited Variants in the MEFV Gene in Acute Lymphocytic Leukemia.

Sayan O, Kilicaslan E, Celik S, Tangi F, Erikci AA, Ipcioglu O, Sanisoglu YS, Nalbant S, Oktenli C.

In the present study, we aimed to determine the frequency of inherited variants in the MEFV (Mediterranean FeVer), the gene responsible for familial Mediterranean fever (FMF), gene in patients with acute lymphocytic leukemia (ALL). The eight MEFV gene variants (M694I, M694V, M680I (G/C-A), V726A, R761H, E148Q and P369S) were detected in 36 patients with ALL and 65 healthy controls; none had own and/or family history compatible with FMF. We identified 11 heterozygous inherited variants in the MEFV gene in both ALL patients and controls. The mean overall frequency of inherited variants in the MEFV gene rate was higher in ALL patients than healthy controls ( $P = 0.040$ ). It is interesting to note that M680I/0 is predominant variant in patients with ALL. In addition, E148Q variant frequency was also significantly higher in the patient group than the controls ( $P = 0.012$ ). In conclusion, overall frequency of inherited variants in the MEFV gene was found to be higher in patients with ALL. Based on the present data, it is difficult to reach a definitive conclusion regarding the possibility that inherited variants in the MEFV gene could represent a causative role in ALL. However, the data of our study may provide some new insights in understanding of individual genetic differences in susceptibility to these neoplasms. Further investigations are needed to determine the actual role of inherited variants in the MEFV gene in pathogenesis of ALL.

DOI: 10.1007/s12288-011-0095-x

PMCID: PMC3155719

PMID: 22942567

2610. Clin Immunol. 2012 Oct;145(1):77-81. doi: 10.1016/j.clim.2012.08.003. Epub 2012 Aug 16.

A novel mutation in the interleukin-1 receptor antagonist associated with intrauterine disease onset.

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Deficiency of the IL-1 receptor antagonist (DIRA) is a recently described rare autoinflammatory disease, caused by loss of function mutations in IL1RN leading to the unopposed activation of the IL-1 pathway. We describe a novel nonsense mutation in the IL1RN gene, associated with early intrauterine onset, death and multiorgan involvement in a prematurely born baby. The protein prediction model indicated that the novel Q119X mutation would result in a nonfunctional protein by impairing the ability of the IL-1Ra to bind and antagonize signaling through the IL-1R. Since the disorder may mimic severe bacterial infections and the treatment with anakinra is life saving, we intend to raise awareness of the syndrome and the possibility of a founder mutation that may lead to the diagnosis of additional cases in Turkey. The clinical suspicion of DIRA is critical to avoid improper management of the patients with antibiotics alone and death from multiorgan failure.

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DOI: 10.1016/j.clim.2012.08.003

PMCID: PMC3463868

PMID: 22940634 [Indexed for MEDLINE]

2611. Clin Immunol. 2012 Oct;145(1):69-76. doi: 10.1016/j.clim.2012.07.012. Epub 2012 Aug 4.

Attenuated TLR4/MAPK signaling in monocytes from patients with CRMO results in impaired IL-10 expression.

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Chronic recurrent multifocal osteomyelitis (CRMO) is an autoinflammatory bone disorder of unknown origin. We previously demonstrated that monocytes from CRMO patients fail to express the immune-modulatory cytokine interleukin-10 (IL-10) in a chromatin dependent manner. Here, we demonstrate that attenuated extracellular-signal regulated kinase (ERK)1 and 2 signaling in response to TLR4 activation results in failure to induce IL-10 expression in monocytes from CRMO patients. Attenuated ERK1/2 activation results in 1) reduced levels of Sp-1, a transcription factor that induces IL-10 expression in monocytes, and 2) impaired H3S10 phosphorylation of the IL10 promoter, an activating epigenetic mark. The pro-inflammatory cytokines tumor necrosis factor (TNF) $\alpha$  and IL-6 are not negatively affected, resulting in an imbalance towards pro-inflammatory cytokines. Thus, impaired ERK1/2 signaling with subsequently reduced Sp-1 expression and H3S10 phosphorylation of the IL10 promoter may centrally contribute to the pathophysiology of CRMO.

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DOI: 10.1016/j.clim.2012.07.012

PMID: 22940633 [Indexed for MEDLINE]

2612. Eur J Intern Med. 2012 Oct;23(7):661-4. doi: 10.1016/j.ejim.2012.04.007. Epub 2012 May 3.

Mean platelet volume and  $\beta$ -thromboglobulin levels in familial Mediterranean fever: effect of colchicine use?

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**BACKGROUND:** Many studies have shown that subclinical inflammation persisted during remission period of Familial Mediterranean Fever (FMF) patients but long term effects of subclinical inflammation in these patients aren't clearly known. Besides, a few of the recent studies revealed that risk of atherosclerosis had increased in FMF patients.  $\beta$ -Thromboglobulin ( $\beta$ -TG) is considered as a sensitive marker of platelet activation. In this study Mean Platelet Volume (MPV) and  $\beta$ -TG

levels were evaluated in FMF patients.

**METHODS:** Following the Local Ethics Committee's consent, 25 FMF patients were included in the study. Twenty eight age and sex matched healthy volunteers were recruited as a control group. Lipid profile, inflammatory parameters, hemogram,  $\beta$ -TG, MPV were assessed. Statistical analysis was performed with SPSS for Windows 16.00.

**RESULTS:** Group I consisted of 25 FMF cases (16 females, 9 males; mean age:  $35.72 \pm 12.34$  years), Group II consisted of 28 cases (22 females, 6 males; mean age  $31.78 \pm 10.31$  years). There was no statistically significant difference between the groups in terms of age and gender distribution, smoking status, total cholesterol, triglyceride, LDL and MPV ( $p > 0.05$ ). HDL levels were found to be statistically lower in Group I ( $p: 0.04$ ). Median  $\beta$ -TG levels was significantly higher in Group II than Group I (129.50 (range: 372.00) ng/mL versus 104.00 (range: 212.80) ng/mL respectively;  $p: 0.03$ ).

**CONCLUSION:** In this study MPV and  $\beta$ -TG were evaluated for FMF cases and healthy controls,  $\beta$ -TG levels were found significantly lower among patients; we hypothesized that this difference may have resulted from the effect of colchicine use on platelet functions.

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DOI: 10.1016/j.ejim.2012.04.007

PMID: 22939812 [Indexed for MEDLINE]

2613. Rev Med Interne. 2013 Jan;34(1):47-52. doi: 10.1016/j.revmed.2012.07.016. Epub 2012 Aug 29.

[Palindromic rheumatism].

[Article in French]

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Palindromic rheumatism is characterized by episodes of arthritis or para-arthritis leaving no residual or radiographic changes. Several diseases should be ruled out in the differential diagnosis. Evolution to rheumatoid arthritis is common, especially in patient with positive rheumatoid factor and anticitrullinated peptides. In seronegative patients, palindromic rheumatism could be part of the spectrum of autoinflammatory diseases because of a high frequency of MEFV mutations. Treatment remains discussed. The use of antimalarials could delay the development of rheumatoid arthritis or another connective tissue disease.

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DOI: 10.1016/j.revmed.2012.07.016

PMID: 22939655 [Indexed for MEDLINE]

2614. Acta Ophthalmol. 2013 Dec;91(8):763-8. doi: 10.1111/j.1755-3768.2012.02505.x. Epub 2012 Aug 31.

Factors associated to temporal artery biopsy result in suspects of giant cell arteritis: a retrospective, multicenter, case-control study.

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**PURPOSE:** To evaluate the positivity rate of temporal artery biopsies (TAB) performed in suspects of giant cell arteritis (GCA) and to study the epidemiological and clinical factors associated to the biopsy result.

**METHODS:** A retrospective, multicenter, case-control study was performed, including three hundred and thirty-five patients who underwent TAB for a suspicion of GCA from 2001 to 2010. Clinical, epidemiological and pathology data were recovered from the patients' clinical records. Histologic diagnosis of GCA

was made when active inflammation or giant cells were found in the arterial wall.

**RESULTS:** Eighty-one biopsies (24.2%) were considered positive for GCA. Clinical factors independently associated to TAB result in a logistic regression analysis were temporal cutaneous hyperalgesia (OR = 10.8;  $p < 0.001$ ), jaw claudication (OR = 4.6;  $p = 0.001$ ), recent-onset headache (OR = 4.4;  $p = 0.001$ ), decreased temporal pulse (OR = 2.8;  $p = 0.02$ ), pain and stiffness in neck and shoulders (OR = 2.3;  $p = 0.05$ ), unintentional weight loss (OR = 1.33;  $p = 0.003$ ) and age (OR = 1.085;  $p = 0.004$ ). Other factors such as length of the surgical specimen (OR = 1.079;  $p = 0.028$ ) and erythrocyte sedimentation rate (OR = 1.042;  $p < 0.001$ ) were also statistically significant. The model was accurate (C-index = 0.921), reliable (pHosmer-Lemeshow = 0.733) and consistent in the bootstrap sensitivity analysis. No significant association was detected between TAB result and number of days of previous systemic corticosteroid treatment ( $p = 0.146$ ). However, an association was observed between TAB result and the total accumulated dose of previous systemic corticotherapy ( $p = 0.043$ ).

**CONCLUSIONS:** Exhaustive anamnesis and clinical examination remain of paramount importance in the diagnosis of GCA. To improve the yield of TAB, it should be performed specially in older patients with GCA-compatible clinic. TAB could be avoided in patients with an isolated elevation of acute phase reactants, without GCA-compatible clinic.

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DOI: 10.1111/j.1755-3768.2012.02505.x  
PMID: 22938720 [Indexed for MEDLINE]

2615. Clin Exp Rheumatol. 2012 May-Jun;30(3 Suppl 72):S3-6. Epub 2012 Sep 25.

The impact of MEFV gene identification on FMF: an appraisal after 15 years.

Ben-Chetrit E, Touitou I.

PMID: 22935552 [Indexed for MEDLINE]

2616. Clin Exp Rheumatol. 2012 Nov-Dec;30(6):943-6. Epub 2012 Dec 17.

# Long-term clinical course of patients carrying the Q703K mutation in the NLRP3 gene: a case series.

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**BACKGROUND:** Cryopyrin-associated periodic syndromes (CAPS) comprise a spectrum of apparently distinct, rare, autosomal dominant autoinflammatory disorders of increasing severity caused by NLRP3 gene mutations. The Q703K allele is a variant of unknown pathogenetic significance, and has been considered to be both a clinically unremarkable polymorphism and a low- penetrance mutation.

**OBJECTIVES:** To analyse the long-term clinical course in a cohort of patients presenting with periodic fever attacks and carrying the Q703K mutation in the NLRP3 gene.

**METHODS:** Seven Caucasian patients (mean age  $37.3 \pm 8.5$  years, 2 males and 5 females) were identified as carriers of the Q703K mutation among 71 patients with CAPS-like symptoms.

**RESULTS:** The mean age at disease onset was  $25.58 \pm 16.08$  years and the mean disease duration was  $12.28 \pm 8.36$ . The mean number of febrile episodes was  $7.56 \pm 6.48$  and the mean duration of fever attacks was  $6.66 \pm 4.71$  days. Six out of 7 patients had a low grade fever, while 1 patient had no fever episodes. All patients were characterised by symptoms consistent with recurrent inflammatory syndrome. Six patients out of 7 presented skin lesions, 4/7 arthralgia, 4/7 myalgia, 4/7 conjunctivitis, 3/7 headache. All patients also complained of severe fatigue. In 4/7 patients symptoms were triggered or worsened by generalised cold exposure.

**CONCLUSIONS:** We suggest that patients carrying the low-penetrance Q703K mutation in the NLRP3 gene may present with FCAS-like symptoms. However, given the high frequency of healthy carriers, the role of additional, still unknown genetic and/or environmental modifiers is conceivable.

PMID: 22935299 [Indexed for MEDLINE]

Serum leptin, resistin, visfatin and adiponectin levels in tumor necrosis factor receptor-associated periodic syndrome (TRAPS).

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**OBJECTIVES:** The aims of our study were to evaluate serum leptin, resistin, visfatin and adiponectin levels in patients with tumour necrosis factor receptor-associated periodic syndrome (TRAPS), in comparison to healthy controls, and to correlate their levels to parameters of disease activity and/or severity.

**METHODS:** Serum leptin, resistin, visfatin and adiponectin levels were obtained from 14 TRAPS patients carrying mutations involving cysteine residues, from 16 TRAPS patients carrying other mutations, and from 16 healthy controls.

Demographic, clinical and laboratory parameters, including amyloidosis were entered for each patient. Comparisons between groups as well as reciprocal comparisons have been evaluated.

**RESULTS:** Serum leptin, resistin, visfatin and adiponectin did not significantly differ among the 3 groups. Patients carrying cysteine residues mutations showed lower visfatin serum levels than patients carrying other mutations ( $p<0.02$ ).

Serum leptin significantly correlated with the number of attacks/year (multiple  $R=0.32$ , multiple adjusted  $R^2=0.19$ ,  $p<0.03$ ). Serum adiponectin levels significantly correlated with the presence of amyloidosis (multiple  $R=0.79$ , multiple adjusted  $R^2=0.57$ ,  $p<0.03$ ). Adiponectin values were a significant predictor for amyloidosis (AUC 0.75, 95 CI: 0.56-0.94,  $p<0.03$ ), with a predicting cut-off value set at 23.16 pg/ml, the predictive positive value was 53.8%.

Visfatin serum levels resulted respectively related to leptin ( $r_s=0.42$ ,  $r^2=0.18$ ,  $p<0.02$ ) and to resistin ( $r_s=0.57$ ,  $r^2=0.32$ ,  $p<0.01$ ) serum levels; whilst leptin and resistin serum levels did not reciprocally correlate.

**CONCLUSIONS:** Although a prospective design study and larger cohort are mandatory, adipokines serum levels and their correlations with parameters of disease activity and/or severity seem to show a baseline pattern in TRAPS patients.

PMID: 22935190 [Indexed for MEDLINE]

2618. Clin Exp Rheumatol. 2012 May-Jun;30(3 Suppl 72):S117. Epub 2012 Sep 25.

A case of Takayasu's arteritis associated with familial Mediterranean fever.

Alibaz-Oner F, Yilmaz N, Can M, Direskeneli H.

PMID: 22935091 [Indexed for MEDLINE]

2619. Scand J Rheumatol. 2013;42(2):159-62. doi: 10.3109/03009742.2012.699551. Epub 2012 Aug 31.

Apoptosis-associated speck-like protein containing a CARD (ASC) expression profiles in familial Mediterranean fever (FMF) patients with different MEFV mutation patterns.

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**OBJECTIVES:** The inflammasome complex and the inflammatory pathway have been implicated in the pathogenesis of the most common autoinflammatory disorder, familial Mediterranean fever (FMF). Pyrin, the protein product of the FMF gene MEFV, interacts with the inflammasome complex adaptor protein ASC/PYCARD (apoptosis-associated speck-like protein with a CARD). Pyrin and ASC can both function as either inducers or suppressors of the cellular inflammatory response. We aimed to characterize ASC-induced gene expression profiles in FMF patients with different MEFV mutation patterns.

**METHODS:** A total of 165 Caucasian patients with clinical and molecular FMF diagnoses were enrolled in the study. ASC gene expression was quantified by real-time quantitative reverse transcriptase polymerase chain reaction (qRT-PCR).

**RESULTS:** ASC mRNA expression was increased in the MEFV mutation-positive group



compared to the mutation-negative group ( $p = 0.001$ ). The fold changes of ASC expression in the M694V homozygous ( $p = 0.02$ ), M694V heterozygous ( $p = 0.012$ ), compound heterozygous ( $p = 0.002$ ), and R202Q/P369S/R408Q ( $p = 0.00$ ) groups relative to the MEFV mutation-negative group were +2.4, +2.7, +3, and +3.4, respectively. qRT-PCR did not reveal a significant difference in ASC mRNA expression levels among the MEFV mutation-positive groups ( $p > 0.05$ ).

CONCLUSION: ASC mRNA expression was up-regulated in patients carrying MEFV mutations independent of mutation type. There was no significant relationship between specific MEFV genotypes and the level of ASC expression in the patient group analysed. Thus, the findings of this work may suggest a crucial relationship between mutant MEFV/pyrin and remarkable ASC up-regulation in FMF inflammation.

DOI: 10.3109/03009742.2012.699551

PMID: 22934972 [Indexed for MEDLINE]

2620. Ophthalmic Genet. 2012 Dec;33(4):179-86. doi: 10.3109/13816810.2012.695421. Epub 2012 Aug 27.

Ocular manifestations of the autoinflammatory syndromes.

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The autoinflammatory syndromes are rare inherited disorders characterized by recurrent attacks of multi-system inflammation caused by genetic mutations that result in abnormal upregulation of key innate immune mediators. The term autoinflammatory syndromes includes a broad variety of disorders, including cryopyrin-associated periodic syndromes (CAPS) such as neonatal onset multisystem inflammatory disease (NOMID), familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), periodic fever syndromes, including familial Mediterranean fever (FMF), TNF receptor-1 associated periodic syndrome (TRAPS), and Blau syndrome. Ocular manifestations are frequent and diverse in affected patients, and visual impairment and blindness are not uncommon sequelae of chronic active disease. Novel therapeutic interventions targeting specific pathophysiologic mechanisms have been extremely promising in the treatment of

these disorders. The purpose of this article is to provide a review of these disorders with a focus on pathogenesis, clinical manifestations, ophthalmologic involvement, and available treatment options.

DOI: 10.3109/13816810.2012.695421

PMID: 22924780 [Indexed for MEDLINE]

2621. Case Rep Pediatr. 2012;2012:323681. doi: 10.1155/2012/323681. Epub 2012 Aug 9.

Early-onset chronic inflammatory disease associated with maternal microchimerism.

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Maternal microchimerism (mMc) refers to the presence of a small population of cells originating from the mother. Whether mMc leads to autoimmune responses in children remains controversial. We describe here an 11-year-old boy with persistent fever and elevated levels of C-reactive protein from infancy onward. During infancy, the patient presented with high fever, skin rashes, and hepatic dysfunction. Careful examination including a liver biopsy failed to reveal the cause. At 4 years old, petechiae developed associated with thrombocytopenia and positive anti-dsDNA autoantibodies. Steroid pulse therapy was effective, but the effect of low-dose prednisone was insufficient. At age 9, an extensive differential diagnosis was considered especially for infantile onset autoinflammatory disorders but failed to make a definitive diagnosis. On admission, the patient exhibited short stature, hepatosplenomegaly, generalized superficial lymphadenopathy, and rashes. Laboratory findings revealed anemia, elevated levels of inflammation markers, and hypergammaglobulinemia. Serum complement levels were normal. Serum levels of IL-6 and B-cell activating factor were elevated. Viral infections were not identified. Although HLA typing revealed no noninherited maternal antigens in lymphocytes, female cells were demonstrated in the patient's skin and lymph nodes, suggesting that maternal microchimerism might be involved in the pathogenesis of fever without source in infants.

DOI: 10.1155/2012/323681

PMCID: PMC3423865

2622. Blood. 2012 Oct 11;120(15):3126-35. doi: 10.1182/blood-2012-04-425595. Epub 2012 Aug 24.

PSTPIP2 deficiency in mice causes osteopenia and increased differentiation of multipotent myeloid precursors into osteoclasts.

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Missense mutations that reduce or abrogate myeloid cell expression of the F-BAR domain protein, proline serine threonine phosphatase-interacting protein 2 (PSTPIP2), lead to autoinflammatory disease involving extramedullary hematopoiesis, skin and bone lesions. However, little is known about how PSTPIP2 regulates osteoclast development. Here we examined how PSTPIP2 deficiency causes osteopenia and bone lesions, using the mouse PSTPIP2 mutations, cmo, which fails to express PSTPIP2 and Lupo, in which PSTPIP2 is dysfunctional. In both models, serum levels of the pro-osteoclastogenic factor, MIP-1 $\alpha$ , were elevated and CSF-1 receptor (CSF-1R)-dependent production of MIP-1 $\alpha$  by macrophages was increased. Treatment of cmo mice with a dual specificity CSF-1R and c-Kit inhibitor, PLX3397, decreased circulating MIP-1 $\alpha$  and ameliorated the extramedullary hematopoiesis, inflammation, and osteopenia, demonstrating that aberrant myelopoiesis drives disease. Purified osteoclast precursors from PSTPIP2-deficient mice exhibit increased osteoclastogenesis in vitro and were used to probe the structural requirements for PSTPIP2 suppression of osteoclast development. PSTPIP2 tyrosine phosphorylation and a functional F-BAR domain were essential for PSTPIP2 inhibition of TRAP expression and osteoclast precursor fusion, whereas interaction with PEST-type phosphatases was only required for suppression of TRAP expression. Thus, PSTPIP2 acts as a negative feedback regulator of CSF-1R signaling to suppress inflammation and osteoclastogenesis.

2623. Cell Biochem Biophys. 2013 Mar;65(2):181-6. doi: 10.1007/s12013-012-9416-4.

Analysis of cytotoxic T lymphocyte antigen-4 (CTLA-4) promoter -318C/T and +49A/G gene polymorphisms in Turkish patients with familial Mediterranean fever.

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Either the role of the adaptive immune system or the interaction between innate and adaptive immune systems in familial Mediterranean fever (FMF) is not clear so far. So, we planned to search for the interaction between the innate and adaptive immune systems in the pathogenesis of FMF by investigating polymorphism for CTLA-4 gene, which plays a role in controlling antigen presentation to T cells. We also aimed to investigate whether there is an association between -318C/T and +49A/G polymorphisms in the CTLA-4 gene and the main clinical features of the disease. 75 FMF patients and 179 controls were studied. Polymorphism was detected by the PCR-RFLP technique. The CT genotype and T allele frequencies of the -318C/T polymorphism and the haplotype frequency for the -318T/+49A in the CTLA-4 gene were higher in the FMF (21.3, 21.3, and 10.7 %) when compared with the controls (10.6, 10.6, and 5.3 %;  $P = 0.029$ ,  $0.044$ , and  $0.029$ ). However, these differences did not reach a statistically significant level after the Bonferroni correction. A significant linkage disequilibrium was found between the -318C/T and +49A/G polymorphisms in the CTLA-4 gene ( $D' = 0.997$ ,  $r(2) = 0.027$ ,  $P = 0.0002$ ). Genotype and carrier frequencies of the CTLA-4 gene +49A/G polymorphism were not significantly different between FMF patients and healthy controls. No association was found between the studied polymorphisms and the main clinical features of the disease. Our findings suggest that although not statistically significant, higher frequencies of CTLA-4 gene -318CT genotype, T allele, and -318T/+49A haplotype in FMF patients may be related to the non-autoimmune pathogenesis of FMF.

DOI: 10.1007/s12013-012-9416-4

PMID: 22923220 [Indexed for MEDLINE]

2624. J Microbiol Immunol Infect. 2014 Dec;47(6):550-4. doi: 10.1016/j.jmii.2012.07.003. Epub 2012 Aug 24.

Recurrent abdominal pain as the presentation of tumor necrosis factor receptor-associated periodic syndrome (TRAPS) in an Asian girl: a case report and review of the literature.

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Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is characterized by periodic fever, cutaneous rash, conjunctivitis, lymphadenopathy, abdominal pain, myalgia, and arthralgia. It is a rare autosomal dominant disease and strongly associated with heterozygous mutations in the tumor necrosis factor (TNF) receptor super family 1A (TNFRSF1A) gene. It is believed to be more common in Western countries than in Asian countries. Here, we present the case of a 14-year-old girl with periodic fever and abdominal pain with elevation of inflammatory markers for 2 years. After extensive work-up of infectious etiology with negative results, the diagnosis of TRAPS was made although no gene mutations were identified in the TNFRSF1A gene, MVK gene, and NALP3/CIAS1 gene. She had partial clinical response to corticosteroids and immunomodulatory agents. However, the treatment response to TNF- $\alpha$  inhibitor etanercept was dramatic. She has remained symptom free under regular weekly to biweekly etanercept treatment for 2 years. We also reviewed the related literature and summarized the data of 10 Asian cases of TRAPS.

DOI: 10.1016/j.jmii.2012.07.003

PMID: 22921805 [Indexed for MEDLINE]

2625. J Am Acad Dermatol. 2013 Feb;68(2):270-7. doi: 10.1016/j.jaad.2012.07.018. Epub 2012 Aug 22.

Decreased prevalence of atopic features in patients with psoriatic arthritis, but not in psoriasis vulgaris.

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**BACKGROUND:** The prevalence of atopic disorders is reduced in patients with various autoinflammatory diseases but, to our knowledge, this association has not been studied in psoriasis vulgaris or psoriatic arthritis (PSA).

**OBJECTIVE:** Prevalence of hay fever, asthma, and sensitization to common aeroallergens was compared in patients with psoriasis vulgaris to patients with PSA and control subjects; we also investigated whether atopy influences the arthritis activity and severity scores in patients with PSA.

**METHODS:** In a cross-sectional cohort study design, the differences in patient-reported lifetime prevalence of atopic disorders and serum IgE directed against common aeroallergens were compared. The effect of atopy on arthritis severity was assessed using the 28-joint Disease Activity Score and Health Assessment Questionnaire. Logistic regression models were used to calculate crude and adjusted odds ratios with 95% confidence intervals (CI) for presence of atopy.

**RESULTS:** A total of 168 patients with PSA, 133 patients with psoriasis vulgaris, and 147 control subjects were included. The lifetime prevalence of hay fever did not differ across groups. Patients with PSA were less likely to have had asthma than control subjects (adjusted odds ratio 0.20; 95% CI 0.04-0.92) and they were less likely to be sensitized (adjusted odds ratio 0.50; 95% CI 0.25-0.99). Health Assessment Questionnaire-visual analog scales for pain and for patient global score were significantly reduced by sensitization to common aeroallergens (beta-coefficients -0.54 [95% CI -0.84 to -0.25] and -18.4 [95% CI -28.5 to -8.25], respectively.)

LIMITATIONS: This was a cross-sectional, small-numbered study.

CONCLUSION: Atopy may protect against development of PSA and diminish its severity.

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DOI: 10.1016/j.jaad.2012.07.018

PMID: 22921106 [Indexed for MEDLINE]

2626. *Mod Rheumatol*. 2013 Mar;23(2):210-7. doi: 10.1007/s10165-012-0737-3. Epub 2012 Aug 24.

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) in Japan: a review of the literature.

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Erratum in

*Mod Rheumatol*. 2013 Mar;23(2):218.

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is a dominantly inherited autoinflammatory syndrome that is characterized by recurrent episodes of fever attacks associated with rashes, abdominal pain, myalgia, conjunctivitis, chest pain, and arthralgia. Some patients have severe abdominal pain leading to abdominal surgery. Most reported cases of TRAPS involve patients of European ancestry, but there have been nine reports of patients with TRAPS in Japan. Here, we review these nine case reports. Reported TNFRSF1A gene mutations in these nine index patients were C70S, T61I, C70G, C30Y, C30R, N101K, and N25D. Fever (100 %) was seen in all 23 cases. Most patients developed rash (erythema) (84.6 %) and arthralgia (73.3 %), and half suffered from myalgia (54.5 %) and abdominal pain (50.0 %). Although one-half of the patients suffered from abdominal pain, none underwent surgery. In contrast, only a small percentage of

patients suffered from chest pain (20.0 %), conjunctivitis (20.0 %), and headache (10.0 %). Almost all cases (95.7 %) concerned patients whose relatives suffered from periodic fever. These findings suggest that the clinical features of Japanese TRAPS patients may be milder than those of patients in Western countries.

DOI: 10.1007/s10165-012-0737-3

PMID: 22918594 [Indexed for MEDLINE]

2627. Postgrad Med. 2012 Jul;124(4):189-96. doi: 10.3810/pgm.2012.07.2579.

Effect of cyclosporine on the pharmacokinetics of colchicine in healthy subjects.

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**OBJECTIVE:** Colchicine and cyclosporine are often administered together, particularly in patients who have undergone solid-organ transplantation. However, the potential for drug-drug interactions between these agents resulting in colchicine toxicity is high.

**METHODS:** This study sought to determine the effect of cyclosporine (100-mg capsule) on the pharmacokinetics of the US Food and Drug Administration-approved formulation of colchicine (0.6-mg tablet) after single oral-dose administration in 24 healthy subjects under fasted conditions in a phase 1, single-sequence, 2-period drug-drug interaction trial.

**RESULTS:** Coadministration of cyclosporine increased colchicine maximum observed plasma concentration, area under the plasma concentration-time curve to the last measurable time point, and area under the plasma concentration-time curve to time infinity on average by 224%, 216%, and 215% (ie, almost doubled), respectively, and decreased colchicine oral clearance on average by 72% (from 48.24 to 13.42 L/h), indicating substantially higher colchicine exposures when combined with cyclosporine, compared with colchicine alone.

**CONCLUSION:** The dose of colchicine should be reduced by  $\geq 50\%$  when colchicine and cyclosporine are administered concurrently for treatment and prophylaxis of gout flares or treatment of patients with familial Mediterranean fever. Health care professionals should be vigilant for potential adverse events during



colchicine/cyclosporine coadministration, notably in patients who have undergone solid-organ transplantation.

TRIAL REGISTRATION: [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) identifier NCT00983931 (<http://clinicaltrials.gov/ct2/show/NCT00983931>).

DOI: 10.3810/pgm.2012.07.2579

PMID: 22913907 [Indexed for MEDLINE]

2628. Curr Rheumatol Rep. 2012 Oct;14(5):395-401. doi: 10.1007/s11926-012-0273-3.

Juvenile spondyloarthropathies.

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Spondyloarthropathy (or spondyloarthritis) can begin in childhood (defined as individuals less than 16 years of age). These diseases are distinct in childhood, when compared with adult-onset disease. Because of overlapping features, especially sacroiliac joint involvement, diagnostic difficulty may arise from Behcet's disease, as well as familial Mediterranean fever. Despite advances in diagnostic techniques such as magnetic resonance imaging, the diagnosis of juvenile spondyloarthropathy may still be delayed many years from the onset of symptoms. Treatment of juvenile spondyloarthropathy has advanced rapidly in the last several years, with increasing evidence that agents targeting tumor necrosis factor are effective. These agents also have serious complications, including induction of other autoimmune diseases.

DOI: 10.1007/s11926-012-0273-3

PMID: 22911266 [Indexed for MEDLINE]

2629. Intern Med J. 2012 Aug;42(8):952-4. doi: 10.1111/j.1445-5994.2012.02853.x.

Late presentation of familial Mediterranean fever associated with P369S/R408Q variant in the MEFV gene.

Hannan LM, Ward J, Ebringer R, McDonald CF.

DOI: 10.1111/j.1445-5994.2012.02853.x

PMID: 22906030 [Indexed for MEDLINE]

2630. Clin Genet. 2013 Jun;83(6):576-81. doi: 10.1111/j.1399-0004.2012.01940.x. Epub 2012 Aug 20.

Misdiagnosis of familial Mediterranean fever in patients with Anderson-Fabry disease.

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Comment in

Clin Genet. 2013 Jun;83(6):582-3.

Fabry disease (FD) is an underdiagnosed pathology due to its symptomatology that overlaps with various systemic and rheumatic disorders, including familial Mediterranean fever (FMF). We examined the Mediterranean fever (MEFV) and  $\alpha$ -galactosidase A (GLA) genes, whose mutations are responsible for FMF and FD, respectively, in 42 unrelated patients diagnosed with FMF, which revealed significant ambiguity regarding some of the symptoms which are also present in FD. The objective of this study was to determine the spectrum of mutations present in these genes, in order to identify cases of mistaken diagnosis of FMF and/or missed diagnosis of FD. Ten out of 42 patients had one mutation in homozygosis or two different mutations in heterozygosis in the MEFV gene; 20/42 had a single heterozygous mutation, and 12/42 did not have genetic alterations in MEFV. The analysis of the GLA gene conducted on all the samples revealed that three subjects, and some members of their families, had two different exonic mutations associated with FD. Family studies allowed us to identify eight other cases of FD, bringing the total undiagnosed subjects to 11/53. Analyzing the MEFV and GLA genes in patients with clinical diagnoses of FMF proved to be

fundamentally important for the reduction of diagnostic errors.

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DOI: 10.1111/j.1399-0004.2012.01940.x

PMID: 22905681 [Indexed for MEDLINE]

2631. Adv Exp Med Biol. 2012;750:116-32. doi: 10.1007/978-1-4614-3461-0\_9.

Immunoregulation by naturally occurring and disease-associated autoantibodies : binding to cytokines and their role in regulation of T-cell responses.

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The role of naturally occurring autoantibodies (NAbs) in homeostasis and in disease manifestations is poorly understood. In the present chapter, we review how NAbs may interfere with the cytokine network and how NAbs, through formation of complement-activating immune complexes with soluble self-antigens, may promote the uptake and presentation of self-molecules by antigen-presenting cells. Both naturally occurring and disease-associated autoantibodies against a variety of cytokines have been reported, including NAbs against interleukin (IL)-1 $\alpha$ , IL-6, IL-8, IL-10, granulocyte-macrophage colony-stimulating factor, interferon (IFN)- $\alpha$ , IFN- $\beta$ , IFN- $\gamma$ , macrophage chemotactic protein-1 and IL-21. NAbs against a variety of other self-antigens have also been reported, and using thyroglobulin as an example we discuss how NAbs are capable of promoting uptake of immune complexes via complement receptors and Fc-receptors on antigen-presenting cells and thereby regulate T-cell activity. Knowledge of the influence of NAbs against cytokines on immune homeostasis is likely to have wide-ranging implications both in understanding pathogenesis and in treatment of many immunoinflammatory disorders, including a number of autoimmune and autoinflammatory diseases.

DOI: 10.1007/978-1-4614-3461-0\_9

PMID: 22903670 [Indexed for MEDLINE]

2632. Eur J Pediatr. 2012 Dec;171(12):1775-85. doi: 10.1007/s00431-012-1803-8. Epub 2012 Aug 19.

Familial Mediterranean fever in Germany: epidemiological, clinical, and genetic characteristics of a pediatric population.

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Familial Mediterranean fever (FMF) is an autoinflammatory disease and belongs to the heterogeneous group of hereditary recurrent fever syndromes (HRFs). AIMS: The aims of the study were to determine the incidence of FMF in Germany and to describe the spectrum of pyrin mutations and the clinical characteristics in children. A prospective surveillance of children with HRF including FMF was conducted in Germany during a time period of 3 years by the German paediatric surveillance unit for rare paediatric diseases (ESPED). Monthly inquiries were sent to 370 children's hospitals (Clinic-ESPED, n1) and to 23 laboratories (Laboratory-ESPED, n2). Inclusion criteria were children  $\leq 16$  years of age, disease-associated pyrin mutations, and more than three self-limiting episodes of fever  $>38.5^{\circ}\text{C}$  with increased inflammation markers. In n1, 122 patients with FMF and 225 pyrin mutations were identified. Ninety-two of 122 (75 %) children were of Turkish origin. The minimum incidence of FMF was estimated to be 3 (95 % CI: 2.48-3.54) per 10(6) person-years in the whole children population and 55 (95 % CI: 46-66) per 10(6) person-years in Turkish children living in Germany. N1 U n2 amounted to 593 asymptomatic and symptomatic carriers of 895 mutations (overlap of 73 cases with 134 mutations). p.Met694Val (45 %), p.Met680Ile (14 %), p.Val726Ala (12 %), and p.Glu148Gln (11.5 %) were the most common pyrin mutations.

CONCLUSIONS: Despite FMF being the most frequent of the HRFs, its incidence in Germany is low. Twenty-five to 50 FMF patients  $\leq 16$  years are newly diagnosed per year. The disease is most commonly observed in individuals of Turkish ancestry.

DOI: 10.1007/s00431-012-1803-8

2633. Semin Arthritis Rheum. 2013 Feb;42(4):413-6. doi: 10.1016/j.semarthrit.2012.06.003. Epub 2012 Aug 15.

Canakinumab in Schnitzler syndrome.

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**OBJECTIVES:** Daily injections of anakinra, an interleukin-1-receptor antagonist, have been reported to control effectively the symptoms and signs of Schnitzler syndrome, a rare acquired autoinflammatory disorder, presenting in adulthood by intermittent fever, urticarial rash, and paraproteinemia, usually IgM.

Canakinumab, a fully human interleukin-1 $\beta$  monoclonal antibody, approved for the cryoporin-associated periodic syndrome, may offer a practical advantage because its half-life of  $\sim$ 28 days may allow less frequent dosing. The present trial was designed to test canakinumab in patients with Schnitzler syndrome.

**METHODS:** A patient with Schnitzler syndrome was treated with canakinumab, 150 mg subcutaneously injection every 8 weeks for 6 consecutive months. Injections were resumed in case of a flare following discontinuation.

**RESULTS:** Canakinumab induced a swift and sustained clinical response, with disappearance of fever and arthralgias, near abolishment of fatigue and rash, and substantial reduction of C-reactive protein levels. Interruption of canakinumab after four 8-weekly injections led to a flare 10 weeks after the last administration, which was countered as soon as canakinumab injections were resumed. The patient remained in complete remission. Canakinumab was well tolerated. No injection site reactions, other adverse events, or laboratory abnormalities were observed.

**CONCLUSIONS:** Canakinumab has potential for the treatment of Schnitzler syndrome (ClinicalTrials.gov.number, NCT01245127).

DOI: 10.1016/j.semarthrit.2012.06.003  
PMID: 22901459 [Indexed for MEDLINE]

2634. Intern Med. 2012;51(16):2239-44. Epub 2012 Aug 15.

An atypical familial Mediterranean fever patient who developed ulcers in the terminal ileum and recurrent abscess-like lesions in multiple organs.

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We herein describe the case of a 25-year-old woman who suffered from atypical familial Mediterranean fever for more than a decade. She presented with a periodic fever, abdominal pain and persistent ulcers in the terminal ileum. Colchicine was effective, and familial Mediterranean fever was diagnosed. A genetic study showed a heterozygous E148Q mutation in the MEFV gene. Multiple, recurrent, abscess-like lesions developed asynchronously in the spleen, liver, and a lung. Infliximab was administered when colchicine treatment became ineffective. However, infliximab treatment soon became ineffective, probably because antibodies were generated against it. Therefore, etanercept treatment was started, and the patient showed an immediate response.

PMID: 22892512 [Indexed for MEDLINE]

2635. Isr Med Assoc J. 2012 Jun;14(6):367-71.

Large hemorrhagic pericardial effusion.

Barski L(1), Shalev L, Zektser M, Malada-Mazri H, Abramov D, Rafaely Y.

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**BACKGROUND:** Establishing the etiology of a large pericardial effusion is of crucial importance since it is likely the result of a serious underlying disease. However, there is a paucity of literature on the diagnostic management of patients with large hemorrhagic effusions.

**OBJECTIVES:** To analyze the management of patients with large hemorrhagic pericardial effusion.

**METHODS:** We reviewed seven cases of large hemorrhagic pericardial effusions hospitalized in Soroka University Medical Center in 2010.

**RESULTS:** All seven patients underwent a comprehensive evaluation followed by pericardiocentesis. Six of the seven cases demonstrated echocardiographic signs of tamponade. Large amounts of hemorrhagic pericardial effusion (> 600 ml) were aspirated from each patient. A pericardial window was performed in two of the seven patients. The causes for the hemorrhagic effusions were malignancy, streptococcal infection, familial Mediterranean fever exacerbation, and idiopathic. Four patients completely recovered. The condition of one patient improved after initiation of chemotherapy for lung cancer, and two patients with progressive malignancies passed away shortly after discharge. Two cases of massive pulmonary embolism were diagnosed and resolved spontaneously without anticoagulation therapy after the effusion was treated.

**CONCLUSIONS:** All cases of pericardial effusion resolved after rapid diagnosis and initiation of specific treatment. Pulmonary embolism in situ may be a complication of large pericardial effusions that does not require anticoagulation treatment after the effusion resolves.

PMID: 22891398 [Indexed for MEDLINE]

2636. Curr Opin Allergy Clin Immunol. 2012 Oct;12(5):477-84. doi: 10.1097/ACI.0b013e3283574d0c.

The role of interleukin-1 in allergy-related disorders.

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**PURPOSE OF REVIEW:** Interleukin-1 $\beta$  (IL-1 $\beta$ ) is a potent proinflammatory cytokine, which is involved in many inflammatory conditions including autoinflammatory and allergic disorders. This review provides insights into recent advances of our understanding of the pathogenesis of IL-1 $\beta$ -associated allergy-related disorders.

**RECENT FINDINGS:** In autoinflammatory as well as allergic diseases such as contact hypersensitivity, atopic dermatitis and bronchial asthma, dysfunctional inflammasome processing has been demonstrated to account for IL-1 $\beta$ -induced inflammation. IL-1-neutralizing drugs have been shown to completely suppress or markedly reduce inflammatory responses in clinical studies and experimental models of urticarial autoinflammatory diseases as well as common allergic disorders.

**SUMMARY:** The recent findings support a crucial role for IL-1 $\beta$  and inflammasome components in a variety of allergy-related disorders.

DOI: 10.1097/ACI.0b013e3283574d0c

PMID: 22885885 [Indexed for MEDLINE]

2637. Indian Pediatr. 2012 Jul;49(7):583-5.

Novel mutations causing hyperimmunoglobulin D and periodic fever syndrome.

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Hyperimmunoglobulin D and periodic fever syndrome (HIDS) is a rare, hereditary autoinflammatory condition characterized by recurrent inflammatory episodes. We report a 9-year-old boy, diagnosed with HIDS due to two novel mutations, c.62C>T (p.Ala21Val) and c.372-6T>C (probable splicing defect), in the mevalonate kinase (MVK) gene. The pathogenicity of these mutations was confirmed by measurement of low MVK enzyme activity in cultured primary skin fibroblasts of the patient. The symptoms have been refractory to therapy with steroids and non steroidal anti inflammatory drugs. This report expands the genetic and ethnic spectrum of HIDS.



PMID: 22885443 [Indexed for MEDLINE]

2638. Autoimmun Rev. 2012 Nov;12(1):44-51. doi: 10.1016/j.autrev.2012.07.028. Epub 2012 Aug 2.

Blau syndrome, clinical and genetic aspects.

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Blau syndrome (BS) is a rare autosomal dominant, autoinflammatory syndrome characterized by the clinical triad of granulomatous recurrent uveitis, dermatitis and symmetric arthritis. The gene responsible for BS has been identified in the caspase recruitment domain gene CARD15/NOD2. In the majority of patients, the disease is characterized by early onset, usually before 3-4 years of age. The manifestations at disease onset are usually represented by articular and cutaneous involvement signs, generally followed later by ocular manifestations which are often the most relevant morbidity of BS. In some cases the presence of fever is also observed; atypical cases of BS have been reported with cardiovascular, neurological, renal, intestinal and other organ involvement. The rarity and the variations in the severity and evolution of its expressions do not permit sufficient data about optimal treatment for patients with BS. The first step of therapy is represented by the use of corticosteroids and successively, in case of unsatisfactory response, by additional treatment with immunosuppressive agents. The results with biologic anti-cytokine agents, such as anti-TNF $\alpha$  and anti-IL1 $\beta$ , are different, particularly with regard to ocular morbidity. Clinical and genetic aspects of the familial and the sporadic form of BS will be discussed and focused on. A description of a case study of an Italian family is also included.

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DOI: 10.1016/j.autrev.2012.07.028

PMID: 22884558 [Indexed for MEDLINE]

2639. Autoimmun Rev. 2012 Nov;12(1):66-71. doi: 10.1016/j.autrev.2012.07.024. Epub 2012 Aug 2.

Gout as autoinflammatory disease: new mechanisms for more appropriated treatment targets.

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Gout is probably one of the oldest diseases affecting men. This is not surprising especially for the active role that innate immunity seems to play in its pathogenesis. It is fascinating to observe as this ancestral mechanism of defense feels that microcrystals are a danger, quite similar to infectious agents. New advances have revealed that at the base of the powerful inflammatory reaction stimulated by monosodium urate crystals there are many complexes cellular mechanisms, mainly involving inflammasome and toll-like receptors. Subsequently, there is an early increase of proinflammatory cytokines responsible for the acute attack, followed in few days by their reduction along with an increase of anti-inflammatory cytokines, probably main actors of the resolution phase. New targets have also been identified for the reduction of hyperuricemia, the prerequisite of gout, in order to prevent new attacks and the deposition of urate crystals in and around the joints. All these aspects, leading to deeper insight, have suggested new treatments, some of which are already available while others are likely to become available in the near future.

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DOI: 10.1016/j.autrev.2012.07.024

PMID: 22884557 [Indexed for MEDLINE]

2640. Autoimmun Rev. 2012 Nov;12(1):60-5. doi: 10.1016/j.autrev.2012.07.023. Epub 2012 Aug 2.

## Recurrent pericarditis: autoimmune or autoinflammatory?

Maestroni S(1), Di Corato PR, Cumetti D, Chiara DB, Ghidoni S, Prisacaru L, Cantarini L, Imazio M, Penco S, Pedrotti P, Caforio AL, Doria A, Brucato A.

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Idiopathic recurrent acute pericarditis (IRAP) represents the most troublesome complication of acute pericarditis and occurs in up to 20-50% of patients. It is generally idiopathic or postcardiac injury. IRAP is a disease of suspected immune-mediated pathogenesis. On the other hand, it has been suggested that some of these patients might have an atypical or subclinical form of an autoinflammatory disease, e.g. genetic disorders characterized by primary dysfunction of the innate immune system and caused by mutations of genes involved in the inflammatory response. We found that IRAP patients were negative for mutations associated with familial Mediterranean fever, but 6% (8/131 patients) carry a mutation in the TNFRSF1A gene, encoding the receptor for tumor necrosis factor- $\alpha$ . C-reactive protein (CRP) may be useful to follow the disease activity and guide the appropriate length of therapy, with continuation of the attack doses of the drugs until CRP normalization, at which time tapering may be considered. IRAP often needs a multidrug therapy: NSAIDs or aspirin at high dosages every 6-8h, corticosteroids only rarely, at low dosages and with a very gradual tapering (months) and colchicine at low dosages if tolerated. Anakinra could be a solution for patients who do not tolerate other therapies.

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DOI: 10.1016/j.autrev.2012.07.023

PMID: 22884556 [Indexed for MEDLINE]

2641. Autoimmun Rev. 2012 Nov;12(1):72-6. doi: 10.1016/j.autrev.2012.07.025. Epub 2012 Aug 2.

Incomplete response to colchicine in M694V homozygote FMF patients.

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**BACKGROUND:** Previous studies have shown that with prophylactic colchicine 65% of the patients suffering from Familial Mediterranean fever (FMF) will show a complete response, 30% a partial response and about 5% will show minimum or no response. These studies were performed before the isolation of the disease gene.

Genotyping enables us to study the response rates according to specific mutations. We have witnessed a large number of M694V homozygotes who do not respond well to colchicine despite being treated with maximal sustained doses.

**AIM:** To assess the response rates to colchicine in M694V homozygote FMF patients in comparison to other prevalent genotypes.

**METHODS:** We conducted a telephonic survey which included 112 FMF patients: 40 M694V homozygotes, and 2 comparison groups of 41 M694V/V726A compound heterozygotes and 31 V726A homozygotes. The questionnaire included demographic, social and clinical features, colchicine dose, response rates and reported side effects.

**RESULTS:** M694 homozygotes showed a more severe disease, and were treated with higher doses of colchicine (average dose  $1.98 \pm 0.56$  compared to  $1.47 \pm 0.58$ ,  $p=0.0001$  and  $1.13 \pm 0.41$ ,  $p<0.001$  in the M694V/V726A compound heterozygotes and the V726A homozygotes, respectively); Colchicine related side effects were noted in 40% of the M694V homozygotes. The average rate of attacks in treated M694V homozygotes ( $0.70 \pm 1.06$ ) was higher compared to the two other groups ( $0.14 \pm 0.26$ ,  $p=0.002$  and  $0.08 \pm 0.20$ ,  $p=0.0009$ , respectively) and only 25% of them reported no attacks in the last year. None of the patients who took part in this study had amyloidosis. Side effects limiting the dose of colchicine were noted in 40% of the M694V homozygotes.

**CONCLUSIONS:** Despite receiving higher doses of colchicine the prevalence of complete responders among M694V homozygotes is much lower than previously appreciated. The results highlight the need for additional treatment modalities for these patients.

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DOI: 10.1016/j.autrev.2012.07.025

PMID: 22884555 [Indexed for MEDLINE]

2642. Autoimmun Rev. 2012 Nov;12(1):38-43. doi: 10.1016/j.autrev.2012.07.020. Epub 2012 Aug 2.

Tumour necrosis factor receptor-associated periodic syndrome (TRAPS): state of the art and future perspectives.

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Tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is an autosomal dominant autoinflammatory disorder characterized by periodic fever episodes, arthralgia, myalgia, abdominal pain, serositis, and skin rash. TRAPS is caused by mutations in the gene encoding the TNF Receptor Super Family 1A (TNFRSF1A) on chromosome 12p13. The identification of TNFRSF1A mutations as the genetic cause of TRAPS coincided with the wider use of biological agents in medicine and raised the possibility that blocking TNF could potentially represent the primary therapeutic goal in TRAPS, thus disclosing new treatment choices for this complex disease. Anti-TNF therapy in TRAPS has been based on etanercept, a recombinant human TNFR (p75)-Fc fusion protein comprising two receptors linked by an IgG(1) Fc fragment. However a decrease in responsiveness to etanercept over time has been described, and it may be due to a non-specific action of etanercept in TRAPS; its efficacy may reflect 'generic' anti-inflammatory properties. Long-term adherence to etanercept is poor and a significant number of patients need to switch to anti-interleukin (IL)-1 $\beta$  therapy. In fact, the IL-1 receptor antagonist anakinra has recently been shown to prevent disease relapses both in the short- and in the long-term, and to induce a prompt and stable disease remission.

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DOI: 10.1016/j.autrev.2012.07.020

PMID: 22884554 [Indexed for MEDLINE]

2643. Autoimmun Rev. 2012 Nov;12(1):81-6. doi: 10.1016/j.autrev.2012.07.027. Epub 2012 Aug 2.

Biologic drugs in autoinflammatory syndromes.

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**PURPOSE OF THE REVIEW:** Inherited autoinflammatory syndromes are conditions caused by mutations of proteins playing a pivotal role in the regulation of the innate immunity leading to an uncontrolled inflammation. The understanding of the molecular pathways involved in these disorders has shed a new light on the pattern of activation and maintenance of the inflammatory response and disclosed new molecular therapeutic targets. In this review we give a start of the art of the use of biologics in these disorders.

**MAIN TOPICS:** The dramatic response to anti IL-1 drugs in cryopyrin-associated periodic syndromes represents the brightest example of the possibility to completely dampen inflammation in these severe disorders with the selective blockade of a single pivotal cytokine. Periodic fevers are characterized by recurrent episodes of fever, usually treated with on demand steroids. However the increasing frequency of fever episodes or the development of a chronic disease course may require a continuous long-term treatment, with anti-TNF or IL-1 blockers in mevalonate kinase deficiency and TNF-receptor associated periodic syndrome. Anti-IL-1 treatment is also effective in FMF patients resistant or partially responsive to colchicine. The deficiency of the interleukin-1-receptor antagonist (DIRA) is caused by mutations in the gene encoding for the interleukin-1 receptor antagonist (IL-1Ra). In this case the recombinant IL-1Ra (anakinra) is the treatment of choice. Due to their extreme rarity the response to the available biologic drugs in other autoinflammatory diseases is still largely anecdotal.

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DOI: 10.1016/j.autrev.2012.07.027

PMID: 22884553 [Indexed for MEDLINE]

2644. Autoimmun Rev. 2012 Nov;12(1):56-9. doi: 10.1016/j.autrev.2012.07.022. Epub 2012 Aug 2.

Systemic juvenile idiopathic arthritis.

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Systemic juvenile idiopathic arthritis (sJIA) sets well apart from all the other forms of JIA. Several observations show that sJIA is etiopathogenically different from all the other forms of JIA and has a prominent autoinflammatory component. A major role in the pathogenesis is played by two proinflammatory cytokines, interleukin-6 and interleukin-1. The specific inhibition of these two cytokines is going to change not only the therapeutic approach to the disease but also, presumably, its long term prognosis.

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DOI: 10.1016/j.autrev.2012.07.022

PMID: 22884552 [Indexed for MEDLINE]

2645. Autoimmun Rev. 2012 Nov;12(1):1-4. doi: 10.1016/j.autrev.2012.07.013. Epub 2012 Aug 2.

Autoinflammatory diseases: how to put the fire inside the body out?

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Autoinflammatory diseases (AIDs) are a group of distinct hereditary disorders characterized by unexplained, recurrent episodes of fever and severe inflammation, most commonly involving skin, joints, gut, and eyes. Mutations in inflammasome-related proteins, particularly in NOD-like receptor (NLR) genes, have been strongly associated with the occurrence of AIDs. However, new genes and dysfunctional proteins have recently been identified and the spectrum of AIDs is ever-expanding. In fact, it has been suggested to encompass other disorders which share some clinical features with AIDs, but are not clearly familial, or are not characterized by fever as a prominent symptom, or are polygenic. In this issue of Autoimmunity Reviews some novel and burning aspects of AIDs were covered and the relationship between AIDs and autoimmune diseases was discussed.

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DOI: 10.1016/j.autrev.2012.07.013

PMID: 22884550 [Indexed for MEDLINE]

2646. MMW Fortschr Med. 2012 Jun 28;154(12):18-20, 22.

[When the fever will not respond].

[Article in German]

Füessl HS.

PMID: 22880289 [Indexed for MEDLINE]

2647. Autophagy. 2012 Sep;8(9):1286-99. doi: 10.4161/auto.21212. Epub 2012 Aug 14.

Autophagy in immunity: implications in etiology of autoimmune/autoinflammatory diseases.

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Autophagy is now emerging as a spotlight in trafficking events that activate innate and adaptive immunity. It facilitates innate pathogen detection and antigen presentation, as well as pathogen clearance and lymphocyte homeostasis. In this review, we first summarize new insights into its functions in immunity, which underlie its associations with autoimmunity. As some lines of evidence are emerging to support its role in autoimmune and autoinflammatory diseases, we further discuss whether and how it affects autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis, diabetes mellitus and multiple sclerosis, as well as autoinflammatory diseases, such as Crohn disease and vitiligo.

DOI: 10.4161/auto.21212

PMCID: PMC3442876

PMID: 22878595 [Indexed for MEDLINE]

2648. Autoimmun Rev. 2012 Nov;12(1):22-30. doi: 10.1016/j.autrev.2012.07.018. Epub 2012 Aug 2.

Autoinflammation and autoimmunity: bridging the divide.

Doria A(1), Zen M, Bettio S, Gatto M, Bassi N, Nalotto L, Ghirardello A, Iaccarino L, Punzi L.

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As soon as autoinflammatory diseases (AIDs) emerged as new entities, they have been linked to the well known world of autoimmunity. In fact, AIDs and systemic autoimmune diseases (ADs), share some characteristics: they start with the prefix "auto" to define a pathological process directed against self; they are systemic diseases, frequently involving musculoskeletal system; both include monogenic and polygenic diseases. From the pathogenetic point of view, they are characterized by a chronic activation of immune system, which eventually leads to tissue

inflammation in genetically predisposed individuals. Nevertheless, the specific effectors of the damage are different in the two groups of diseases: in AIDs the innate immune system directly causes tissue inflammation, whereas in ADs the innate immune system activates the adaptive immune system which, in turn, is responsible for the inflammatory process. Mutations in inflammasome-related proteins, particularly in NOD-like receptor (NLR) genes, have been strongly associated to the occurrence of AIDs, whereas the link between inflammasome and ADs is less clear. However, a role for this multiprotein-complex in some ADs can be postulated, since a wide spectrum of endogenous danger signals can activate NLRs and inflammasome products, including IL-1 $\beta$ , can activate adaptive immunity. An association between single nucleotide polymorphisms (SNPs) localized in the inflammasome gene NLRP1 and systemic lupus erythematosus has recently been reported. AIDs and ADs are currently subdivided into two different groups, but looking at their similarities they might be considered as a single group of diseases with a large immune pathological and clinical spectrum which includes at one end pure ADs and at the other end pure AIDs.

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DOI: 10.1016/j.autrev.2012.07.018

PMID: 22878274 [Indexed for MEDLINE]

2649. Autoimmun Rev. 2012 Nov;12(1):31-7. doi: 10.1016/j.autrev.2012.07.019. Epub 2012 Aug 2.

Familial Mediterranean fever: new phenotypes.

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Familial Mediterranean fever (FMF) is an inherited autosomal recessive disorder, ethnically restricted and commonly found among individuals of Mediterranean descent, caused by MEditerranean FeVer gene (MEFV) mutations on chromosome 16. It is the most frequent periodic febrile syndrome among the autoinflammatory syndromes. Clinically, FMF can be distinguished into three phenotypes: type 1,

which is commonly associated with recurrent short episodes of inflammation and serositis, including fever, peritonitis, synovitis, pleuritis, but also pericarditis, orchitis or meningitis episodes; type 2, characterized by the evidence of reactive amyloid-associated (AA) amyloidosis, the most severe complication of FMF, as the first clinical manifestation of the disease in an otherwise asymptomatic individual; type 3, referred to the 'silent' homozygous or compound heterozygote state, in which two MEFV mutations are detected without signs or symptoms of FMF nor of AA amyloidosis. In the recent years it has been observed that also heterozygous mutation carriers can suffer from a mild or incomplete form of FMF, named 'FMF-like' disease. The influence of other modifiers genes and/or environmental factors can contribute to the variable penetrance and to the phenotypic variability of FMF. The insight into complex clinical and genetic cases will provide adjunctive details for the comprehension of the mechanisms of this kaleidoscopic disease.

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DOI: 10.1016/j.autrev.2012.07.019

PMID: 22878273 [Indexed for MEDLINE]

2650. Autoimmun Rev. 2012 Nov;12(1):52-5. doi: 10.1016/j.autrev.2012.07.021. Epub 2012 Aug 2.

Periodic fevers with aphthous stomatitis, pharyngitis, and adenitis (PFAPA).

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PFAPA syndrome (acronym of periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis) is the most common cause of periodic fever in childhood. Nowadays, it is considered part of the wide family of the autoinflammatory diseases, but a genetic or molecular marker hasn't been identified yet, therefore, its etiology is still unknown. Diagnosis is essentially based on clinical criteria but, especially in younger children, it is sometimes difficult to differentiate it from other hereditary periodic fever syndromes. Fever attacks

in PFAPA have a spontaneous resolution and in a high rate of patients the syndrome ends spontaneously over time. Treatment is still a matter of debate. Usually a single administration of oral corticosteroids aborts attacks. Tonsillectomy may be an alternative option but its role remains to be clarified.

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DOI: 10.1016/j.autrev.2012.07.021

PMID: 22878272 [Indexed for MEDLINE]

2651. Autoimmun Rev. 2012 Nov;12(1):5-9. doi: 10.1016/j.autrev.2012.07.014. Epub 2012 Aug 2.

New genetic interpretation of old diseases.

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The title of this section, "New genetic interpretation of old diseases," perfectly reflects the unique history of our understanding of autoinflammatory diseases (AIDs). Indeed, the main clinical feature of most AIDs is the recurrent fever, a symptom that has been extensively documented for centuries. However, the first clear description of a patient suffering from the AID prototype, familial Mediterranean fever (FMF), has only been reported in 1908, although dating studies have shown that ancestral mutations appeared in biblical times. FMF and 11 other AID genes were identified between 1997 and 2011. The patient's care has dramatically benefited from the elucidation of the molecular defect underlying similar diseases of the innate immune system. However, accumulation of present and future sequence data let us anticipate that interpretation of genetic diagnosis will be increasingly difficult.

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DOI: 10.1016/j.autrev.2012.07.014

PMID: 22878270 [Indexed for MEDLINE]

2652. Autoimmun Rev. 2012 Nov;12(1):14-7. doi: 10.1016/j.autrev.2012.07.016. Epub 2012 Aug 2.

Amyloidosis in autoinflammatory syndromes.

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AA amyloidosis may still dramatically impact on the outcome of patients with autoinflammatory diseases, particularly when diagnosis is delayed. Clinicians should maintain a high level of attention to identify early this severe complication. Initial signs mostly reflect kidney damage, with proteinuria, with or without renal failure, being the more frequent presenting feature. If SAA levels are not rapidly normalized, progression toward end-stage kidney disease and dialysis invariably occurs. Over time, multiple organ failure, including heart, autonomic and adrenal insufficiency usually complicates the disease course. Limited tools are still available to predict the occurrence of AA, therefore close monitoring of at risk patients is required to detect promptly the "early red flags" through periodic search for preclinical amyloid deposits and regular assessment of proteinuria and SAA concentration. Effective control of the underlying inflammatory process may halt disease progression and even reverse damage. Anti-cytokine agents are becoming the mainstay of therapy to prevent and treat AA, including patients with FMF that do not respond or do not tolerate adequate colchicine dosages. Renal transplantation can be considered in selected patients progressing to end-stage kidney disease. Novel treatments are under development, targeting key molecular events in the fibrillogenesis process.

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DOI: 10.1016/j.autrev.2012.07.016

PMID: 22878269 [Indexed for MEDLINE]

2653. Autoimmun Rev. 2012 Nov;12(1):10-3. doi: 10.1016/j.autrev.2012.07.015. Epub 2012

Aug 2.

The diagnostic evaluation of patients with potential adult-onset autoinflammatory disorders: our experience and review of the literature.

Muscari I(1), Iacoponi F, Cantarini L, Lucherini OM, Simonini G, Brizi MG, Vitale A, Frediani B, Cimaz R, Galeazzi M.

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Hereditary periodic fever syndromes (HPFSs) are a group of inherited disorders of the innate immune system caused by mutations of genes involved in the regulation or activation of the inflammatory response, which belong to the category of autoinflammatory disorders. Most HPFs typically have an onset in pediatric age, while a limited number of patients experience disease onset during adulthood. The relative rarity and lack of information on adult-onset autoinflammatory diseases make it likely that genetic testing is often inconclusive. Recently, we have identified a set of variables related to the probability of detecting gene mutations in MEFV, responsible for familial Mediterranean fever, and TNFRSF1A, responsible for tumor necrosis factor receptor-associated periodic syndrome. In addition, we have proposed a diagnostic score for identifying those patients at high risk of carrying mutations in these genes. However, before the score can be recommended for application, further evaluation by means of longitudinal studies on different ethnicities and different populations deriving from other geographical areas is needed in order to definitively verify both its sensitivity and its specificity. The present manuscript offers our suggestions on how to establish a differential diagnosis for adult-onset HPFs, as well as a review of the literature, and we also provide a score revision available online.

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DOI: 10.1016/j.autrev.2012.07.015

PMID: 22878268 [Indexed for MEDLINE]

2654. Georgian Med News. 2012 May;(206):44-8.

[The role of aldosterone and IL-6 in the pathogenesis of inflammation in familial Mediterranean fever].

[Article in Russian]

Dzhndoian ZT, Martirosian NG.

The aim of the article was to study the role of aldosterone and IL-6 - in the pathogenesis of familial Mediterranean fever (FMF). The hypersecretion of IL-6 and "the syndrome of aldosterone excess" in patients with FMF was revealed. The hyperactivity of the inflammatory process in FMF is one of the phenotypic factors of defective gene expression in FMF. In the course of the development of familial Mediterranean fever in presence of amyloidosis, the inhibition of mineralocorticoid function, and constantly elevated IL-6 levels, which gradually progresses bringing to an exhaustion of that function and to the dissociation of the adaptative-regulatory homeostasis. The given introduction enlarges view points of pathogenesis of FMF and confirms the multifactorial nature of FMF, in the development of which besides the genetic factors, has a great role of phenotypic factors, as well. From the phenotypic factors is hyperaldosteronemia, hyperinterleukinemia-6, which reacts with defective gene and promotes its expression, and brings to the development of FMF attacks.

PMID: 22870837 [Indexed for MEDLINE]

2655. J Leukoc Biol. 2012 Nov;92(5):951-8. doi: 10.1189/jlb.0512265. Epub 2012 Aug 2.

Redox control of NLRP3 inflammasome activation in health and disease.

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Shifts in the redox balance between ROS and antioxidants regulate innate immunity at various levels. Changes in the redox microenvironment modulate the activation

potential of the NLRP3 inflammasome, a signaling platform that activates caspase-1, allowing the maturation of IL-1 $\beta$ . However, a clear definition of the underlying mechanism is missing. In this essay, I review the most-credited theories on inflammasome activation. In particular, I will focus on the redox-mediated mechanisms that regulate the assembly of NLRP3 inflammasome and discuss how aberrations in them are implicated in the pathogenesis of autoinflammatory diseases.

DOI: 10.1189/jlb.0512265

PMID: 22859832 [Indexed for MEDLINE]

2656. J Clin Rheumatol. 2012 Aug;18(5):227-8. doi: 10.1097/RHU.0b013e318269430d.

Pericarditis: sometimes an autoinflammatory disease?

Goldsmith DP.

Erratum in

J Clin Rheumatol. 2012 Sep;18(6):309.

DOI: 10.1097/RHU.0b013e318269430d

PMID: 22854783 [Indexed for MEDLINE]

2657. Cleve Clin J Med. 2012 Aug;79(8):569-81. doi: 10.3949/ccjm.79a.11184.

Autoinflammatory syndromes: fever is not always a sign of infection.

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Autoinflammatory syndromes are a newly understood group of conditions characterized by recurrent episodes of fever, rash, and serositis. Generalists and specialists should know about and consider these syndromes in the differential diagnosis of recurrent fever. This article reviews the genetics,



pathophysiology, clinical presentation, and treatment of several of these relatively recently discovered diseases.

DOI: 10.3949/ccjm.79a.11184

PMID: 22854436 [Indexed for MEDLINE]

2658. Nat Rev Drug Discov. 2012 Aug;11(8):633-52. doi: 10.1038/nrd3800.

Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases.

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Interleukin-1 (IL-1) is a highly active pro-inflammatory cytokine that lowers pain thresholds and damages tissues. Monotherapy blocking IL-1 activity in autoinflammatory syndromes results in a rapid and sustained reduction in disease severity, including reversal of inflammation-mediated loss of sight, hearing and organ function. This approach can therefore be effective in treating common conditions such as post-infarction heart failure, and trials targeting a broad spectrum of new indications are underway. So far, three IL-1-targeted agents have been approved: the IL-1 receptor antagonist anakinra, the soluble decoy receptor rilonacept and the neutralizing monoclonal anti-IL-1 $\beta$  antibody canakinumab. In addition, a monoclonal antibody directed against the IL-1 receptor and a neutralizing anti-IL-1 $\alpha$  antibody are in clinical trials.

DOI: 10.1038/nrd3800

PMCID: PMC3644509

PMID: 22850787 [Indexed for MEDLINE]

2659. Rheumatol Int. 2013 Apr;33(4):993-9. doi: 10.1007/s00296-012-2496-z. Epub 2012 Jul 31.

Revisiting secondary amyloidosis for an inadequately investigated feature: dyslipidemia.

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Secondary amyloidosis is the most frequent form of the systemic amyloidosis around the world. Data on frequency and nature of dyslipidemia in patients with secondary amyloidosis are not conclusive. We evaluated the lipid abnormalities and their association with clinical and laboratory characteristics of the patients with secondary amyloidosis. The reports of the kidney biopsies performed in our hospital were reviewed. Clinical and laboratory data of the patients with biopsy-proven secondary amyloidosis were analyzed retrospectively. A total of 102 patients were diagnosed as having secondary amyloidosis. Familial Mediterranean fever was the leading cause of secondary amyloidosis accounting for 42.2 % of the cases. The most frequent indication for kidney biopsy was the nephrotic range proteinuria. The most common clinical and laboratory characteristics at the time of the diagnosis were edema, proteinuria and impaired renal function. The frequency of the nephrotic range proteinuria and microscopic hematuria were 75.5 and 18.6 %, respectively. Dyslipidemia was found in 88 % of the cases. Serum lipids significantly correlated with estimated glomerular filtration rate (eGFR), but not with serum albumin or urine protein levels. We demonstrated that majority of the patients with secondary amyloidosis had serum lipid abnormalities. Dyslipidemia was closely associated with GFR in a manner that patients with advanced stage kidney disease had lower serum lipid levels.

DOI: 10.1007/s00296-012-2496-z

PMID: 22847292 [Indexed for MEDLINE]

2660. Reumatismo. 2012 Jul 19;64(3):172-4. doi: 10.4081/reumatismo.2012.172.

Familial Mediterranean fever without cardinal symptoms and role of genetic screening.

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Familial Mediterranean fever is an autosomal recessive disorder characterized by paroxysmal episodes of fever and serosal inflammation. The classical presentation is fever and severe recurrent abdominal pain due to serositis that lasts for one to three days and the resolves spontaneously. Between the episodes patients are asymptomatic. Ninety-five percent of patients with familial mediterranean fever have painful episodes localized to the abdomen, which is usually the dominant manifestation of the disease. Herein, we present a case of 34-year-old man with incomplete abdominal pain episode of familial mediterranean fever limited to the epigastrium and had no cardinal symptoms of this disease. The diagnosis was made by genetic screening. Successful treatment response was achieved by colchicine.

DOI: 10.4081/reumatismo.2012.172

PMID: 22842301 [Indexed for MEDLINE]

2661. Clin Rheumatol. 2012 Oct;31(10):1517-9. doi: 10.1007/s10067-012-2039-8. Epub 2012 Jul 27.

Periodic fever as the manifestation of primary Sjogren's syndrome: a case report and literature review.

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A 56-year-old male had periodic fever for 5 years and suffered from auditory hallucination and hearing impairment for 3 years. Xerostomia, xerophthalmia, elevated anti-SSA/Ro titer, positive Schirmer's test, and lymphocyte infiltrate of mucoserous gland in lip biopsy of this case confirmed the diagnosis of primary Sjogren's syndrome (pSS). We review literature for fever and neuropsychiatric involvement in pSS case series. Though fever is present in 6-41 % pSS cases, periodic fever has not been reported. Auditory hallucination was rare in cases

with pSS. The literature review alerts clinicians that fever and neurological manifestations were not uncommon in pSS cases.

DOI: 10.1007/s10067-012-2039-8

PMID: 22837018 [Indexed for MEDLINE]

2662. Clin Kidney J. 2012 Apr;5(2):146-149.

AA amyloidosis in the renal allograft: a report of two cases and review of the literature.

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AA amyloidosis is a disorder characterized by the abnormal formation, accumulation and systemic deposition of fibrillary material that frequently involves the kidney. Recurrent AA amyloidosis in the renal allograft has been documented in patients with tuberculosis, familial Mediterranean fever, ankylosing spondylitis, chronic pyelonephritis and rheumatoid arthritis. De novo AA amyloidosis is rarely described. We report two cases of AA amyloidosis in the renal allograft. Our first case is a 47-year-old male with a history of ankylosing spondylitis who developed end-stage renal disease reportedly from tubulointerstitial nephritis from non-steroidal anti-inflammatory agent use. A biopsy was never performed. One year after transplantation, AA amyloidosis was identified in the femoral head and 8 years post-transplantation, AA amyloidosis was identified in the renal allograft. He was treated with colchicine and adalimumab and has stable renal function at 1 year-follow-up. Our second case is a 57-year-old male with a long history of intravenous drug use and hepatitis C infection who developed end-stage kidney disease due to AA amyloidosis. Our second patient's course was complicated by renal adenovirus, pulmonary aspergillosis and hepatitis C with AA amyloidosis subsequently being identified in the allograft 2.5 years post-transplantation. Renal allograft function remains stable 4-years post-transplantation. These reports describe clinical and pathologic features of two cases of AA amyloidosis presenting with proteinuria and focal involvement of the renal allograft.

DOI: 10.1093/ckj/sfs019

PMCID: PMC3341841

PMID: 22833808

2663. Curr Opin Rheumatol. 2012 Sep;24(5):506-14. doi: 10.1097/BOR.0b013e32835689b9.

Monogenic causes of inflammatory disease in rheumatology.

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**PURPOSE OF REVIEW:** To review the single-gene defects that can mimic rheumatologic diseases.

**RECENT FINDINGS:** Monogenic disorders can cause a variety of diseases that may be seen by a rheumatologist. Many of these illnesses present with recurrent episodes of arthritis, rash, fever and inflammation, and serositis. Recent discoveries have defined inflammatory diseases due to mutations in the IL-1 and IL-36 receptor antagonists, as well as the immunoproteasome. Further study of well defined monogenic causes of inflammatory diseases, such as FMF, PAPA, TRAPS, and HIDS, has elucidated the pathophysiology of these diseases leading to targeted immunotherapy with anticytokine biological medications.

**SUMMARY:** A rheumatologist should be aware of the genetic causes of inflammatory disease mimics. This will not only help with the prognosis of these diseases, but also help to guide therapy to prevent long-term complications associated with these disorders.

DOI: 10.1097/BOR.0b013e32835689b9

PMID: 22832824 [Indexed for MEDLINE]

2664. Pediatr Int. 2012 Aug;54(4):552-5. doi: 10.1111/j.1442-200X.2011.03525.x.

Successful treatment of a patient with tumor necrosis factor receptor-associated periodic syndrome using a half-dose of etanercept.

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TNF receptor-associated periodic syndrome (TRAPS) is caused by mutations of TNFRSF1A gene and characterized by recurrent febrile episodes of prolonged duration and initial good response to steroids. Etanercept, a TNF blocker, has been used as a putative molecular-targeted agent for TRAPS, with some patients showing limited efficacy. Here, we report a patient with TRAPS who recovered from steroid dependency by etanercept and kept remission with a reduced dose of etanercept. The pathophysiology of TRAPS still remains to be elucidated and several hypotheses have been proposed. In the most recent hypothesis, the concerted action of wild-type and mutant TNF receptors plays an important role in provoking enhanced inflammation in TRAPS. The excellent response to etanercept in our patient suggested that there is heterogeneity in TRAPS patients in terms of the contribution of normal TNF signaling to autoinflammation.

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DOI: 10.1111/j.1442-200X.2011.03525.x

PMID: 22830546 [Indexed for MEDLINE]

2665. Eksp Klin Gastroenterol. 2012;(3):114-7.

[Celiac disease is a 33-year-old man with periodic disease].

[Article in Russian]

Krums LM, Golovanova EV, Khomeriki SG, Varlamicheva AA, Dorofeev AS.

The article presents a clinical case of a 33-year-old Armenian man, who suffered from two rare diseases: Familial Mediterranean fever and celiac. The diagnosis of Familial Mediterranean fever: abdominal-feverish form, is confirmed by genetic markers. The morphological study of duodenal mucosa's specimens confirms the

celiac.

PMID: 22830235 [Indexed for MEDLINE]

2666. Nat Rev Immunol. 2012 Jul 25;12(8):570-80. doi: 10.1038/nri3261.

Lighting the fires within: the cell biology of autoinflammatory diseases.

Park H(1), Bourla AB, Kastner DL, Colbert RA, Siegel RM.

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Autoinflammatory diseases are characterized by seemingly unprovoked pathological activation of the innate immune system in the absence of autoantibodies or autoreactive T cells. Discovery of the causative mutations underlying several monogenic autoinflammatory diseases has identified key regulators of innate immune responses. Recent studies have highlighted the role of misfolding, oligomerization and abnormal trafficking of pathogenic mutant proteins in triggering autoinflammation, and suggest that more common rheumatic diseases may have an autoinflammatory component. This coincides with recent discoveries of new links between endoplasmic reticulum stress and inflammatory signalling pathways, which support the emerging view that autoinflammatory diseases may be due to pathological dysregulation of stress-sensing pathways that normally function in host defence.

DOI: 10.1038/nri3261

PMCID: PMC4165575

PMID: 22828911 [Indexed for MEDLINE]

2667. Mod Rheumatol. 2013 Jul;23(4):837-9. doi: 10.1007/s10165-012-0720-z. Epub 2012 Jul 21.

A case of infantile Takayasu arteritis with a p.D382E NOD2 mutation: an unusual

phenotype of Blau syndrome/early-onset sarcoidosis?

Inoue Y(1), Kawaguchi Y, Shimojo N, Yamaguchi K, Morita Y, Nakano T, Arima T, Tomiita M, Kohno Y.

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Blau syndrome/early-onset sarcoidosis (Blau/EOS) is an autoinflammatory disease characterized by granulomatous arthritis, uveitis, and skin rash. It has been shown that gain-of-function NOD2 mutations cause Blau/EOS. In this paper, we describe a patient with a gain-of-function NOD2 mutation who developed infantile Takayasu arteritis, which is rare in Blau/EOS, but who has not yet had significant granulomatous changes in joints, eyes, or skin. We suspect that this case is an unusual phenotype of Blau/EOS.

DOI: 10.1007/s10165-012-0720-z

PMID: 22821420 [Indexed for MEDLINE]

2668. Rheumatol Int. 2013 Apr;33(4):893-7. doi: 10.1007/s00296-012-2453-x. Epub 2012 Jul 20.

The factors considered as trigger for the attacks in patients with familial Mediterranean fever.

Karadag O(1), Tufan A, Yazisiz V, Ureten K, Yilmaz S, Cinar M, Akdogan A, Erdem H, Ozturk MA, Pay S, Dinc A.

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Although the inflammatory cascade of familial Mediterranean fever (FMF) is partially understood, triggering factors of those attacks has not been studied well. It is supposed that physical stresses such as cold exposure, tiredness and emotional stresses could provoke attacks. This study is aimed to survey the factors regarded as triggering the attacks in patients with FMF and their relationship with MEFV gene mutations. Clinical findings and genetic mutations



(consist of M694V, M694I, M680I, V726A, E148Q) of patients were recorded. Patients were questioned about cold exposure, emotional stress, tiredness, long-lasting standing, long-duration travel, starvation, high intake of food, trauma, and infection as triggering factors for the attacks with both serositis and musculoskeletal pain. The study is comprised of 275 FMF patients (male/female: 177/98). The most common triggering factors for the attacks with serositis were cold exposure (59.3 %), emotional stress (49.8 %), tiredness (40.0 %) and menstruation (33.7 % in females). Long-lasting standing (78.8 %), long-duration travel (64.1 %) and tiredness (47.8 %) were the triggering factors for the attacks with musculoskeletal symptoms. The relationships between MEFV mutations and triggering factors were found as M694V allele with starvation, E148Q allele with high intake of food and V726A allele with long-duration travel. The attacks with serositis seem to be triggered by those factors to which whole body exposed, whereas the attacks with musculoskeletal complaints seem to be triggered by those factors to which regional or local part of body exposed. Since the number of alleles was small, a clear conclusion for a relationship between a particular gene variant and a specific trigger was not made.

DOI: 10.1007/s00296-012-2453-x

PMID: 22814791 [Indexed for MEDLINE]

2669. Respiration. 2012;84(4):334-6. Epub 2012 Jul 19.

A 44-year-old Japanese female with recurrent pleuritis.

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DOI: 10.1159/000339410

PMID: 22813955 [Indexed for MEDLINE]

2670. J Clin Gastroenterol. 2013 Mar;47(3):e23-7. doi: 10.1097/MCG.0b013e3182597992.

Association of the MEFV gene variations with inflammatory bowel disease in

Turkey.

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**BACKGROUND:** Association of NOD2 (CARD15) gene mutations with inflammatory bowel diseases (IBD) is well known. We herein aimed to investigate the role of familial Mediterranean fever-associated MEFV variations in IBD patients as additional regional-specific risk factor.

**STUDY:** One hundred thirty-seven (78 female, 56.9%) IBD patients [62 Crohn's disease (CD), 75 ulcerative colitis (UC)] were enrolled into the study. The diagnosis of all patients was confirmed by colonoscopy, histopathology, and the clinical findings. One hundred one healthy donors' samples were used as healthy controls. All patients were genotyped for the most common E148Q, M608I, M694V, and V726A variations of the MEFV and R702W, G908R, and 1007fs of the NOD2.

**RESULTS:** The overall MEFV variation frequency was found to be higher in the IBD (25.5%) patients (28% in UC, 22.6% in CD) compared with controls (9.9%,  $P=0.006$ ). This association was stronger with the penetrant exon 10 variations (M694V, M680I, V726A; odds ratio =4.5,  $P=0.001$ ). Contribution of M694V was higher compared with the other variations (14.5% in CD, 17.3% in UC and 3% in controls, odds ratio =6.039, 95% confidence intervals, 1.7-20.7,  $P=0.002$ ). The overall frequency of 3 NOD2 variants in the IBD group was not different from that of controls.

**CONCLUSIONS:** The results of this study suggest that the MEFV variations may be an additional susceptibility factor for IBD in certain parts of the world where the carrier rate is high, and the genetic background of the IBD patients may show regional changes.

DOI: 10.1097/MCG.0b013e3182597992

PMID: 22810105 [Indexed for MEDLINE]

2671. West Indian Med J. 2012 Jan;61(1):28-31.

Mediterranean fever gene mutations in Greek patients with Behcet's disease.

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**OBJECTIVE:** It is known that clinical similarities between Behcet's disease and Familial Mediterranean Fever have led to the hypothesis of a common pathogenesis. Familial Mediterranean Fever is caused by MEFV gene mutations coding for pyrin. Therefore, we examined whether these pyrin mutations are also associated with Behcet's disease.

**METHODS:** Molecular testing for pyrin mutations was performed in 96 unrelated Greek patients with an established diagnosis of Behcets disease. The results were compared with an analysis for pyrin mutations in 140 unrelated healthy Greek controls.

**RESULTS:** We found no pyrin mutations among the Behcet cases tested; this result is comparable with the control group.

**CONCLUSIONS:** Pyrin gene mutations in Greek patients with Behcet's disease are not more common than those in the general population. This finding is not in agreement with the findings in other populations. It is suggested that screening for pyrin mutations not be included in the evaluation of Greeks suspected to have Behcet's disease.

PMID: 22808562 [Indexed for MEDLINE]

2672. Z Rheumatol. 2012 Aug;71(6):515-7. doi: 10.1007/s00393-012-0989-5.

[Therapy refractory polyarthritis and fever].

[Article in German]

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Primary manifestation of an autoinflammatory systemic disease was found in a 15-year-old patient, which initially ran a fulminant course. The course was first controlled by therapy with steroids and cyclosporin A. In the course of the disease, the patient developed a therapy refractory polyarthritis, which failed to respond to a combination of disease-modifying antirheumatic drugs (DMARDs) and tumor necrosis factor (TNF) inhibitors. A good disease control could only be achieved with an interleukin 6 (IL-6) blockade and DMARDs.

DOI: 10.1007/s00393-012-0989-5

PMID: 22802026 [Indexed for MEDLINE]

2673. Biochemistry. 2012 Aug 21;51(33):6545-55. doi: 10.1021/bi3006626. Epub 2012 Aug 8.

TNFR1 signaling is associated with backbone conformational changes of receptor dimers consistent with overactivation in the R92Q TRAPS mutant.

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The widely accepted model for tumor necrosis factor 1 (TNFR1) signaling is that ligand binding causes receptor trimerization, which triggers a reorganization of cytosolic domains and thus initiates intracellular signaling. This model of stoichiometrically driven receptor activation does not account for the occurrence of ligand independent signaling in overexpressed systems, nor does it explain the constitutive activity of the R92Q mutant associated with TRAPS. More recently, ligand binding has been shown to result in the formation of high molecular weight, oligomeric networks. Although the dimer, shown to be the preligand structure, is thought to remain present within ligand-receptor networks, it is unknown whether network formation or ligand-induced structural change to the dimer itself is the trigger for TNFR1 signaling. In the present study, we investigate the available crystal structures of TNFR1 to explore backbone

dynamics and infer conformational transitions associated with ligand binding. Using normal-mode analysis, we characterize the dynamic coupling between the TNFR1 ligand binding and membrane proximal domains and suggest a mechanism for ligand-induced activation. Furthermore, our data are supported experimentally by FRET showing that the constitutively active R92Q mutant adopts an altered conformation compared to wild-type. Collectively, our results suggest that the signaling competent architecture is the receptor dimer and that ligand binding modifies domain mobilities intrinsic to the receptor structure, allowing it to sample a separate, active conformation mediated by network formation.

DOI: 10.1021/bi3006626

PMID: 22799488 [Indexed for MEDLINE]

2674. Turk J Gastroenterol. 2012 Jun;23(3):290-3.

A rare cause of massive ascites: familial Mediterranean fever.

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Familial Mediterranean fever is an autosomal recessive disease characterized by recurrent fever and peritoneal and pleural inflammation. It is an inherited disorder commonly found in Armenians, Turks, Arabs, Balkans, and Jews originating from North African countries. A small amount of peritoneal fluid collection can be observed during peritoneal attacks in patients with Familial Mediterranean fever, but chronic ascites has been described rarely in these patients. A 42-year-old female patient was admitted to our clinic in June 2010 with fever, severe abdominal pain and abdominal distention that had continued for one month. There was no family history of periodic fevers or abdominal pain. We could not find any cause for ascites, including tuberculosis. A diagnosis of Familial Mediterranean fever was suspected based on the clinical findings and her family history. She was screened for mutations causing Familial Mediterranean fever, and when found to be homozygous for M694V, treatment with colchicine was initiated. After treatment, the amount of ascites decreased, and relief of symptoms was

confirmed during a follow-up. In conclusion, because Familial Mediterranean fever is common in our country, it should be considered in the differential diagnosis of patients with ascites of unknown etiology in populations where hereditary inflammatory disease is endemic.

PMID: 22798132 [Indexed for MEDLINE]

2675. Curr Clin Pharmacol. 2012 Nov;7(4):271-5.

An overview of interleukin-1 receptor antagonist, anakinra, in the treatment of cutaneous diseases.

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Interleukin (IL)-1 is a pivotal proinflammatory cytokine consisting of two molecular species, IL-1 $\alpha$  and IL-1 $\beta$ . Anakinra (Kineret), a recombinant human IL-1 receptor antagonist, is regarded as a biological agent which blocks the inflammatory effects of IL-1. The aim of this review was to search the literatures and summarizes in vivo, in vitro and human studies on anakinra uses in dermatological disorders. The results show that anakinra is currently used clinically for the treatment of a variety of skin conditions such as psoriasis, atopic dermatitis, photoaging, melanoma, Schnitzler syndrome, pyoderma gangraenosum, PAPA syndrome, hidradenitis suppurativa, lamellar ichthyosis, Sweet's syndrome, panniculitis, Muckle-Wells syndrome, familial Mediterranean fever, SAPHO syndrome and other disorders. Notably, anakinra is expensive to produce and administer. Injection is the route of therapy and allergic reaction is most possible.

PMID: 22794157 [Indexed for MEDLINE]

2676. Intern Med. 2012;51(13):1765-8. Epub 2012 Jul 1.

Three family members with familial Mediterranean fever carrying the M694V mutation showed different clinical presentations.

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Familial Mediterranean fever (FMF) is an inherited disease characterized by recurrent episodes of fever and serositis. FMF is caused by mutations in the MEFV gene that encodes pyrin/marenostrin. The 5 most frequent mutations are M694V, M694I, V726A, M680I and E148Q. Here, we reported 3 FMF patients, a sister and two brothers, who have the same M694V mutation with different clinical presentations. While the sister presented with abdominal pain, one of the brothers presented with erysipelas-like erythema and the other brother with bilateral sacroiliitis. Here, we report the different clinical courses of FMF in a family carrying the same M694V mutation.

PMID: 22790142 [Indexed for MEDLINE]

2677. Gene. 2012 Sep 10;506(1):43-5. doi: 10.1016/j.gene.2012.06.074. Epub 2012 Jul 3.

Significance of MEFV gene R202Q polymorphism in Turkish familial Mediterranean fever patients.

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**OBJECTIVE:** Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent attacks of fever and inflammation in the peritoneum, synovium, or pleura, accompanied by pain. The disease is associated with mutations in the Mediterranean fever (MEFV) gene, which encodes for the pyrin

protein. The aim of this study was to explore the frequency and clinical significance of the R202Q (c.605G>A) polymorphism in exon 2 of the MEFV gene in a cohort of Turkish patients with FMF.

**METHODS:** The study included 191 patients with FMF and 150 healthy controls. Genomic DNA was isolated and genotyped using polymerase chain reaction (PCR)-based restriction fragment length polymorphism (RFLP) assay for the MEFV gene R202Q polymorphism.

**RESULTS:** The genotype and allele frequencies of R202Q polymorphism showed a statistically significant difference between FMF patients and controls ( $p < 0.0001$  and  $p = 0.0004$ , respectively) and especially the homozygous AA genotype was significantly higher in FMF patients than healthy controls ( $p = 0.0002$ ; odds ratio = 6.27; 95% CI = 2.1-18.3). However no significant association was observed between clinical and demographic features of FMF patients and R202Q polymorphism.

**CONCLUSION:** The results of this study showed that there was a high association between MEFV gene R202Q polymorphism and FMF. R202Q polymorphism should be included in routine molecular diagnosis of FMF patients.

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DOI: 10.1016/j.gene.2012.06.074

PMID: 22771921 [Indexed for MEDLINE]

2678. Mod Rheumatol. 2013 May;23(3):604-7. doi: 10.1007/s10165-012-0693-y. Epub 2012 Jul 6.

Magnetic resonance imaging can detect thoracic inflammation due to familial Mediterranean fever.

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A 32-year-old man presented to our hospital complaining of periodic fever and unilateral chest pain. We suspected that he had familial Mediterranean fever



because of his symptoms. Magnetic resonance imaging (MRI) showed an increased intensity within the anterior chest wall, which was consistent with the site of his pain. Genomic analysis showed the patient to be heterozygous for the E148Q/M694I mutation in the MEFV gene, and we diagnosed familial Mediterranean fever. The ability of MRI to detect inflammatory changes could provide useful additional information for evaluating thoracic symptoms in FMF patients, and the detection of inflammatory changes using MRI may aid in early diagnosis, thus contributing to early and adequate treatment.

DOI: 10.1007/s10165-012-0693-y

PMID: 22766764 [Indexed for MEDLINE]

2679. Clinics (Sao Paulo). 2012;67(6):685-8.

Abdominal pain, arthritis, and nephrotic syndrome in a Syrian patient.

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PMCID: PMC3370326

PMID: 22760913 [Indexed for MEDLINE]

2680. Dan Med J. 2012 Jul;59(7):A4452.

Periodic fever associated with aphthous stomatitis, pharyngitis and cervical adenitis.

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**INTRODUCTION:** The periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome is a non-hereditary idiopathic febrile syndrome belonging to the group of autoinflammatory diseases. PFAPA does not cause long-lasting sequelae. An early diagnosis provides treatment possibilities for the patient and comfort to the family.

**MATERIAL AND METHODS:** This study is a retrospective review of the medical records of patients diagnosed with PFAPA and admitted to our clinic from January 1999 to January 2010 (n = 31).

**RESULTS:** The study population (n = 31) consisted of 21 males and ten females: 30 Caucasians and 1 Asian. Normal growth was seen in 30 patients. The median age at onset was 33 months. The mean duration of fever episodes was 4.45 days (95% confidence interval (CI): 3.92-4.98 days), and the mean duration of intervals between fever episodes was 29.66 days (95% CI: 25.31-34.01 days). Concomitantly with the fever, all patients had characteristic symptoms. All patients were asymptomatic in between their fever episodes. Prodromal symptoms were seen in 12 patients. Oral prednisolone was used in 24 patients and caused immediate fever reduction in 87.5%. A reduction in the duration of the asymptomatic interval after treatment was seen in 75.0%. Tonsillectomy was performed in 20 of the 31 patients causing cessation of fever episodes in 70%. Fever episodes continued in 15%, and the postoperative status remained unknown in the last 15%. Spontaneous resolution was seen in four patients. The diagnostic delay had a median duration of 28 months (range 2-160 months).

**CONCLUSION:** The long diagnostic delay of PFAPA gives cause for concern and it indicates a need for greater awareness of the disease so that the diagnosis may be made earlier.

**FUNDING:** not relevant.

**TRIAL REGISTRATION:** not relevant.

PMID: 22759839 [Indexed for MEDLINE]

2681. Ann Rheum Dis. 2013 May;72(5):678-85. doi: 10.1136/annrheumdis-2011-201268. Epub 2012 Jun 29.

Treatment of autoinflammatory diseases: results from the Eurofever Registry and a literature review.

Ter Haar N(1), Lachmann H, Özen S, Woo P, Uziel Y, Modesto C, Koné-Paut I,

Cantarini L, Insalaco A, Neven B, Hofer M, Rigante D, Al-Mayouf S, Touitou I, Gallizzi R, Papadopoulou-Alataki E, Martino S, Kuemmerle-Deschner J, Obici L, Iagaru N, Simon A, Nielsen S, Martini A, Ruperto N, Gattorno M, Frenkel J; Paediatric Rheumatology International Trials Organisation (PRINTO) and the Eurofever/Eurotraps Projects.

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**OBJECTIVE:** To evaluate the response to treatment of autoinflammatory diseases from an international registry and an up-to-date literature review.

**METHODS:** The response to treatment was studied in a web-based registry in which clinical information on anonymised patients with autoinflammatory diseases was collected retrospectively as part of the Eurofever initiative. Participating hospitals included paediatric rheumatology centres of the Paediatric Rheumatology International Trial Organisation network and adult centres with a specific interest in autoinflammatory diseases. The following diseases were included: familial Mediterranean fever (FMF), cryopyrin-associated periodic syndromes (CAPS), tumour necrosis factor (TNF)-receptor associated periodic syndrome (TRAPS), mevalonate kinase deficiency (MKD), pyogenic arthritis pustulosis acne (PAPA) syndrome, deficiency of interleukin-1 receptor antagonist (DIRA), NLRP12-related periodic fever and periodic fever aphthosis pharyngitis adenitis (PFAPA) syndrome. Cases were independently validated by experts for each disease. A literature search regarding treatment of the abovementioned diseases was also performed using Medline and Embase.

**RESULTS:** 22 months from the beginning of the enrolment, complete information on 496 validated patients was available. Data from the registry in combination with evidence from the literature confirmed that colchicine is the treatment of choice

for FMF and IL-1 blockade for DIRA and CAPS. Corticosteroids on demand probably represent a valid therapeutic strategy for PFAPA, but also for MKD and TRAPS. Patients with poorly controlled MKD, TRAPS, PAPA or FMF may benefit from IL-1 blockade; anti-TNF treatment may represent a possible valuable alternative. CONCLUSIONS: In the absence of high-grade evidence, these results could serve as a basis for therapeutic guidelines and to identify candidate drugs for future therapeutic trials.

DOI: 10.1136/annrheumdis-2011-201268

PMID: 22753383 [Indexed for MEDLINE]

2682. Mod Rheumatol. 2013 Mar;23(2):330-3. doi: 10.1007/s10165-012-0688-8. Epub 2012 Jun 30.

Is familial Mediterranean fever (FMF) common in patients with negative appendectomy?

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OBJECTIVES: Familial Mediterranean fever (FMF) is an autosomal-recessive disease characterized by recurrent attacks of fever with serositis. Differential diagnosis of a FMF abdominal attack with acute abdomen is difficult. Acute appendicitis is the most common cause of acute abdominal pain that requires surgical treatment. The aim of this study was to investigate frequency of FMF in patients with negative appendectomy.

METHODS: We assessed 278 patients (female/male 127/151) who were operated with preoperative diagnosis of acute appendicitis. In 250 of the patients, definitive diagnosis of acute appendicitis was established by histo-pathological examination. Patients with negative appendectomy were assessed for FMF by rheumatologist.

RESULTS: Negative appendectomy was detected in 28 patients (M/F 5/23, mean age  $25.3 \pm 8.4$  years). Negative appendectomy ratio was 10.1 %. Among 28 patients two had FMF (7.7 %).

CONCLUSIONS: FMF were established in 7.7 % of patients with negative appendectomy. Our study suggests patients having negative appendectomy should be evaluated for FMF. Further large sample studies are needed to define the real prevalence of FMF among negative appendectomy patients.

DOI: 10.1007/s10165-012-0688-8

PMID: 22752503 [Indexed for MEDLINE]

2683. J Rheumatol Suppl. 2012 Jul;89:7-10. doi: 10.3899/jrheum.120232.

Pathogenetic overview of psoriatic disease.

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Psoriatic arthritis (PsA) is an inflammatory musculoskeletal disease with both autoimmune and autoinflammatory features. Evidence supports the distinct nature of PsA regarding its clinical, genetic, immunohistochemical, and imaging features. Such features can help to distinguish PsA from other common rheumatic diseases. Apart from peripheral joint involvement, the musculoskeletal lesions in PsA include enthesitis and involvement of the distal interphalangeal joint (frequently associated with nail involvement, dactylitis, and axial involvement). The traditional model of pathogenesis in PsA has identified it as an autoimmune disease; however, an alternative model classifies it as having autoinflammatory features. Similarly, there are important new genetic observations focusing on the HLA region, and genome-wide association that confirms the genetic heterogeneity of patients with psoriasis and patients with PsA. Newer imaging techniques have also provided a much more detailed characterization of tissue abnormalities, in particular highlighting the extent of new bone formation, which is quite distinct from rheumatoid arthritis.

DOI: 10.3899/jrheum.120232

PMID: 22751581 [Indexed for MEDLINE]

2684. Ann Endocrinol (Paris). 2012 Jun;73(3):170-89. doi: 10.1016/j.ando.2012.04.010. Epub 2012 Jun 28.

How to diagnose a lipodystrophy syndrome.

Vantyghem MC(1), Balavoine AS, Douillard C, Defrance F, Dieudonne L, Mouton F, Lemaire C, Bertrand-Escouflaire N, Bourdelle-Hego MF, Devemy F, Evrard A, Gheerbrand D, Girardot C, Gumuche S, Hober C, Topolinski H, Lamblin B, Mycinski B, Ryndak A, Karrouz W, Duvivier E, Merlen E, Cortet C, Weill J, Lacroix D, Wémeau JL.

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The spectrum of adipose tissue diseases ranges from obesity to lipodystrophy, and is accompanied by insulin resistance syndrome, which promotes the occurrence of type 2 diabetes, dyslipidemia and cardiovascular complications. Lipodystrophy refers to a group of rare diseases characterized by the generalized or partial absence of adipose tissue, and occurs with or without hypertrophy of adipose tissue in other sites. They are classified as being familial or acquired, and generalized or partial. The genetically determined partial forms usually occur as Dunnigan syndrome, which is a type of laminopathy that can also manifest as muscle, cardiac, neuropathic or progeroid involvement. Gene mutations encoding for PPAR-gamma, Akt2, CIDEA, perilipin and the ZMPSTE 24 enzyme are much more rare. The genetically determined generalized forms are also very rare and are linked to mutations of seipin AGPAT2, FBN1, which is accompanied by Marfan syndrome, or of BANF1, which is characterized by a progeroid syndrome without insulin resistance and with early bone complications. Glycosylation disorders are sometimes involved. Some genetically determined forms have recently been found to be due to autoinflammatory syndromes linked to a proteasome anomaly (PSMB8). They result in a lipodystrophy syndrome that occurs secondarily with fever, dermatosis and panniculitis. Then there are forms that are considered to be acquired. They may be iatrogenic (protease inhibitors in HIV patients, glucocorticosteroids, insulin, graft-versus-host disease, etc.), related to an immune system disease (sequelae of dermatopolymyositis, autoimmune polyendocrine syndromes, particularly associated with type 1 diabetes, Barraquer-Simons and Lawrence syndromes), which are promoted by anomalies of the complement system. Finally,

lipomatosis is currently classified as a painful form (adiposis dolorosa or Dercum's disease) or benign symmetric multiple form, also known as Launois-Bensaude syndrome or Madelung's disease, which are sometimes related to mitochondrial DNA mutations, but are usually promoted by alcohol. In addition to the medical management of metabolic syndrome and the sometimes surgical treatment of lipodystrophy, recombinant leptin provides hope for genetically determined lipodystrophy syndromes, whereas modifications in antiretroviral treatment and tesamorelin, a GHRH analog, is effective in the metabolic syndrome of HIV patients. Other therapeutic options will undoubtedly be developed, dependent on pathophysiological advances, which today tend to classify genetically determined lipodystrophy as being related to laminopathy or to lipid droplet disorders.

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DOI: 10.1016/j.ando.2012.04.010

PMID: 22748602 [Indexed for MEDLINE]

2685. Arthritis Rheum. 2012 Nov;64(11):3799-808. doi: 10.1002/art.34604.

The limited role of interferon- $\gamma$  in systemic juvenile idiopathic arthritis cannot be explained by cellular hyporesponsiveness.

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**OBJECTIVE:** Systemic juvenile idiopathic arthritis (JIA) is an autoinflammatory syndrome in which the myelomonocytic lineage appears to play a pivotal role. Inflammatory macrophages are driven by interferon- $\gamma$  (IFN $\gamma$ ), but studies have failed to demonstrate an IFN- induced gene signature in active systemic JIA. This study sought to characterize the status of an IFN-induced signature within affected tissue and to gauge the integrity of IFN signaling pathways within peripheral monocytes from patients with systemic JIA.

**METHODS:** Synovial tissue from 12 patients with active systemic JIA and 9 with active extended oligoarticular JIA was assessed by real-time polymerase chain reaction to quantify IFN-induced chemokine gene expression. Peripheral monocytes

from 3 patients with inactive systemic JIA receiving anti-interleukin-1 $\beta$  (anti-IL-1 $\beta$ ) therapy, 5 patients with active systemic JIA, and 8 healthy controls were incubated with or without IFN $\gamma$  to gauge changes in gene expression and to measure phosphorylated STAT-1 (pSTAT-1) levels.

RESULTS: IFN-induced chemokine gene expression in synovium was constrained in active systemic JIA compared to the known IFN-mediated extended oligoarticular subtype. In unstimulated peripheral monocytes, IFN-induced gene expression was similar between the groups, except that lower levels of STAT1, MIG, and PIAS were observed in patients with active disease, while higher levels of PIAS1 were observed in patients with inactive disease. Basal pSTAT-1 levels in monocytes tended to be higher in systemic JIA patients compared to healthy controls, with the highest levels seen in those with inactive disease. Upon stimulation of monocytes, the fold increase in gene expression was roughly equal between groups, except for a greater increase in STAT1 in patients with inactive systemic JIA compared to controls, and a greater increase in IRF1 in those with active compared to inactive disease. Upon stimulation, the fold increase in pSTAT-1 was highest in monocytes from patients with inactive systemic JIA.

CONCLUSION: Monocytes in patients with active systemic JIA retain the ability to respond to IFN $\gamma$ , suggesting that the lack of an IFN-induced gene signature in patients with active disease reflects a limited in vivo exposure to IFN $\gamma$ . In patients with inactive systemic JIA who received treatment with anti-IL-1 $\beta$ , hyperresponsiveness to IFN $\gamma$  was observed.

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DOI: 10.1002/art.34604

PMCID: PMC3482423

PMID: 22740319 [Indexed for MEDLINE]

2686. Curr Allergy Asthma Rep. 2012 Aug;12(4):288-91. doi: 10.1007/s11882-012-0268-1.

Biologic agents in the treatment of urticaria.

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Numerous controlled studies as well as case reports have demonstrated that Omalizumab can be employed successfully in approximately 75 % of patients with chronic spontaneous urticaria, leading to a dramatic decrement in symptoms with very few side effects. No other drug currently available is comparable, and the success rate in patients resistant to antihistamines is no different. In the U.S., Phase I and Phase II trials are complete and we await the results of a Phase III multicenter study, with a view to eventual submission to the Food and Drug Administration in the U.S. and to comparable agencies abroad seeking approval for this indication. Omalizumab is currently marketed for the treatment of severe allergic asthma. Case reports suggest efficacy in difficult cases of physical urticaria, but no controlled trials have been done. Other agents require further evaluation for possible efficacy in the treatment of chronic spontaneous urticaria, including antibody to CD20, a B-lymphocyte cell surface marker, anti-TNF $\alpha$ , and anti-Interleukin 1. Thus far, targeting TNF $\alpha$  has been disappointing for this indication, while targeting Interleukin 1 has dramatically ameliorated autoinflammatory disorders with urticaria or urticaria-vasculitic-like lesions such as cold-induced autoinflammatory syndrome, Muckle-Wells syndrome, and Schnitzler syndrome.

DOI: 10.1007/s11882-012-0268-1

PMID: 22740008 [Indexed for MEDLINE]

2687. J Pediatr. 2012 Dec;161(6):1142-6. doi: 10.1016/j.jpeds.2012.05.047. Epub 2012 Jun 26.

Colchicine is a safe drug in children with familial Mediterranean fever.

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OBJECTIVE: To identify any adverse effects of colchicine in a pediatric patients with familial Mediterranean fever (FMF).

**STUDY DESIGN:** Clinical presentation, Mediterranean fever gene genotype, disease duration, colchicine dose, laboratory tests, and reported adverse effects in children with FMF were analyzed.

**RESULTS:** Of the 153 patients with FMF, 22 (14.4%) developed diarrhea during a follow-up of 4 years; the colchicine dose was reduced to control this symptom in only 4 patients. In 18 (11.8%) patients, a mild transitory increase of transaminases (45-158 IU/L) was found during a follow-up of 1 year. Blood cell counts and kidney function tests were normal in all patients. No correlation was found between the adverse effects and patient's age, disease onset, treatment duration, or any of the clinical characteristics of the disease.

**CONCLUSION:** Colchicine is a safe drug in the treatment of children with FMF, even in infancy. The only significant adverse effects are diarrhea (in a small number of patients), which can be controlled by a decrease in the colchicine dose and transitory elevation of transaminases.

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DOI: 10.1016/j.jpeds.2012.05.047

PMID: 22738946 [Indexed for MEDLINE]

2688. Mod Rheumatol. 2013 Jan;23(1):140-5. doi: 10.1007/s10165-012-0687-9. Epub 2012 Jun 27.

The role of TNF- $\alpha$  and PAI-1 gene polymorphisms in familial Mediterranean fever.

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**OBJECTIVES:** Familial Mediterranean fever (FMF) is one of the most serious inherited inflammatory disorders among Jewish, Armenian, Turkish and Arab populations. The imbalance between pro- and anti-inflammatory cytokines may play a role in its etiology. We have investigated whether tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and plasminogen activator inhibitor 1 (PAI-1) gene polymorphisms are associated with FMF and evaluated the relationship between these polymorphisms

and genotypic manifestation of FMF.

**METHODS:** We investigated single nucleotide polymorphisms of the TNF- $\alpha$  promoter at positions -308 G/A and the PAI-1 4G/5G gene polymorphism in peripheral blood leukocytes collected from 177 individuals with FMF with different genotype combinations. All of the polymorphisms of TNF- $\alpha$  and PAI-1 were detected by PCR and restriction fragment length polymorphism analysis.

**RESULTS:** There were no association between the TNF- $\alpha$ /308 genotypes and mutations in FMF. In contrast, the PAI-1 4G/5G gene polymorphism may have a significant effect in FMF disease.

**CONCLUSIONS:** Screening with PAI-1 gene polymorphism tests may be beneficial for tracing future FMF patients. However, further investigations are needed to reach a conclusion on the association between PAI-1 polymorphisms and FMF.

DOI: 10.1007/s10165-012-0687-9

PMID: 22736074 [Indexed for MEDLINE]

2689. Proc Natl Acad Sci U S A. 2012 Jul 10;109(28):11282-7. doi: 10.1073/pnas.1117765109. Epub 2012 Jun 25.

Critical role for calcium mobilization in activation of the NLRP3 inflammasome.

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The NLRP3 (nucleotide-binding domain, leucine-rich-repeat-containing family, pyrin domain-containing 3) inflammasome mediates production of inflammatory mediators, such as IL-1 $\beta$  and IL-18, and as such is implicated in a variety of inflammatory processes, including infection, sepsis, autoinflammatory diseases, and metabolic diseases. The proximal steps in NLRP3 inflammasome activation are not well understood. Here we elucidate a critical role for Ca(2+) mobilization in activation of the NLRP3 inflammasome by multiple stimuli. We demonstrate that blocking Ca(2+) mobilization inhibits assembly and activation of the NLRP3 inflammasome complex, and that during ATP stimulation Ca(2+) signaling is pivotal in promoting mitochondrial damage. C/EPB homologous protein, a transcription factor that can modulate Ca(2+) release from the endoplasmic reticulum, amplifies

NLRP3 inflammasome activation, thus linking endoplasmic reticulum stress to activation of the NLRP3 inflammasome. Our findings support a model for NLRP3 inflammasome activation by Ca(2+)-mediated mitochondrial damage.

DOI: 10.1073/pnas.1117765109

PMCID: PMC3396518

PMID: 22733741 [Indexed for MEDLINE]

2690. J Cell Biochem. 2012 Nov;113(11):3536-46. doi: 10.1002/jcb.24231.

The effect of colchicine on pyrin and pyrin interacting proteins.

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MEFV which encodes pyrin, cause familial Mediterranean fever (FMF), the most common auto-inflammatory disease. Pyrin is believed to be a regulator of inflammation, though the nature of this regulatory activity remains to be identified. Prophylactic treatment with colchicine, a microtubule toxin, has had a remarkable effect on disease progression and outcome. It has been thought that, inhibition of microtubule polymerization is the main mechanism of action of colchicine. But, the exact cellular mechanism explaining the efficacy of colchicine in suppressing FMF attacks is still unclear. Given the ability of colchicine treatment to be considered as a differential diagnosis criteria of FMF, we hypothesized that colchicine may have a specific effect on pyrin and pyrin interacting proteins. This study showed that colchicine prevents reticulated fibrils formed by PSTPIP1 filaments and reduces ASC speck rates in transfected cells. We further noted that, colchicine down-regulates MEFV expression in THP-1 cells. We also observed that colchicine causes re-organization of actin cytoskeleton in THP-1 cells. Pyrin is an actin-binding protein that specifically localizes with polymerizing actin filaments. Thus, MEFV expression might be affected by re-organization of actin cytoskeleton. The data presented here reveal an important connection between colchicine and pyrin which might explain the remarkable efficacy of colchicine in preventing FMF attacks.

DOI: 10.1002/jcb.24231

PMID: 22730186 [Indexed for MEDLINE]

2691. Curr Pharm Des. 2012;18(35):5746-52.

Mevalonate kinase deficiency: disclosing the role of mevalonate pathway modulation in inflammation.

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Inflammation is a highly regulated process involved both in the response to pathogens as well as in tissue homeostasis. In recent years, a complex network of proteins in charge of inflammation control has been revealed by the study of hereditary periodic fever syndromes. Most of these proteins belong to a few families and share the capability of sensing pathogen-associated and damage-associated molecular patterns. By interacting with each other, these proteins participate in the assembly of molecular platforms, called inflammasomes, which ultimately lead to the activation of cytokines, to the transcription of inflammatory genes or to the induction of cell apoptosis. Among hereditary periodic fever syndromes, mevalonate kinase deficiency (MKD) is the sole in which the phenotype did not directly associate with a deficiency of these proteins, but with a metabolic defect of the mevalonate pathway, highlighting the importance of this metabolic pathway in the inflammation control. Noteworthy, drugs acting on this pathway can greatly influence the inflammatory response. The modulation of inflammation by mevalonate pathway is of interest, since it may involve mechanisms not directly referable to inflammasomes. MKD provides a model to study these mechanisms and possibly to develop new classes of anti-inflammatory drugs.

PMID: 22726114 [Indexed for MEDLINE]

2692. Blood. 2012 Aug 9;120(6):1299-308. doi: 10.1182/blood-2012-03-417881. Epub 2012 Jun 21.

Induced pluripotent stem cells from CINCA syndrome patients as a model for dissecting somatic mosaicism and drug discovery.

Tanaka T(1), Takahashi K, Yamane M, Tomida S, Nakamura S, Oshima K, Niwa A, Nishikomori R, Kambe N, Hara H, Mitsuyama M, Morone N, Heuser JE, Yamamoto T, Watanabe A, Sato-Otsubo A, Ogawa S, Asaka I, Heike T, Yamanaka S, Nakahata T, Saito MK.

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Chronic infantile neurologic cutaneous and articular (CINCA) syndrome is an IL-1-driven autoinflammatory disorder caused mainly by NLRP3 mutations. The pathogenesis of CINCA syndrome patients who carry NLRP3 mutations as somatic mosaicism has not been precisely described because of the difficulty in separating individual cells based on the presence or absence of the mutation. Here we report the generation of NLRP3-mutant and nonmutant-induced pluripotent stem cell (iPSC) lines from 2 CINCA syndrome patients with somatic mosaicism, and describe their differentiation into macrophages (iPS-MPs). We found that mutant cells are predominantly responsible for the pathogenesis in these mosaic patients because only mutant iPS-MPs showed the disease relevant phenotype of abnormal IL-1 $\beta$  secretion. We also confirmed that the existing anti-inflammatory compounds inhibited the abnormal IL-1 $\beta$  secretion, indicating that mutant iPS-MPs are applicable for drug screening for CINCA syndrome and other NLRP3-related inflammatory conditions. Our results illustrate that patient-derived iPSCs are useful for dissecting somatic mosaicism and that NLRP3-mutant iPSCs can provide a valuable platform for drug discovery for multiple NLRP3-related disorders.

DOI: 10.1182/blood-2012-03-417881

PMID: 22723549 [Indexed for MEDLINE]

2693. Platelets. 2013;24(4):320-3. doi: 10.3109/09537104.2012.697591. Epub 2012 Jun 21.

Does mean platelet volume influence the attack or attack-free period in the patients with Familial Mediterranean fever?

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Familial Mediterranean fever (FMF) is an autosomal recessive hereditary disease which is characterized by recurrent attacks of fever and peritonitis, pleuritis, arthritis, or erysipelas-like skin disease. Mean platelet volume (MPV) is a sign of platelet activation. There are limited studies in the literature about MPV levels in FMF patients. We aimed to investigate MPV levels during the attack period (group 1) and attack-free periods (group 2) in FMF patients, and to compare them with healthy controls (group 3). The study consisted of the data of: 60 group 1 patients, 120 group 2 patients, and 75 group 3 patients. Erythrocyte sedimentation rate, C-reactive protein, white blood cell count, platelet count, and MPV levels were retrospectively recorded from patient files. Statistical analyses showed that MPV was significantly lower in FMF patients both in group 1 and group 2 than in group 3 ( $p = 0.004$ ,  $p = 0.002$ , respectively); however, there was no difference among group 1 and group 2 in patients with FMF ( $p = 0.279$ ). The mean platelet count of group 1 was higher than that of group 3 ( $p = 0.010$ ). In conclusion, this study results suggested that MPV level did not increase on the contrary, it decreased in patients with FMF both in group 1 and/or group 2 when compared to group 3. It was concluded that the lower MPV level was an expected result of secondary thrombocytosis in FMF patients.

DOI: 10.3109/09537104.2012.697591

PMID: 22720903 [Indexed for MEDLINE]

2694. Swiss Med Wkly. 2012 Jun 19;142:w13602. doi: 10.4414/smw.2012.13602. eCollection 2012.

The autoinflammatory diseases.

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The monogenic autoinflammatory syndromes are conditions caused by mutations of genes coding for proteins that play a pivotal role in the regulation of the inflammatory response. Due to their genetic nature, most of these disorders have an early onset. Clinically they are characterised by recurrent flares of systemic inflammation presenting most of the time as sudden fever episodes associated with elevation of acute phase reactants and with a number of clinical manifestations such as rash, serositis, lymphadenopathy and arthritis. Symptom-free intervals are characterised by complete wellbeing, normal growth and complete normalisation of acute phase reactants. Familial Mediterranean fever (FMF), mevalonate-kinase deficiency (MKD) and tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) are the three monogenic disorders subsumed under the term periodic fevers, while a systemic inflammation dominated by a characteristic urticarial rash associated with a number of other clinical manifestations is typical of familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and chronic infantile neurological cutaneous and articular syndrome (CINCA). These diseases represent the clinical spectrum of different mutations of a gene named cold-induced autoinflammatory syndrome 1 (CIAS-1, or NLRP3) coding for a protein called cryopyrin. Hence these disorders are also known as cryopyrin-associated periodic syndromes (CAPS). Other conditions are characterised by typical granulomatous formations (granulomatous disorders). Blau's syndrome (familial juvenile systemic granulomatosis) presents with non-caseating granulomatous inflammation affecting the joint, skin, and uveal tract (the triad of arthritis, dermatitis and uveitis) and is associated with mutations of the NACHT domain of the gene CARD15 (or NOD2).

DOI: 10.4414/smw.2012.13602

PMID: 22714396 [Indexed for MEDLINE]

2695. Obstet Gynecol Surv. 2012 Jun;67(6):357-64. doi: 10.1097/OGX.0b013e318259ed3a.

The impact of familial Mediterranean fever on women's health.

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Familial Mediterranean fever (FMF) is the most common hereditary recurrent febrile disorder, characterized by the sudden onset of high fever and severe abdominal pain. The implications of this disorder on a woman's health are significant and not well known among obstetrician/gynecologists. The goal of this review is to familiarize providers caring for women on the ramifications of FMF on different aspects of a woman's life, including puberty, fertility, pregnancy, and menopause, as well as to help them to diagnose and manage FMF when these patients become pregnant.

DOI: 10.1097/OGX.0b013e318259ed3a

PMID: 22713162 [Indexed for MEDLINE]

2696. Ann Intern Med. 2012 Jun 19;156(12):907-8. doi: 10.7326/0003-4819-156-12-201206190-00027.

Successful treatment of tumor necrosis factor receptor-associated periodic syndrome with canakinumab.

Brizi MG, Galeazzi M, Lucherini OM, Cantarini L, Cimaz R.

DOI: 10.7326/0003-4819-156-12-201206190-00027

PMID: 22711098 [Indexed for MEDLINE]

2697. Ann Saudi Med. 2012 Jul-Aug;32(4):343-8.

A molecular analysis of familial Mediterranean fever disease in a cohort of Turkish patients.

Dundar M(1), Kiraz A, Emirogullari EF, Saatci CE, Taheri S, Baskol M, Polat S, Ozkul Y.

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**BACKGROUND AND OBJECTIVES:** Familial Mediterranean fever (FMF) is an autosomal recessive disorder caused by mutations in MEFV gene, which encodes pyrin. FMF is

especially prevalent among Turks, Armenians, non-Ashkenazi Jews, and Arabs. The aim of this study was to determine the frequency and spectrum of 12 MEFV mutations of these patients and any genotype-phenotype correlation in this large Turkish group.

**DESIGN AND SETTING:** A retrospective study at Erciyes University Medical Faculty, from January 2007 to June 2009.

**PATIENTS AND METHODS:** We enrolled 446 Turkish FMF patients and identified the known 12 MEFV mutations with clinical investigations. DNA was amplified by PCR and subjected to reverse hybridization for the detection of MEFV gene mutations.

**RESULTS:** Among the 446 patients, 103 (46.6%) had a heterozygous genotype, 44 (19.9%) had a homozygous genotype, and 74 (33.49%) had a compound heterozygous genotype. The most common mutation detected was heterozygote M694V (46/221). Of the included 446 patients, 218 (48.87%) were male and 228 (51.12%) were female. High parental consanguinity rates affect FMF development. The clinical spectrum varied with different mutation profiles.

**CONCLUSIONS:** This study plays an important role in detecting the distribution of MEFV mutations and determining clinical approaches among Turk FMF patients. Also, we seemed to detect a distinctive clinical picture, specifically a lower frequency of amyloidosis.

PMCID: PMC6081005

PMID: 22705602 [Indexed for MEDLINE]

2698. J Radiol Case Rep. 2012 Mar;6(3):1-8. doi: 10.3941/jrcr.v6i3.745. Epub 2012 Mar 1.

NOMID: the radiographic and MRI features and review of literature.

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Neonatal onset multisystem inflammatory disease (NOMID) is a rare autoinflammatory disorder, which manifests early in infancy. We describe a case of a 10-year-old boy who has been unwell since infancy. He presented with

urticarial rash, intermittent fever and hepatosplenomegaly followed by progressive arthropathy. His joint symptoms started at two years of age, which progressively involved multiple joints, resulting in bone and joint deformities. A series of joint radiographs demonstrated bizarre enlarging physeal mass with heterogenous calcification. Magnetic resonance imaging (MRI) of the involved right ankle and knee showed characteristic thickened and calcified physeal lesions, which enhanced post-gadolinium. This debilitating disease is also known to involve the central nervous system and eyes. This case report aims to highlight the conventional radiographic and magnetic resonance imaging (MRI) findings of this physeal abnormality in NOMID syndrome.

DOI: 10.3941/jrcr.v6i3.745

PMCID: PMC3370707

PMID: 22690285 [Indexed for MEDLINE]

2699. Int J Rheumatol. 2012;2012:310206. doi: 10.1155/2012/310206. Epub 2012 May 21.

Update: Cytokine Dysregulation in Chronic Nonbacterial Osteomyelitis (CNO).

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Chronic nonbacterial osteomyelitis (CNO) with its most severe form chronic recurrent multifocal osteomyelitis (CRMO) is a non-bacterial osteitis of yet unknown origin. Secondary to the absence of both high-titer autoantibodies and autoreactive T lymphocytes, and the association with other autoimmune diseases, it was recently reclassified as an autoinflammatory disorder of the musculoskeletal system. Since its etiology is largely unknown, the diagnosis is based on clinical criteria, and treatment is empiric and not always successful. In this paper, we summarize recent advances in the understanding of possible etiopathogenetic mechanisms in CNO.

DOI: 10.1155/2012/310206

PMCID: PMC3364585

PMID: 22685464

2700. Ann Rheum Dis. 2012 Dec;71(12):2035-43. doi: 10.1136/annrheumdis-2011-201197. Epub 2012 Jun 7.

Involvement of X-box binding protein 1 and reactive oxygen species pathways in the pathogenesis of tumour necrosis factor receptor-associated periodic syndrome.

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**OBJECTIVES:** To investigate convergence of endoplasmic reticulum stress pathways and enhanced reactive oxygen species (ROS) production, due to intracellular retention of mutant tumour necrosis factor receptor 1 (TNFR1), as a disease mechanism in TNFR-associated periodic syndrome (TRAPS).

**METHODS:** Peripheral blood mononuclear cells from patients with TRAPS (n=16) and healthy controls (HC) (n=22) were studied alongside HEK293T cells expressing wild type-TNFR1 or TRAPS-associated mutations. Unfolded protein response (UPR)-associated proteins (protein kinase-like endoplasmic reticulum kinase, PERK), phosphorylated-PERK (p-PERK), phosphorylated inositol-requiring enzyme 1 $\alpha$  (p-IRE1 $\alpha$ ) and spliced X-box binding protein 1 (sXBP1)) were measured by flow cytometry. XBP1 splicing and UPR-associated transcript expression were assessed by reverse transcription PCR/quantitative real-time PCR. ROS levels were measured using CM-H(2)DCFDA and MitoSOX Red in patients' monocytes or HEK293T cells by flow cytometry.

**RESULTS:** Mutant TNFR1-expressing HEK293T cells had increased TNFR1 expression associated with intracellular aggregation. TRAPS patients had increased sXBP1 transcripts (p<0.01) compared with HC. Raised p-PERK protein was seen, indicative of an UPR, but other UPR-associated transcripts were normal. Increased ROS levels were observed in TRAPS monocytes compared with HCs (p<0.02); these increased further upon IL-6 stimulation (p<0.01). Lipopolysaccharide-stimulated peripheral blood mononuclear cells of patients with TRAPS, but not HCs, demonstrated increased sXBP1 levels (p<0.01), which were reduced by antioxidant treatment

( $p < 0.05$ ).

**CONCLUSIONS:** Patients with TRAPS have evidence of increased sXBP1 and PERK expression but without other signs of classical UPR, and also with high ROS generation that may contribute to the pro-inflammatory state associated with TRAPS. The authors propose a non-traditional XBP1 pathway with enhanced sXBP1 as a novel disease-contributing mechanism in TRAPS.

DOI: 10.1136/annrheumdis-2011-201197

PMID: 22679299 [Indexed for MEDLINE]

2701. Isr Med Assoc J. 2012 Apr;14(4):232-3.

Familial Mediterranean fever, an amyloid thyroid goiter and an enlarged parathyroid gland.

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PMID: 22675840 [Indexed for MEDLINE]

2702. Isr Med Assoc J. 2012 Apr;14(4):229-31.

"Trap" the diagnosis: a man with recurrent episodes of febrile peritonitis, not just familial Mediterranean fever.

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Monogenic periodic fever syndromes are characterized by recurrent episodes of fever, accompanied by localized inflammatory manifestations. Among them, familial

Mediterranean fever (FMF) is the most studied and is by far the most prevalent periodic fever syndrome in Israel. We present a diagnostic workup of a patient suffering from a periodic fever syndrome, initially thought to be FMF and characterized by attacks of fever, severe abdominal pain, a migratory erythematous rash and conjunctivitis. The development of periorbital edema presenting as diplopia led to consideration of tumor necrosis factor receptor-1-associated periodic syndrome (TRAPS). Genetic tests confirmed the diagnosis. This case should alert us that even in Israel, a patient with periodic fever not fully consistent with the typical features of FMF, should be evaluated for other periodic fever syndromes.

PMID: 22675839 [Indexed for MEDLINE]

2703. Isr Med Assoc J. 2012 Apr;14(4):225-8.

QT variability in amyloidosis of familial Mediterranean fever.

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**BACKGROUND:** The association between familial Mediterranean fever (FMF) and increased risk for ventricular arrhythmias is controversial, and data on this subject are meager.

**OBJECTIVES:** To evaluate QT variability index (QTVI) and other repolarization markers associated with arrhythmogenicity in patients with amyloidosis of FMF.

**METHODS:** The study group comprised 12 FMF patients with amyloidosis, and 14 age and gender-matched healthy subjects served as the control group. QT measurements were conducted according to accepted procedure, using computerized software for recording and analysis.

**RESULTS:** No differences were found in clinical and demographic parameters in the study and control groups, except for hypertension which was more common in the FMF amyloidosis group. QTc and power spectral analysis of QT variability parameters were similar in both groups. Nevertheless, QTVI values in FMF amyloidosis patients were significantly higher than in healthy individuals (-1.02

+/- 0.38, vs. -1.36 +/- 0.32 respectively,  $P = 0.02$ ).

**CONCLUSIONS:** Compared with healthy controls, amyloidosis of FMF is associated with increased QTVI. It remains unknown whether this finding is solely amyloidosis related and whether it has any prognostic significance.

PMID: 22675838 [Indexed for MEDLINE]

2704. Isr Med Assoc J. 2012 Apr;14(4):221-4.

Risk factors for amyloidosis and impact of kidney transplantation on the course of familial Mediterranean fever.

Ben-Zvi I(1), Danilesko I, Yahalom G, Kukuy O, Rahamimov R, Livneh A, Kivity S.

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**BACKGROUND:** Amyloidosis of familial Mediterranean fever (FMF) may lead to end-stage renal failure, culminating in kidney transplantation in some patients.

**OBJECTIVES:** To assess demographic, clinical and genetic risk factors for the development of FMF amyloidosis in a subset of kidney-transplanted patients and to evaluate the impact of transplantation on the FMF course.

**METHODS:** Demographic, clinical and genetic data were abstracted from the files, interviews and examinations of 16 kidney-transplanted FMF amyloidosis patients and compared with the data of 18 FMF patients without amyloidosis.

**RESULTS:** Age at disease onset and clinical severity of the FMF amyloidosis patients prior to transplantation were similar to FMF patients without amyloidosis. Compliance with colchicine treatment, however, was much lower (50% vs. 98%). Posttransplantation, FMF amyloidosis patients experienced fewer of the typical serosal attacks than did their counterparts (mean 2214 days since last attack vs. 143 days). Patients with FMF amyloidosis carried only M694V mutations in the FMF gene, while FMF without amyloidosis featured other mutations as well.

**CONCLUSIONS:** Compliance with treatment and genetic makeup but not severity of FMF constitutes major risk factors for the development of amyloidosis in FMF.

Transplantation seems to prevent FMF attacks. The protective role of immunosuppressive therapy cannot be excluded.

PMID: 22675837 [Indexed for MEDLINE]

2705. Isr Med Assoc J. 2012 Apr;14(4):219-20.

The Israeli Annual FMF, Amyloidosis and Other Autoinflammatory Diseases Meeting (July 2011): a bridge spanning these entities.

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PMID: 22675836 [Indexed for MEDLINE]

2706. Clin Rev Allergy Immunol. 2012 Dec;43(3):275-80. doi: 10.1007/s12016-012-8319-x.

Behçet syndrome: is it one condition?

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Behçet's syndrome (BS) is a disease of unknown etiology, and as such, there have been efforts to classify BS within the popular nosological identities of the times such as seronegative spondarthritides, autoimmune, and more recently autoinflammatory diseases. Current evidence suggests that BS does not easily fit into any one of these lumps, while on occasion, it might be impossible to tell BS from Crohn's disease, especially when the main clinical presentation is intestinal ulceration. There are distinct regional differences in disease expression of BS with fewer cases of intestinal disease in the Mediterranean basin and less severe eye disease and less frequent skin pathergy among patients



reported from northern Europe or America. The clustering of symptoms, especially with the recently described increased frequency of the acne/arthritis cluster in familial cases, suggests that more than one pathological pathway is involved in what we call BS today. Supportive evidence for this contention also comes from the observations that (a) the genetic component is very complex with perhaps different genetic modes of inheritance in the adult and in the pediatric patients; and (b) there are differing organ responses to one same drug. For example, the anti-TNF agents successfully control the oral ulcers while they have no effect on the pathergy reaction.

DOI: 10.1007/s12016-012-8319-x

PMID: 22674015 [Indexed for MEDLINE]

2707. Clin Rheumatol. 2012 Aug;31(8):1267-71. doi: 10.1007/s10067-012-2009-1. Epub 2012 Jun 7.

Infliximab therapy for familial Mediterranean fever-related amyloidosis: case series with long term follow-up.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent self-limited attacks of fever and polyserositis. Reactive amyloid A amyloidosis is the most devastating complication of FMF, and amyloidosis continues to occur in the colchicine era in untreated and noncompliant patients. Unfortunately, there is no proven effective treatment for established amyloidosis. In this report, we present four FMF-related amyloidosis patients that were treated with long term infliximab therapy with the longest duration of follow-up, together with the literature review. Infliximab was very effective in controlling gastrointestinal system findings and protracted arthritis, and it also had a favorable impact on the clinical findings of nephrotic syndrome in these patients. In conclusion, by controlling debilitating complaints of amyloidosis with infliximab, quality of life increases in these patients, and they get rid of recurrent hospitalizations and return to school or

work.

DOI: 10.1007/s10067-012-2009-1

PMID: 22673790 [Indexed for MEDLINE]

2708. Med Clin (Barc). 2012 Oct 6;139(8):348-53. doi: 10.1016/j.medcli.2012.03.017. Epub 2012 Jun 4.

[A 37-years old man with recurrent episodes of fever and abdominal pain].

[Article in Spanish]

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DOI: 10.1016/j.medcli.2012.03.017

PMID: 22672967 [Indexed for MEDLINE]

2709. Harefuah. 2012 Jan;151(1):9-11.

[Autoimmune or autoinflammatory syndromes induced by adjuvants].

[Article in Hebrew]

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PMID: 22670492 [Indexed for MEDLINE]

2710. Amyloid. 2012 Sep;19(3):161-2. doi: 10.3109/13506129.2012.687701. Epub 2012 Jun

5.

Diffuse amyloid deposition in thyroid gland: a cause for concern in familial Mediterranean fever.

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Thyroid gland is among the many organs that could be infiltrated in systemic amyloidosis. However, diffuse infiltration of the thyroid gland secondary to systemic amyloidosis associated with Familial Mediterranean fever (FMF) is rare. Here, we present a 49-year-old woman diagnosed with FMF and systemic amyloidosis, who had a large goiter and multiple nodules that developed slowly through the years and was complicated by tracheal compression symptoms and a mild thyroid dysfunction. Multiple fine needle aspiration biopsies of the nodules and the thyroid parenchyma revealed amyloid deposits. We would like to point out that amyloidosis may have a significant impact on the thyroid gland and fine needle aspiration biopsy is a valuable tool for diagnosis.

DOI: 10.3109/13506129.2012.687701

PMID: 22663145 [Indexed for MEDLINE]

2711. Ann Rheum Dis. 2012 Oct;71(10):1599-605. doi: 10.1136/annrheumdis-2011-201271. Epub 2012 Jun 1.

Guidelines for the genetic diagnosis of hereditary recurrent fevers.

Shinar Y(1), Obici L, Aksentijevich I, Bennetts B, Austrup F, Ceccherini I, Costa JM, De Leener A, Gattorno M, Kania U, Kone-Paut I, Lezer S, Livneh A, Moix I, Nishikomori R, Ozen S, Phylactou L, Risom L, Rowczenio D, Sarkisian T, van Gijn ME, Witsch-Baumgartner M, Morris M, Hoffman HM, Touitou I; European Molecular Genetics Quality Network.

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Hereditary recurrent fevers (HRFs) are a group of monogenic autoinflammatory diseases characterised by recurrent bouts of fever and serosal inflammation that are caused by pathogenic variants in genes important for the regulation of innate immunity. Discovery of the molecular defects responsible for these diseases has initiated genetic diagnostics in many countries around the world, including the Middle East, Europe, USA, Japan and Australia. However, diverse testing methods and reporting practices are employed and there is a clear need for consensus guidelines for HRF genetic testing. Draft guidelines were prepared based on current practice deduced from previous HRF external quality assurance schemes and data from the literature. The draft document was disseminated through the European Molecular Genetics Quality Network for broader consultation and amendment. A workshop was held in Bruges (Belgium) on 18 and 19 September 2011 to ratify the draft and obtain a final consensus document. An agreed set of best practice guidelines was proposed for genetic diagnostic testing of HRFs, for reporting the genetic results and for defining their clinical significance.

DOI: 10.1136/annrheumdis-2011-201271

PMCID: PMC3500529

PMID: 22661645 [Indexed for MEDLINE]

2712. Int J Pediatr Otorhinolaryngol. 2012 Aug;76(8):1145-7. doi: 10.1016/j.ijporl.2012.04.022. Epub 2012 Jun 1.

C-reactive protein and procalcitonin during febrile attacks in PFAPA syndrome.

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**OBJECTIVES:** To assess the levels of procalcitonin (PCT) and C-reactive protein (CRP) in children diagnosed with PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis) during their febrile attacks.

**METHODS:** 23 patients with diagnosis of PFAPA included into the study prospectively during a three years period. In these patients, CRP and PCT values

were recorded during 78 febrile episodes. Furthermore, 20 patients with diagnosis of pneumonia were chosen as a control group and their CRP and PCT values were measured. Normal reference values for CRP and PCT were 0-10 mg/L and 0-0.5 ng/mL, respectively.

RESULTS: Mean CRP and PCT values of patients with PFAPA were  $94.8 \pm 71.6$  mg/L and  $0.29 \pm 0.14$  ng/mL, respectively. In control group, mean CRP value was  $153.2 \pm 26$  mg/L and PCT was  $1.59 \pm 0.53$  ng/mL. CRP and PCT were high in control group. CRP was detected high and PCT was normal in PFAPA. Compared to control group, in PFAPA group, CRP values were not significantly ( $p > 0.05$ ) and PCT values were significantly lower ( $p < 0.001$ ).

CONCLUSION: During febrile episodes in the patients with diagnosis of PFAPA, CRP values were substantially elevated, whereas PCT values were within normal levels. Concomitant assessment of CRP and PCT in addition to clinical diagnostic criteria may be of help in making diagnosis and distinguishing febrile attacks from infections. However, studies in larger groups are required.

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DOI: 10.1016/j.ijporl.2012.04.022

PMID: 22658448 [Indexed for MEDLINE]

2713. Libyan J Med. 2012;7. doi: 10.3402/ljm.v7i0.18482. Epub 2012 May 29.

Diffuse pulmonary amyloidosis due to Familial Mediterranean Fever, a rare presentation.

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DOI: 10.3402/ljm.v7i0.18482

PMCID: PMC3364798

PMID: 22654976

2714. Swiss Med Wkly. 2012 May 31;142:w13590. doi: 10.4414/smw.2012.13590. eCollection

2012.

Interleukin-1, inflammasomes, autoinflammation and the skin.

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Interleukin 1, one of the first cytokines discovered in the 1980s, and a potent mediator of fever, pain and inflammation, is at present experiencing a revival in biology and medicine. Whereas the mechanism of activation and secretion of interleukin 1 $\beta$ , which critically regulates the function of this molecule, has remained mysterious for some 30 years following its discovery, the identification of a new cytoplasmic complex of proteins regulating IL-1 $\beta$  activation and secretion has carried our understanding of the role of IL1 in biology and disease one big step further. The inflammasomes, recently identified innate immune complexes that sense intracellular danger- (e.g. uric acid, ATP, cytoplasmic DNA) or pathogen-associated molecular patterns (e.g. muramyl dipeptide, flagellin, anthrax lethal toxin), are now known to be responsible for triggering inflammation in response to several molecular patterns, including, for example, uric acid, a danger-associated molecular pattern and trigger of gout. Dysregulation of inflammasome function is however also the cause of a family of genetic autoinflammatory diseases known as cryopyrin-associated periodic syndromes (CAPS) characterised by recurrent episodes of fever, urticarial-like skin lesions, systemic inflammation and arthritis. In mouse models recapitulating mutations observed in CAPS, neutrophilic inflammation of the skin is a cardinal feature, in a manner similar to several autoinflammatory diseases with skin involvement such as PAPA (pyoderma gangrenosum, acne and pyogenic arthritis) and Schnitzler's syndrome, in which IL-1 $\beta$  very probably plays a pathogenic role. In this article the role of the inflammasome in IL-1 biology, autoinflammation and disease is reviewed, together with new avenues for the therapy of these diseases.

DOI: 10.4414/smw.2012.13590

PMID: 22653747 [Indexed for MEDLINE]

2715. Swiss Med Wkly. 2012 May 31;142:w13580. doi: 10.4414/smw.2012.13580. eCollection 2012.

AA amyloidosis: basic knowledge, unmet needs and future treatments.

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Systemic AA amyloidosis is a long-term complication of several chronic inflammatory disorders, including rheumatoid arthritis, ankylosing spondylitis, autoinflammatory syndromes, Crohn's disease, malignancies and conditions predisposing to recurrent infections. Organ damage results from the extracellular deposition of proteolytic fragments of the acute-phase reactant serum amyloid A (SAA) as amyloid fibrils. A sustained high concentration of SAA is the prerequisite for developing AA amyloidosis. However, only a minority of patients with long-standing inflammation actually presents with this complication, pointing to the existence of disease-modifying factors, the best characterised of which being SAA1 genotype. The kidneys, liver and spleen are the main target organs of AA amyloid deposits. In more than 90% of patients proteinuria, nephrotic syndrome and/or renal dysfunction dominate the clinical picture at onset. If not effectively treated, this disease invariably leads to end stage kidney disease and renal replacement therapy, that are still associated with a poor outcome. Although the incidence of AA in rheumatoid arthritis and other chronic arthritides has continuously decreased over the past ten years, thanks to the increasing availability of more effective anti-inflammatory and immunosuppressive therapies, AA remains a life-threatening disease with several areas of uncertainty and unmet needs, deserving continuous efforts at prevention and effective treatment. The deeper understanding of the molecular mechanisms of amyloid formation and regression is now driving the development of novel treatments targeting different steps in the amyloidogenic cascade. These therapies will hopefully improve the quality of life and outcome of these patients in a near future.

DOI: 10.4414/smw.2012.13580

PMID: 22653707 [Indexed for MEDLINE]

2716. J Biomed Sci. 2012 May 30;19:55. doi: 10.1186/1423-0127-19-55.

Spontaneous inflammatory pain model from a mouse line with N-ethyl-N-nitrosourea mutagenesis.

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**BACKGROUND:** N-ethyl-N-nitrosourea mutagenesis was used to induce a point mutation in C57BL/6 J mice. Pain-related phenotype screening was performed in 915 G3 mice. We report the detection of a heritable recessive mutant in meiotic recombinant N1F1 mice that caused an abnormal pain sensitivity phenotype with spontaneous skin inflammation in the paws and ears.

**METHODS:** We investigated abnormal sensory processing, neuronal peptides, and behavioral responses after the induction of autoinflammatory disease.

Single-nucleotide polymorphism (SNP) markers and polymerase chain reaction product sequencing were used to identify the mutation site.

**RESULTS:** All affected mice developed paw inflammation at 4-8 weeks. Histological examinations revealed hyperplasia of the epidermis in the inflamed paws and increased macrophage expression in the spleen and paw tissues. Mechanical and thermal nociceptive response thresholds were reduced in the affected mice.

Locomotor activity was decreased in affected mice with inflamed hindpaws, and this reduction was attributable to the avoidance of contact of the affected paw with the floor. Motor strength and daily activity in the home cage in the affected mice did not show any significant changes. Although Fos immunoreactivity was normal in the dorsal horn of affected mice, calcitonin gene-related peptide immunoreactivity significantly increased in the deep layer of the dorsal horn.

The number of microglia increased in the spinal cord, hippocampus, and cerebral cortex in affected mice, and the proliferation of microglia was maintained for a couple of months. Two hundred eighty-five SNP markers were used to reveal the affected gene locus, which was found on the distal part of chromosome 18. A point mutation was detected at A to G in exon 8 of the *pstpip2* gene, resulting in a conserved tyrosine residue at amino acid 180 replaced by cysteine (Y180 C).

**CONCLUSIONS:** The data provide definitive evidence that a mutation in *pstpip2* causes autoinflammatory disease in an N-ethyl-N-nitrosourea mutagenesis mouse model. Thus, our *pstpip2* mutant mice provide a new model for investigating the



potential mechanisms of inflammatory pain.

DOI: 10.1186/1423-0127-19-55

PMCID: PMC3414809

PMID: 22646813 [Indexed for MEDLINE]

2717. Orphanet J Rare Dis. 2012 May 24;7 Suppl 1:S5. doi: 10.1186/1750-1172-7-S1-S5. Epub 2012 May 24.

The role of SH3BP2 in the pathophysiology of cherubism.

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Cherubism is a rare bone dysplasia that is characterized by symmetrical bone resorption limited to the jaws. Bone lesions are filled with soft fibrous giant cell-rich tissue that can expand and cause severe facial deformity. The disorder typically begins in children at ages of 2-5 years and the bone resorption and facial swelling continues until puberty; in most cases the lesions regress spontaneously thereafter. Most patients with cherubism have germline mutations in the gene encoding SH3BP2, an adapter protein involved in adaptive and innate immune response signaling. A mouse model carrying a Pro416Arg mutation in SH3BP2 develops osteopenia and expansile lytic lesions in bone and some soft tissue organs. In this review we discuss the genetics of cherubism, the biological functions of SH3BP2 and the analysis of the mouse model. The data suggest that the underlying cause for cherubism is a systemic autoinflammatory response to physiologic challenges despite the localized appearance of bone resorption and fibrous expansion to the jaws in humans.

DOI: 10.1186/1750-1172-7-S1-S5

PMCID: PMC3359958

PMID: 22640988 [Indexed for MEDLINE]

2718. Mol Cancer Ther. 2012 Aug;11(8):1623-6. doi: 10.1158/1535-7163.MCT-11-0972. Epub 2012 May 25.

Sustained remission of multicentric Castleman disease in children treated with tocilizumab, an anti-interleukin-6 receptor antibody.

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Multicentric Castleman Disease (MCD) is an idiopathic lymphoproliferative disorder, reported exceptionally in children and generally believed to be an autoinflammatory disease resulting in an increase of interleukin-6 secretion. Previous studies in adult patients suggested a beneficial role of the anti-interleukin-6 receptor antibody tocilizumab on the clinical and biologic disease manifestations of MCD. Here, we describe the efficacy and safety of tocilizumab in two children with MCD, which was diagnosed on the basis of clinical and histologic findings. In both cases, tocilizumab was administered intravenously at a dose of 8 mg/kg every 2 weeks. The tocilizumab treatment alleviated fever and restored growth rate in both patients. The patients' hypergammaglobulinemia, high C-reactive protein, and high erythrocyte sedimentation rates normalized simultaneously. Nevertheless, splenomegaly persisted in the first patient, and a secondary hepatic node appeared in the second patient. The side effects, essentially sustained thrombocytopenia, were mild in both cases. For the first patient, following an initial 10-month period, the interval between infusions was increased. This patient benefited from sustained remission for a period of 3 years. Tocilizumab was effective and safe in these two children with MCD.

DOI: 10.1158/1535-7163.MCT-11-0972

PMID: 22638145 [Indexed for MEDLINE]

2719. Curr Opin Rheumatol. 2012 Jul;24(4):389-93. doi: 10.1097/BOR.0b013e32835448b8.

Infections and vaccines in the etiology of antiphospholipid syndrome.

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PURPOSE OF REVIEW: To present scientific evidence supporting the infectious origin for the antiphospholipid syndrome (APS) by molecular mimicry between pathogens, infection and vaccination with  $\beta$ 2-glycoprotein I ( $\beta$ 2-GPI) molecule.

RECENT FINDINGS: APS is characterized by the presence of pathogenic autoantibodies against  $\beta$ 2-GPI. The infection etiology of APS was well established. Likewise, a link between vaccination such as tetanus toxoid may trigger antibodies targeting tetanus toxoid and  $\beta$ 2-GPI, due to molecular mimicry between the two molecules. During the years, the pathogenic potential of anti-tetanus toxoid antibodies cross reactive with  $\beta$ 2-GPI were found to be pathogenic in animal models, inducing experimental APS.

SUMMARY: Accumulated evidence supports that the presence of anti- $\beta$ 2-GPI antibodies is associated with a history of infections and the main mechanism to explain this correlation is molecular mimicry. The relationship between tetanus toxoid vaccination and APS reveals a novel view on the autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA).

DOI: 10.1097/BOR.0b013e32835448b8

PMID: 22617823 [Indexed for MEDLINE]

2720. Genet Mol Res. 2012 May 7;11(2):1185-94. doi: 10.4238/2012.May.7.4.

Frequency of alterations in the MEFV gene and clinical signs in familial Mediterranean fever in Central Anatolia, Turkey.

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Familial Mediterranean fever is a recessive autoinflammatory disease that is

frequent in Armenians, Jews, Arabs, and Turks. The MEFV gene is responsible for this disease. We looked for MEFV gene variations (polymorphism and mutations) in a population that resides in Central Anatolia, Turkey. DNA was extracted from peripheral blood leukocytes of 802 familial Mediterranean fever patients. The DNA sequence data were examined for approximately 150 different mutations and polymorphisms, including single nucleotide polymorphisms in different exons of the MEFV gene. The male:female ratio of these patients was 1.44:1. Mutations were detected in 48.1% of the patients; 7.5% were homozygous, 11.1% were compound heterozygous and 31.5% had only one identifiable mutant allele. No mutations were detected in 51.9% of the patients. The main clinical characteristics of the patients were: abdominal pain in 20.6%, arthritis in 22.9% and amyloidosis in 4.6%. Sixty-six percent of patients had a family history of familial Mediterranean fever; 19.4% of the patients were found to have parental consanguinity. We conclude that the genetics of familial Mediterranean fever is more complex than has previously been reported; heterozygous patients presenting a severe phenotype should be further analyzed for less common secondary MEFV mutations, using gene sequencing.

DOI: 10.4238/2012.May.7.4

PMID: 22614345 [Indexed for MEDLINE]

2721. Int J Inflam. 2012;2012:480373. doi: 10.1155/2012/480373. Epub 2012 Apr 26.

Is Still's Disease an Autoinflammatory Syndrome?

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Systemic juvenile idiopathic arthritis (sJIA), formerly called Still's disease, is officially classified as a subset of juvenile idiopathic arthritis (JIA). Beside arthritis, it is characterized by prominent systemic features and a marked inflammatory response. Even if it is still included in the group of juvenile arthritides, sJIA is set apart from all the other forms of JIA. This disorder has markedly distinct clinical and laboratory features suggesting a different

pathogenesis. sJIA does not show any association with HLA genes or with autoantibodies and is characterised by an uncontrolled activation of phagocytes with hypersecretion of IL-1 and IL-6. Based on clinical and laboratory features, as well as on new acquisitions on the pathogenesis, it seems evident that sJIA is an autoinflammatory disease related to abnormality in innate immune system. The new insights on the pathogenesis of sJIA have therefore dramatically changed the approach to treatment, with the development of targeted treatments (anti-IL-1 and anti-IL-6 agents) more effective and safer than earlier medications.

DOI: 10.1155/2012/480373

PMCID: PMC3350968

PMID: 22611516

2722. Int J Inflam. 2012;2012:317820. doi: 10.1155/2012/317820. Epub 2012 Apr 29.

Anti-Interleukin-1 Agents in Adult Onset Still's Disease.

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Interleukin 1 $\beta$  (IL-1 $\beta$ ) is emerging as a master mediator of adult onset Still's disease (AOSD) pathogenesis. This pleiotropic cytokine, whose expression is under the control of the inflammasome pathway, has a wide type of effects. As a key mediator of innate immunity is a potent pyrogen and facilitates neutrophilic proliferation and diapedesis into the inflamed tissues, which are key AOSD manifestations. The study of proinflammatory cytokines profiles in sera and pathological tissues of AOSD patients has shown elevated levels of IL-1 $\beta$ , these levels being highly correlated with disease activity and severity. These experimental evidences and the analogy with other autoinflammatory diseases that share with AOSD clinical and biological characteristics have suggested the blockade of IL-1 $\beta$  as a possible new therapeutic option for the AOSD, especially in conventional therapy resistant cases. Anakinra, the first anti-IL-1 agent put on the market, has demonstrated capable to induce a rapid response sustained over time, especially in systemic forms, where anti-TNF $\alpha$  failed to control symptoms. While a growing number of evidences supports the utilisation of anakinra in AOSD, a new generation of anti-IL1 $\beta$  antagonists is developing. Canakinumab and

rilonacept, thanks to their higher affinity and longer half-life, could improve the management of this invalidating disease.

DOI: 10.1155/2012/317820

PMCID: PMC3350963

PMID: 22611515

2723. Case Rep Radiol. 2012;2012:515761. doi: 10.1155/2012/515761. Epub 2012 Feb 28.

Case study: chronic recurrent multifocal osteomyelitis in the femoral diaphysis of a young female.

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Chronic recurrent multifocal osteomyelitis (CRMO) is relatively uncommon. Even though the name suggests it is the result of infection, this is not likely the case. Instead it is more likely the result of genetic, autoimmune, or autoinflammatory causes. Although CRMO has a benign course and responds well to anti-inflammatory medications, it can have a very aggressive clinical and imaging presentation overlapping with infectious osteomyelitis and malignancy. Therefore, radiologists and clinicians need to be aware of its clinical and imaging presentation to avoid morbidity associated with more aggressive treatment. We present the case of a ten-year-old female with CRMO as a solitary expansile-mixed lytic and sclerotic lesion in the distal femoral diaphysis. The diaphyseal location and mixed lytic and sclerotic appearance are less common and have an aggressive imaging appearance. We also review the pathophysiology, imaging findings, and therapeutic approach to this uncommon but clinically important condition.

DOI: 10.1155/2012/515761

PMCID: PMC3350087

PMID: 22606567

2724. Clin Appl Thromb Hemost. 2012 Nov;18(6):633-7. doi: 10.1177/1076029611432743. Epub 2012 May 15.

Tumor necrosis factor- $\alpha$  gene polymorphisms in FMF and their association with amyloidosis.

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Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by periodic provocative attacks of fever with peritonitis, pleuritis, arthritis, or erisiplemia. Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) plays an important role in the regulation of the immune response as a part of the cytokine network, including activation of macrophages and apoptosis. We investigated the possible association of TNF- $\alpha$  promoter -1031T/C and -308G/A polymorphisms in 86 FMF patients carrying M694 V homozygous mutation and 100 matched healthy controls both from Iranian Azeri Turks. Our data showed that patients with TNF- $\alpha$  -308 GG are more susceptible to the development of amyloidosis and arthritis (P value <.05). These data also showed that the frequency of TNF- $\alpha$  -308 A allele is considerably low among patients with amyloidosis, and it may have protective role among them (odds ratio [OR] = 0.083,  $\chi^2(2)$  = 5.46, P value = .003). Further evaluation of this polymorphism may be important and need further studies.

DOI: 10.1177/1076029611432743

PMID: 22593232 [Indexed for MEDLINE]

2725. Allergy. 2012 Jul;67(7):943-50. doi: 10.1111/j.1398-9995.2012.02843.x. Epub 2012 May 15.

Efficacy and safety of the interleukin-1 antagonist rilonacept in Schnitzler syndrome: an open-label study.

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**BACKGROUND:** Schnitzler syndrome (SchS) is a rare disease with suspected autoinflammatory background that shares several clinical symptoms, including urticarial rash, fever episodes, arthralgia, and bone and muscle pain with cryopyrin-associated periodic syndromes (CAPS). Cryopyrin-associated periodic syndromes respond to treatment with interleukin-1 antagonists, and single case reports of Schnitzler syndrome have shown improvement following treatment with the interleukin-1 blocker anakinra. This study evaluated the effects of the interleukin-1 antagonist rilonacept on the clinical signs and symptoms of SchS.

**METHODS:** Eight patients with SchS were included in this prospective, single-center, open-label study. After a 3-week baseline, patients received a subcutaneous loading dose of rilonacept 320 mg followed by weekly subcutaneous doses of 160 mg for up to 1 year. Efficacy was determined by patient-based daily health assessment forms, physician's global assessment (PGA), and measurement of inflammatory markers including C-reactive protein (CRP), serum amyloid A (SAA), and S100 calcium-binding protein A12 (S100A12).

**RESULTS:** Treatment with rilonacept resulted in a rapid clinical response as demonstrated by significant reductions in daily health assessment scores and PGA scores compared with baseline levels ( $P < 0.05$ ). These effects, which were accompanied by reductions in CRP and SAA, continued over the treatment duration. Rilonacept treatment was well tolerated. There were no treatment-related severe adverse events and no clinically significant changes in laboratory safety parameters.

**CONCLUSION:** Rilonacept was effective and well tolerated in patients with SchS and may represent a promising potential therapeutic option.

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DOI: 10.1111/j.1398-9995.2012.02843.x

PMID: 22583335 [Indexed for MEDLINE]

2726. Ann Rheum Dis. 2012 Dec;71(12):1961-5. doi: 10.1136/annrheumdis-2011-200977. Epub 2012 May 12.

Clinical impact of MEFV mutations in children with periodic fever in a prevalent



western European Caucasian population.

Federici S(1), Calcagno G, Finetti M, Gallizzi R, Meini A, Vitale A, Caroli F, Cattalini M, Caorsi R, Zulian F, Tommasini A, Insalaco A, Sormani MP, Baldi M, Ceccherini I, Martini A, Gattorno M.

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**OBJECTIVE:** To evaluate the actual impact of MEFV mutations on clinical manifestations associated with fever attacks in Caucasian children with periodic fever.

**METHODS:** 113 children carrying MEFV mutations (44 with mutations in two alleles, 69 heterozygous) and 205 children negative for mutations in genes associated with periodic fevers were analysed. The following groups of patients were considered: patients carrying two high penetrance mutations (M694V, M694I, M680I); one high, one low penetrance mutation; two low penetrance mutations; one high penetrance mutation; one low penetrance mutation; genetically negative patients.

**RESULTS:** Patients with two MEFV mutations displayed a shorter duration of fever attacks and higher prevalence of a positive family history than patients carrying one MEFV mutation and genetically negative patients. Severe abdominal pain, chest pain and pleurisy were also more frequent in patients with two MEFV mutations compared with children with one MEFV mutation and genetically negative patients. Conversely, a higher frequency of exudative and erythematous pharyngitis, enlargement of cervical lymph nodes, aphthous stomatitis and non-specific skin rash was observed in genetically negative patients and, to a lesser extent, in patients with one MEFV mutation. The frequency of 'familial Mediterranean fever (FMF)-like symptoms' decreases from patients carrying two high penetrance mutations towards patients with a single low penetrance mutation with an opposite trend for 'periodic fever, aphthous stomatitis, pharyngitis, adenitis-like symptoms'.

**CONCLUSIONS:** This clinical observation supports recent findings contrasting the notion of FMF being a pure autosomal recessive disorder associated with recurrence of mutations leading to loss of protein function. A dosage effect could be invoked, giving rise to symptom onset even in the presence of one wild-type allele.

DOI: 10.1136/annrheumdis-2011-200977

PMID: 22580583 [Indexed for MEDLINE]

2727. Georgian Med News. 2012 Mar;(204):62-6.

Myocardial infarction in patients with familial Mediterranean fever and cardiac lesions.

Ambartsymian SV.

The investigation of relatively rare affections in familial Mediterranean fever--cardiac and lung lesions and pathogenesis of myocardium infarction in background of cardiac lesions is actual. Clinical-morphological analysis of 68 autopsy cases was done. The investigation data observes that cardiac amyloidosis as a dominated morphological manifestation in FMF can leads to heart failure and death. Macroscopically cardiac lesions as a cardiomegaly was observe. The morphological manifestation of cardiac affections in FMF was amyloidosis of the vessels and myocardium stroma. Amyloidosis of the heart valves leads to deformity and clinical-morphological picture of heart defect perform. The large amyloid areas of myocardium leading to the heart insufficiency according to clinical and instrumental data as pseudoinfarctions were manifested. Myocardium infarction develops in background of cardiac lesions in FMF--amyloid angiopathias, which were more expressed in arteriolar walls, with narrowing or obstructing of lumina, and accompanied with them--coronary vasculitis. The main predisposing pathogenic factors for myocardial infarction can be atherosclerotic changes of the vessels also, which were complicated by amyloid depositions of the vascular walls. Cardiac failure can develop before renal amyloidosis and uremia.

PMID: 22573751 [Indexed for MEDLINE]

2728. Georgian Med News. 2012 Mar;(204):59-62.

Morphological aspects of the familial Mediterranean fever.

Ambartsymian SV.

The study of clinical and morphological features of multiple organ lesions in familial Mediterranean fever (FMF) is important for identification of main

morphologic lesions in thanatogenesis in parallel with the clinical manifestations. Clinical-morphological analysis of 200 patients with FMF and 60 dead from complications of FMF without renal transplantation were done. It was established that renal affection was observed in all patients, who died from complications of FMF, but the severity and nature of the observed changes were different. The kidney affections in investigated material in 3 groups were classified: amyloidosis, nonamyloid affections and glomerulitis accompanied with amyloidosis. Cardiopathic amyloidosis we established in thanatogenesis of FMF manifested with heart failure. The secondary polyorganial amyloidosis in FMF resulting in polyorganial failure revealed. The lung amyloidosis was accompanied with cardiac. Kidney affections were manifested with nonamyloid nephropathias manifested with intracapillary mesangioproliferative or extracapillary productive glomerulonephritis, besides amyloidosis. Amyloidosis of the heart, lungs, adrenals can significantly prevail to kidney damage and be expressed at the forefront of thanatogenesis.

PMID: 22573750 [Indexed for MEDLINE]

2729. J Clin Immunol. 2012 Oct;32(5):922-32. doi: 10.1007/s10875-012-9688-x. Epub 2012 May 8.

Hereditary autoinflammatory syndromes: a Brazilian multicenter study.

Jesus AA(1), Fujihira E, Watase M, Terreri MT, Hilario MO, Carneiro-Sampaio M, Len CA, Oliveira SK, Rodrigues MC, Pereira RM, Bica B, Silva NA, Cavalcanti A, Marini R, Sztajn bok F, Quintero MV, Ferriani VP, Moraes-Vasconcelos D, Silva CA, Oliveira JB.

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Erratum in

J Clin Immunol. 2012 Oct;32(5):933-5.

**OBJECTIVE:** To evaluate the prevalence of genetic defects in clinically suspected autoinflammatory syndromes (AIS) in a Brazilian multicenter study.

**METHODS:** The study included 102 patients with a clinical diagnosis of Cryopyrin

Associated Periodic Syndromes (CAPS), TNF Receptor Associated Periodic Syndrome (TRAPS), Familial Mediterranean Fever (FMF), Mevalonate Kinase Deficiency (MKD) and Pediatric Granulomatous Arthritis (PGA). One of the five AIS-related genes (NLRP3, TNFRSF1A, MEFV, MVK and NOD2) was evaluated in each patient by direct DNA sequencing, based on the most probable clinical suspect.

RESULTS: Clinical diagnoses of the 102 patients were: CAPS (n = 28), TRAPS (n = 31), FMF (n = 17), MKD (n = 17) and PGA (n = 9). Of them, 27/102 (26 %) had a confirmed genetic diagnosis: 6/28 (21 %) CAPS patients, 7/31 (23 %) TRAPS, 3/17 (18 %) FMF, 3/17 (18 %) MKD and 8/9 (89 %) PGA.

CONCLUSION: We have found that approximately one third of the Brazilian patients with a clinical suspicion of AIS have a confirmed genetic diagnosis.

DOI: 10.1007/s10875-012-9688-x

PMID: 22566169 [Indexed for MEDLINE]

2730. J Obstet Gynaecol Res. 2012 Oct;38(10):1240-4. doi: 10.1111/j.1447-0756.2012.01857.x. Epub 2012 May 8.

Subfertility in women with familial Mediterranean fever.

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AIM: The aim of this study was to examine the causes and different modalities used for management of subfertile patients with familial Mediterranean fever (FMF).

MATERIAL AND METHODS: The study comprised of 74 infertile women with FMF. All patients were diagnosed as having FMF. All patients underwent a full infertility work-up. They were scheduled to expectant treatment, ovulation induction and timed intercourse, intrauterine insemination or intracytoplasmic sperm injection.

RESULTS: Anovulation was reported in 18 patients (24.32%). Anovulation was due to polycystic ovary syndrome in 12 (16.22%) cases and due to other causes in six patients (8.11%). Excessive clear peritoneal fluid was present in 56 (57.67%) and male-factor infertility was present in 14 couples (18.91%). Ovulation induction and timed intercourse was adopted for a maximum of six cycles and intrauterine insemination for three cycles. In vitro fertilization/intracytoplasmic sperm

injection was needed in six cases using standard long agonist protocol.

Twenty-six women became pregnant.

**CONCLUSION:** The causes of infertility in patients with FMF are not different from those expected in the general population. Treatment of the problem should be causal, adopting the conventional lines of treatment up to in vitro fertilization/intracytoplasmic sperm injection when appropriate. Colchicine is the treatment of choice and it is important to use it in its proper doses to control the disease.

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DOI: 10.1111/j.1447-0756.2012.01857.x

PMID: 22563801 [Indexed for MEDLINE]

2731. Clin Rheumatol. 2012 Aug;31(8):1183-6. doi: 10.1007/s10067-012-1992-6. Epub 2012 May 5.

Renal transplantation in patients with familial Mediterranean fever.

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Amyloidosis is the most common and devastating complication of familial Mediterranean fever (FMF). Renal transplantation is the choice of treatment of in most end-stage renal disease (ESRD). We report our experience on the outcomes in eight patients who underwent renal transplantation for ESRD due to FMF secondary to amyloidosis, and we provide a discussion on the current evidence on this topic of study. The clinical charts of eight renal transplant patients (seven male, one female) who underwent ESRD due to FMF-related amyloidosis were investigated. Five patients underwent living-donor renal transplantation and three patients underwent deceased-donor renal transplant. The mean follow-up period was 35 months (range 3-72). All patients were on triple immunosuppressive treatment and received colchicine. All allografts are currently functioning well with a mean serum creatinine level of 1.4 (range 0.7-2.6) mg/dL. Posttransplantation

complications included acute rejection (n = 4), chronic rejection (n = 1), severe gastroenteritis (n = 2), and erythrocytosis (n = 5). None of the patients had proteinuria. During follow-up, we did not observe clinically severe FMF attack, septicemia, rhabdomyolysis, symptoms related to vasculitis, and clinical neuropathy. The clinical outcome of the patients in this cohort was similar to that of other renal transplant patients with ESRD due to other causes. This study shows favorable prognosis of eight ESRD patients due to amyloidosis caused by FMF after renal transplantation. Renal transplantation is a safe procedure for ESRD patients having amyloidosis due to FMF. Regular use of colchicine after transplantation should be mentioned.

DOI: 10.1007/s10067-012-1992-6

PMID: 22562368 [Indexed for MEDLINE]

2732. *Pediatr Clin North Am.* 2012 Apr;59(2):447-70. doi: 10.1016/j.pcl.2012.03.005.

Autoinflammatory syndromes.

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There has been an expansion of the autoinflammatory syndromes due to the discovery of new diseases related to mutations in genes regulating the innate immune system and the knowledge gained from these diseases as applied to more common nongenetic inflammatory conditions. Autoinflammatory syndromes are characterized by unprovoked (or triggered by minor events) recurrent episodes of systemic inflammation involving various body systems, which are often accompanied by fever. Inflammation is mediated by polymorphonuclear and macrophage cells through cytokines, particularly interleukin-1. This article reviews the clinical approach to patients with suspected autoinflammatory syndromes, several of the main and new (mostly genetics) syndromes, advances in treatment, and prognosis.

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DOI: 10.1016/j.pcl.2012.03.005

PMID: 22560579 [Indexed for MEDLINE]

2733. *Pediatr Clin North Am.* 2012 Apr;59(2):225-43. doi: 10.1016/j.pcl.2012.03.004.

Principles of inflammation for the pediatrician.

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The immune system consists of 2 branches: innate and adaptive. The former represents the first line of host defense during infection and plays a key role in the early recognition and protection against invading pathogens. The latter orchestrates elimination of pathogens in the late phase of infection and leads to the generation of immunologic memory. Innate and adaptive immunity should not be considered separate compartments. Innate and adaptive immune responses represent an integrated system of host defense. The authors review the mechanisms driving the induction and perpetuation of the inflammatory responses observed during pathogen-associated, autoimmune, and autoinflammatory diseases.

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DOI: 10.1016/j.pcl.2012.03.004

PMID: 22560568 [Indexed for MEDLINE]

2734. *Vnitr Lek.* 2012 Apr;58(4):313-8.

[Interleukin-1 receptor blockade with anakinra provided cessation of fatigue, reduction in inflammation markers and regression of retroperitoneal fibrosis in a patient with Erdheim-Chester disease - case study and a review of literature].

[Article in Czech]

Adam Z(1), Szturz P, Bučková P, Cervinková I, Koukalová R, Rehák Z, Krejčí M, Pour L, Zahradová L, Hájek R, Král Z, Mayer J.

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We describe a case of an Erdheim-Chester disease patient. First line chemotherapy treatment with 2-chlorodeoxyadenosine did not reduce fluorodeoxyglucose accumulation in pathological lesions. The patient had continuously increased CRP values of 17-20 mg/l. The disease continued to cause subfebrile temperatures and significant fatigue that made the patient to spend most of the daytime in bed. To manage the permanently increased inflammation markers, we decided to start treatment with anakinra, successfully used in some other autoinflammatory diseases (e.g. Schnitzler syndrome). We have now been able to evaluate the first 6 months of treatment. Daily subcutaneous administration of anakinra (Kineret<sup>TM</sup> 100 mg daily) led to normalization of CRP values, cessation of subfebrile temperatures and, importantly, significant reduction of fatigue. Time periods the patient was able to spend out of the bed increased significantly. Consequent to the reduced fatigue, the patient was able to perform basic household tasks he was unable to undertake without treatment. After 3 months of treatment, fatigue of the same intensity returned following a short interruption of therapy. The CRP values went up again to 12 mg/l. CRP value returned back to norm and fatigue ceased after re-initiation of daily Kineret injections. Objective treatment response was assessed by measuring the degree of fluorodeoxyglucose accumulation in pathological bone lesions. PET-CT was performed before and 3 and 6 months after anakinra initiation. Intensity of accumulation did not change significantly after the first 3 months of therapy but decreased after 6 month therapy. Follow up CT of abdominal cavity was performed at the end of the 6th month of treatment. Presented CT images from before and 6 months after the treatment evidence an obvious reduction in fibroid changes in the retroperitoneum. Daily administration of anakinra to a patient with active Erdheim-Chester disease significantly reduced intensity of fatigue and improved quality of life, led to a reduction in inflammatory markers and regression in retroperitoneal fibrotization.

PMID: 22559807 [Indexed for MEDLINE]

2735. Rev Med Suisse. 2012 Apr 4;8(335):756-8, 760-1.



[Autoinflammatory syndromes in dermatology].

[Article in French]

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Hereditary periodic fever syndromes, also called autoinflammatory syndromes, are characterized by relapsing fever and additional manifestations such as skin rashes, mucosal manifestations, or arthralgias. Some of these disorders present without fever but with the associated systemic manifestations. The responsible mutated genes have been identified for most of these disorders, which lead to the induction of the uncontrolled and excessive production of interleukin-1beta (IL-1beta). The inhibition of IL-1beta through IL-1 receptor antagonist or monoclonal antibody against IL-1beta is used with success in most of these diseases. In case of TNF-receptor associated periodic syndrome (TRAPS) and paediatric granulomatous arthritis (PGA), TNF-antagonists may also be used; in familial Mediterranean fever (FMF) colchicine remains the first choice.

PMID: 22545497 [Indexed for MEDLINE]

2736. Nat Immunol. 2012 Apr 29;13(6):596-603. doi: 10.1038/ni.2293.

TRIM28 prevents autoinflammatory T cell development in vivo.

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TRIM28 is a component of heterochromatin complexes whose function in the immune system is unknown. By studying mice with conditional T cell-specific deletion of TRIM28 (CKO mice), we found that TRIM28 was phosphorylated after stimulation via

the T cell antigen receptor (TCR) and was involved in the global regulation of CD4(+) T cells. The CKO mice had a spontaneous autoimmune phenotype that was due in part to early lymphopenia associated with a defect in the production of interleukin 2 (IL-2) as well as incomplete cell-cycle progression of their T cells. In addition, CKO T cells showed derepression of the cytokine TGF- $\beta$ 3, which resulted in an altered cytokine balance; this caused the accumulation of autoreactive cells of the T(H)17 subset of helper T cells and of Foxp3(+) T cells. Notably, CKO Foxp3(+) T cells were unable to prevent the autoimmune phenotype in vivo. Our results show critical roles for TRIM28 in both T cell activation and T cell tolerance.

DOI: 10.1038/ni.2293

PMID: 22544392 [Indexed for MEDLINE]

2737. Medicine (Baltimore). 2012 May;91(3):131-6. doi: 10.1097/MD.0b013e3182561a45.

Familial Mediterranean fever: risk factors, causes of death, and prognosis in the colchicine era.

Akar S(1), Yuksel F, Tunca M, Soysal O, Solmaz D, Gerdan V, Celik A, Sen G, Onen F, Akkoc N.

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We assessed the risk factors and causes of death in patients with familial Mediterranean fever (FMF) in an era when colchicine is the standard therapy for all patients. This study included all FMF patients who had presented to any of the internal medicine, rheumatology, or nephrology clinics at Dokuz Eylul University Hospital between 1992 and 2009. Of the 650 patients with FMF identified, 587 (90.3%) had either a face-to-face (n = 380) or telephone (n = 193) interview, or were confirmed as deceased. A structured questionnaire was used to obtain socioeconomic and demographic data, presenting and cumulative clinical features, and disease severity scores. During the follow-up period mortality was analyzed by calculating age- and sex-standardized mortality ratio (SMR) according to the mortality statistics of the Turkish population. Factors predictive of mortality were evaluated using Kaplan-Meier and Cox proportional hazard models. Sixty-three

(9.7%) patients whose initial demographic and major clinical characteristics were similar to the rest of the group could not be contacted during the study period. Most (94.2%) patients were on colchicine at the time of the study. Thirty-seven (6.3%) patients had biopsy-verified amyloidosis, and 44 (7.5%) had renal disease. During a median follow-up of 6 years, 14 patients (9 women) died, and amyloidosis and its related complications were the leading causes of death in 7 patients. Univariate analysis revealed that increasing age, coronary heart disease, hypertension, renal disease, and amyloidosis were associated with mortality. However, Cox regression analysis showed amyloidosis as the only significant predictor of mortality ( $p < 0.001$ ). The overall patient survival rate was not significantly different from the age- and sex-matched Turkish general population (SMR, 1.48; 95% confidence interval, 0.817-2.49). Our findings suggest that although the survival of FMF patients in the colchicine era is comparable to that of the general population, renal involvement still predicts mortality.

DOI: 10.1097/MD.0b013e3182561a45

PMID: 22543627 [Indexed for MEDLINE]

2738. Curr Opin Neurol. 2012 Jun;25(3):349-57. doi: 10.1097/WCO.0b013e3283534a8a.

Autoinflammatory grey matter lesions in humans: cortical encephalitis, clinical disorders, experimental models.

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**PURPOSE OF REVIEW:** In recent years, evidence has accumulated that grey matter abnormalities are common in many inflammatory central nervous system (CNS) disorders, such as multiple sclerosis (MS), which is by far the most frequent autoimmune-mediated CNS disease.

**RECENT FINDINGS:** A recent study described comprehensively the pathology of grey matter lesions in early MS. In this study, cortical demyelination together with inflammation was frequently observed in early MS cases. This study and others serve as a basis for a model of the development of cortical MS lesions in which several consecutive events may be involved. After the activation of T cells,

which may open the blood-brain barrier, the humoral immune system may mediate the inflammatory process. The inflammation may become chronic through the involvement of activated glial cells and the persistence of immune cells in the meninges. Apart from MS, other grey matter CNS disorders exist in which antibodies against neuronal structures contribute to pathophysiological events such as in limbic encephalitis. Humoral and adaptive immunity mediates the pathophysiology of Rasmussen encephalitis.

**SUMMARY:** This review focuses on the difference between inflammatory grey matter and white matter lesions. New insights into inflammatory grey matter lesions in MS and other CNS inflammatory processes such as limbic encephalitis are discussed.

DOI: 10.1097/WCO.0b013e3283534a8a

PMID: 22543404 [Indexed for MEDLINE]

2739. CEN Case Rep. 2012 May;1(1):4-6. doi: 10.1007/s13730-011-0002-1. Epub 2012 Jan 13.

A case of familial Mediterranean fever-associated systemic amyloidosis.

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Familial Mediterranean fever (FMF) is a chronic inflammatory disease, characterized by recurrent fever and polyserositis (pleuritis and/or peritonitis). The most important complication of FMF is amyloidosis, which causes chronic renal failure. Colchicine is the most effective treatment in acute attacks and amyloidosis development. However, the majority of patients with

amyloidosis have a relentless progression to end-stage renal disease despite initiation of colchicine treatment. We present the case of a 38-year-old man with FMF-associated chronic renal failure due to systemic amyloidosis. The patient suffered from periodic fever and renal insufficiency, and was admitted to our hospital. Laboratory examination revealed an inflammatory reaction, renal dysfunction (serum creatinine 2.5 mg/dl), and proteinuria. Renal biopsy revealed segmental mesangial AA amyloid deposits in several glomeruli and the walls of several vessels. Genetic analysis showed that the patient was heterozygous for the MEFV gene (E148Q/M694I). Thus, he was diagnosed with FMF, and colchicine treatment was initiated. He remained almost attack free, with decreasing serum creatinine levels (1.6 mg/dl) and diminishing urinary protein excretion. In conclusion, renal amyloidosis is the most important long-term complication of FMF, and treatment with colchicine is effective for preventing progression. Therefore, colchicine treatment should be initiated as early as possible after the diagnosis of FMF.

DOI: 10.1007/s13730-011-0002-1

PMCID: PMC5387864

PMID: 28509144

2740. Mod Rheumatol. 2013 Mar;23(2):374-8. doi: 10.1007/s10165-012-0649-2. Epub 2012 Apr 25.

Coexistence of polymyositis and familial Mediterranean fever.

Eguchi M(1), Miyashita T, Shirouzu H, Sato S, Izumi Y, Takeoka A, Ohno T, Sumiyoshi R, Nishino A, Jiuchi Y, Nonaka F, Eguchi K, Kawakami A, Migita K.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease affecting populations surrounding the Mediterranean area. In this case report, we report a Japanese female patient with polymyositis (PM) who presented with periodic fever. Genetic analysis revealed that she had compound heterozygous mutations in exon 2 of the MEFV gene (L110P/E148Q/R202Q). Treatment with colchicines (1.0 mg/day)

successfully eliminated febrile attack and normalized the elevated levels of neutrophil CD64 expression, leading to the diagnosis of FMF. The association of FMF and PM has not previously been reported, so we discuss this rare association.

DOI: 10.1007/s10165-012-0649-2

PMID: 22534884 [Indexed for MEDLINE]

2741. *Lupus*. 2012 Aug;21(9):993-8. doi: 10.1177/0961203312441048. Epub 2012 Apr 24.

Familial Mediterranean FeVer gene (MEFV) mutations as a modifier of systemic lupus erythematosus.

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The objective of this study was to assess the prevalence of the Mediterranean FeVer (MEFV) gene mutations in systemic lupus erythematosus (SLE) patients and their effect on organ involvement, as well as disease activity and severity. The frequencies of three familial Mediterranean fever-related MEFV gene mutations (M694V, V726A and E148Q) were investigated in 70 SLE patients. Organ involvement, Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores were correlated with mutation carriage. Eleven of 70 patients (15.7%) were found to carry an MEFV mutation. A single patient harbored two mutations, E148Q and V726A, without overt familial Mediterranean fever while the rest were heterozygous carriers. Four of the 11 carried an M694V mutation, four carried V726A and two carried E148Q. The majority of MEFV mutation carriers were Sephardic while non-carriers were mainly of Ashkenazi origin (72.7% vs. 45.7% and 47.4% vs. 9.1%, respectively,  $p = 0.02$ ). SLE onset was significantly earlier in MEFV carriers ( $27.6 \pm 9.7$  vs.  $38.2 \pm 15.5$  years, in carriers vs. non-carriers,  $p = 0.02$ ). Hematologic and serologic parameters were comparable among mutation carriers and non-carriers. Febrile episodes were more common among MEFV mutation carriers (45.4% vs. 15.2%,  $p = 0.035$ ) and there was a trend for excess episodes of pleuritis as well (54.5% vs. 23.7%,  $p = 0.06$  in

carriers vs. non-carriers, respectively). The frequency of secondary anti-phospholipid antibody syndrome was equivalent among the groups. Conversely, compound urinary abnormalities and renal failure was not observed among MEFV carriers yet was present in 33.4% and 18.6% of non-carriers ( $p = 0.027$  and  $0.19$ , respectively). SLICC damage index and SLEDAI activity index did not differ significantly between the groups. MEFV mutation carriage appears to modify the SLE disease phenotype in that it contributes to an excess of inflammatory manifestations such as fever and pleuritis on the one hand, while thwarting more severe renal involvement on the other.

DOI: 10.1177/0961203312441048

PMID: 22532615 [Indexed for MEDLINE]

2742. Cardiovasc Drugs Ther. 2012 Jun;26(3):273-6. doi: 10.1007/s10557-012-6389-x.

Recombinant human interleukin-1 receptor antagonist provides cardioprotection during myocardial ischemia reperfusion in the mouse.

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**PURPOSE:** Acute myocardial infarction (AMI) drives an intense inflammatory response that contributes to infarct healing and cardiac remodeling. Recently, different studies have identified a role of interleukin-1 (IL-1) in the development of adverse cardiac remodeling. However, in animal models of AMI IL-1 has been shown to be cardioprotective in preconditioning, raising the question of clinical safety of therapeutic IL-1 blockade for autoinflammatory diseases or for the prevention or the treatment of AMI. In this study we proposed to evaluate the effects of pretreatment with recombinant human interleukin-1 receptor antagonist (rhIL-1Ra) on ischemia reperfusion (I/R) injury to the heart.

**METHODS:** RhIL-1Ra was given 4 h or 30 min before the surgical induction of I/R. Left ventricular ejection fraction(LVEF) and infarct size were assessed to determine the effects of the drug pretreatment compared to vehicle treated mice.

**RESULTS:** RhIL-1Ra, given 4 h or 30 min before the onset of the ischemia, showed

marked cardioprotection though preservation of the LVEF (no change vs sham operated mice) and the reduction of the infarct size (-40 % vs vehicle-treated mice). No differences were observed between the two groups of rhIL-1Ra treatment. CONCLUSIONS: IL-1 blockade therapies using rhIL-1Ra prior the onset of AMI protects the myocardium and preserves cardiac function.

DOI: 10.1007/s10557-012-6389-x

PMID: 22527620 [Indexed for MEDLINE]

2743. Z Rheumatol. 2012 Apr;71(3):199-208. doi: 10.1007/s00393-011-0856-9.

[Cryopyrin-associated periodic syndrome].

[Article in German]

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The cryopyrin-associated periodic syndrome is a very rare disease. It is estimated that there are 1-2 cases out of 1 million inhabitants in the USA and 1/360,000 in France. However, many patients are diagnosed very late or not at all. Therefore the real prevalence is likely to be higher. CAPS encompasses the three entities familial cold autoinflammatory syndrome (FCAS), the Muckle-Wells syndrome and the neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic cutaneous and articular (CINCA) syndrome. They have in common a causative mutation in the NLRP3-gene. The altered gene product cryopyrin leads to activation of the inflammasome which in turn is responsible for excessive production of IL-1 $\beta$ . IL-1 $\beta$  causes the inflammatory manifestations in CAPS. These appear as systemic inflammation including fever, headache or fatigue, rash, eye disease, progressive sensorineural hearing loss, musculoskeletal manifestations and CNS symptoms (NOMID/CINCA only). With the advent of the IL-1 inhibitors anakinra, rilonacept and canakinumab for the first time safe and effective therapeutic options are available for this devastating disease. To



prevent severe and possible life-threatening disease sequelae, early and correct diagnosis and immediate initiation of therapy are mandatory.

DOI: 10.1007/s00393-011-0856-9

PMID: 22527214 [Indexed for MEDLINE]

2744. Z Rheumatol. 2012 Apr;71(3):181-6. doi: 10.1007/s00393-011-0857-8.

[Schnitzler syndrome].

[Article in German]

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Schnitzler syndrome is a rare systemic inflammatory disease characterized by the presence of chronic urticarial skin rash and a monoclonal immunoglobulin M (IgM) gammopathy, combined with further, variable disease symptoms. The term refers to a young disease entity which has recently gained increasing acknowledgement and attention, also due to the availability of interleukin-1 (IL-1) blockade as an effective therapeutic option. Insights into the pathophysiology of the disease have resulted in the assumption of Schnitzler syndrome being a special form of an autoinflammatory disease with late onset or an acquired genesis. This article provides an overview on the clinical appearance, current knowledge of pathophysiology and available therapeutic options.

DOI: 10.1007/s00393-011-0857-8

PMID: 22527212 [Indexed for MEDLINE]

2745. Z Rheumatol. 2012 Apr;71(3):172-3. doi: 10.1007/s00393-011-0855-x.

[Autoinflammatory disease].

[Article in German]

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DOI: 10.1007/s00393-011-0855-x

PMID: 22527210 [Indexed for MEDLINE]

2746. J Clin Immunol. 2012 Oct;32(5):907-21. doi: 10.1007/s10875-012-9671-6. Epub 2012 Apr 13.

The spectrum of disease manifestations in patients with common variable immunodeficiency disorders and partial antibody deficiency in a university hospital.

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**BACKGROUND:** Common variable immunodeficiency disorders (CVIDs) represents a heterogeneous disease spectrum that includes recurrent infections and complications such as autoimmunity, inflammatory organ disease and an increased risk of cancer. A diagnostic delay is common in CVIDs patients.

**PURPOSE:** To determine the spectrum of clinical manifestations, immunological characteristics, and the time to diagnosis of 61 adult CVIDs and 18 patients with a partial antibody deficiency (SADNI and IgG subclass deficiency).

**METHODS:** A retrospective cohort study was performed in patients who met the ESID/PAGID for CVIDs, IgG subclass deficiency and SADNI. Medical records were reviewed to obtain patient demographics, clinical and laboratory data.

**RESULTS:** Infections were the main presentation of all antibody deficient patients and the number of patients with infections declined during IgG therapy. The development of bronchiectasis continued despite IgG therapy, as well as the development of autoinflammatory conditions. Non-infectious disease complications

were present in 30% of CVIDs patients at the time of diagnosis and this increased to 51% during follow up despite IgG therapy. The most common complications were autoimmunity or lymphoproliferative disease. The median time to diagnosis was 10 years and in the patients with non-infectious complications the time to diagnosis was considerably longer when compared to the group of patients without complications (17.6 vs. 10.2 years,  $p = 0.026$ ).

**CONCLUSION:** In contrast to the partial antibody deficiencies we found a considerable delay in the diagnosis of CVIDs, especially in those patients who were dominated by non-infectious complications, and thus increased awareness would be beneficial. Pulmonary and other complications may continue despite adequate IgG replacement therapy suggesting other causes responsible for these complications.

DOI: 10.1007/s10875-012-9671-6

PMCID: PMC3443482

PMID: 22526591 [Indexed for MEDLINE]

2747. Clin Rheumatol. 2012 Jul;31(7):1093-6. doi: 10.1007/s10067-012-1982-8. Epub 2012 Apr 18.

Normal QT dispersion in colchicine-resistant familial Mediterranean fever (FMF).

Nussinovitch U(1), Livneh A, Volovitz B, Nussinovitch M, Ben-Zvi I, Lidar M, Nussinovitch N.

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The association between familial Mediterranean fever (FMF) and subclinical cardiac disease remains controversial. The aim of the current study was to evaluate whether FMF patients, who do not respond to colchicine treatment, and thereby endure persistent inflammation, have increased QT dispersion (QTd) values. Twenty-two FMF patients and 22 age- and sex-matched control subjects were included in the study. Repolarization and QT dispersion parameters were computed from 12-lead ECG recording using designated computer software, and results of five beats were subsequently averaged. Both FMF patients and controls had similar comorbidities, similar values of average QT, average corrected QT interval length, average QTd interval, average QT corrected dispersion, QT dispersion

ratio, JT dispersion (JTd), and JT corrected dispersion. In conclusion, FMF patients who were unresponsive to colchicine treatment and did not develop amyloidosis had normal QTd and JTd parameters, indicating a non-increased risk for repolarization-associated ventricular arrhythmias.

DOI: 10.1007/s10067-012-1982-8

PMID: 22526475 [Indexed for MEDLINE]

2748. Curr Opin Pediatr. 2012 Jun;24(3):400-6. doi: 10.1097/MOP.0b013e32835333e3.

Current challenges in the diagnosis and management of fever.

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**PURPOSE OF REVIEW:** We review recommendations from recent publications on the management of fever with antipyretics, the classification and diagnosis of fevers of unknown origin (FUO), and the evaluation of fever in infants under 90 days of age.

**RECENT FINDINGS:** Anxiety about fever persists in the population, while the toxicity of antipyretics is an increasing concern. The numerous opportunities for overdosing with antipyretics have been emphasized by the American Academy of Pediatrics (AAP). The practice of alternating acetaminophen and ibuprofen has limited value. Nonclassic FUO and pseudo-FUO are as important to consider as true FUO, and clinicians should become familiar with the variety of periodic fever syndromes. The clinical utility of low-risk criteria to identify febrile infants at low risk for serious bacterial infection (SBI) was demonstrated in a systematic review of studies.

**SUMMARY:** Pediatricians should spend more time educating parents about fever and antipyretic use. Not all persistent fever is FUO, and testing should be targeted to the child's clinical condition. Existing low-risk criteria should be used to identify febrile infants who can be managed without extensive work-up and antibiotics. Adherence to evidence-based recommendations will lessen the morbidity and mortality associated with febrile illnesses in children.

DOI: 10.1097/MOP.0b013e32835333e3

PMID: 22525720 [Indexed for MEDLINE]

2749. Semin Arthritis Rheum. 2012 Dec;42(3):327-31. doi: 10.1016/j.semarthrit.2012.03.005. Epub 2012 Apr 17.

Muckle-Wells syndrome and male hypofertility: a case series.

Tran TA(1), Koné-Paut I, Marie I, Ninet J, Cuisset L, Meinzer U.

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**OBJECTIVES:** Muckle-Wells syndrome (MWS) is a rare autoinflammatory disorder associated with NLRP3 gene mutations, which cause excessive caspase-1 activation and processing of interleukin (IL)-1 $\beta$  and IL-18. Here we investigated whether MWS disease may be associated with impaired fertility in male patients.

**METHODS:** Medical records of all male MWS patients with NLRP3 mutations followed in our tertiary center for inherited autoinflammatory diseases were reviewed retrospectively for data indicating fertility problems.

**RESULTS:** Six of 9 patients were unable to have children despite regular sexual activity during at least 2 years; 3 succeeded in having children through in vitro fertilization. Infertility was the main reason for divorce in 1 patient.

Spermogram analyses were available in 8 of the 9 patients. Oligozoospermia was observed in 5 patients and azoospermia in 3 patients. In 2 patients, treatment with IL-1-targeting drugs for 6 and 12 months, respectively, had a moderate or no effect on spermatozoa counts. In 2 patients testosterone levels were low and testosterone treatment significantly increased spermatozoa counts in 1 of them.

**CONCLUSIONS:** MWS may be associated with subfertility and infertility in male patients. Consequently, sexual health and fertility should be assessed systematically in adolescent and adult male patients. Additional studies are required to establish the frequency of subfertility in male MWS patients, to understand when subfertility occurs in the disease natural history, and, finally, to investigate whether early management with IL-1-targeting drugs, or testosterone treatment or early sperm cryo-conservation may help to allow

procreation.

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DOI: 10.1016/j.semarthrit.2012.03.005

PMID: 22512814 [Indexed for MEDLINE]

2750. Nat Rev Rheumatol. 2012 Apr 17;8(6):309-10. doi: 10.1038/nrrheum.2012.54.

Diagnosis. Severity scoring system for paediatric FMF.

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Comment in

Nat Rev Rheumatol. 2012 Oct;8(10):621.

Severity scoring systems for adult familial Mediterranean fever (FMF) are established and used as important clinical and analytical tools in disease management and research. A recent paper highlights the need for a paediatric FMF severity measure. How should such a score be built and what challenges might be faced?

DOI: 10.1038/nrrheum.2012.54

PMID: 22508430 [Indexed for MEDLINE]

2751. Int J Gen Med. 2012;5:265-8. doi: 10.2147/IJGM.S30867. Epub 2012 Mar 22.

38-year-old woman with recurrent abdominal pain, but no fever.

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A 38-year-old woman presented with 2 days history of left-flank pain. She had similar episodes of abdominal pain as well as chest pain several times, but symptoms disappeared spontaneously. Each time she developed pain, there was no fever. After ruling out common causes of recurrent abdominal pain, familial Mediterranean fever (FMF) was considered as a potential diagnosis. Genetic tests revealed multiple heterozygote mutations, which may be associated with FMF. Patients with Mediterranean fever mutations may present with atypical presentations without fever, like in this case. Astute clinical suspicion is required to make an accurate diagnosis.

DOI: 10.2147/IJGM.S30867

PMCID: PMC3325009

PMID: 22505824

2752. Inflamm Bowel Dis. 2012 Dec;18(12):2381-91. doi: 10.1002/ibd.22962. Epub 2012 Apr 5.

Plasmablast frequency and trafficking receptor expression are altered in pediatric ulcerative colitis.

Tarltan NJ(1), Green CM, Lazarus NH, Rott L, Wong AP, Abramson ON, Bremer M, Butcher EC, Abramson T.

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**BACKGROUND:** The incidence of pediatric ulcerative colitis (UC), a chronic autoinflammatory disease of the colon, is on the rise. Although an increased infiltration of B cells from the peripheral blood into the colon occurs in UC, B-cell trafficking is understudied. We hypothesized that the frequency of circulating plasmablasts (PBs) and their trafficking receptor (TR) expression may be indicative of the location and degree of pathology in pediatric UC.

**METHODS:** We conducted multicolor flow cytometry analyses of circulating IgA(+/-) PBs and IgA(+) memory B cells (MBCs) in pediatric UC patients with remission, mild, moderate, and severe state of disease (n = 12), and healthy pediatric (n = 2) and adult donors (n = 11).

**RESULTS:** Compared to healthy donors the average frequency of PBs among total

peripheral blood lymphocytes is increased 30-fold during severe UC activity, and positively correlates with Pediatric Ulcerative Colitis Activity Index score, C-reactive protein level, and erythrocyte sedimentation rate. A greater percent of PBs in severe patients express the gut-homing receptors  $\alpha 4\beta 7$  and CCR10, and the inflammatory homing molecule P-selectin ligand (P-sel lig). The percent of IgA(+) MBCs expressing  $\alpha 4\beta 7$ , however, is reduced. Furthermore, expression of the small intestine TR CCR9 is decreased on  $\alpha 4\beta 7$ (high) PBs, and on  $\alpha 4\beta 7$ (high)/CCR10(high) PBs and MBCs in these patients, consistent with preferential cell targeting to the colon.

CONCLUSIONS: Peripheral blood PBs with a colon-homing phenotype ( $\alpha 4\beta 7$ /CCR10/P-sel lig) are elevated in children with severe UC. Screening this B-cell subset may provide a complementary approach in monitoring disease activity or therapeutic efficacy in pediatric UC.

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DOI: 10.1002/ibd.22962

PMCID: PMC3404263

PMID: 22488927 [Indexed for MEDLINE]

2753. Curr Opin Rheumatol. 2012 Jul;24(4):351-8. doi: 10.1097/BOR.0b013e3283534df4.

Pathogenesis of spondyloarthritis: autoimmune or autoinflammatory?

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PURPOSE OF REVIEW: Spondyloarthritis (SpA) is a chronic immune-mediated inflammatory disease of unknown origin. Here we aim to review whether SpA is driven by T-cell and/or B-cell autoreactivity or by abnormal innate immune responses.

RECENT FINDINGS: SpA does not share genetic risk factors, female predominance, presence of disease-specific autoantibodies and response to T-cell or B-cell-targeted therapies with prototypical autoimmune diseases like rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Growing evidence indicates



that increased responsiveness of innate immune cells such as macrophages, mast cells and neutrophils drives inflammation in SpA. The altered innate immune response may be related to nonantigen-presenting functions of HLA-B27, including the induction of an unfolded protein response, and can be triggered by bacterial and mechanical stress. Innate immune cells appear to be the main producers of both pro-inflammatory (tumor necrosis factor, IL-1, IL-23, IL-17) and anti-inflammatory (IL-10) cytokines in SpA.

SUMMARY: The predominance of myeloid above lymphoid alterations suggests an autoinflammatory rather than autoimmune origin of inflammation in SpA. Therefore, targeting innate cells or their inflammatory mediators may be more effective than T-cell or B-cell-directed therapies.

DOI: 10.1097/BOR.0b013e3283534df4

PMID: 22488076 [Indexed for MEDLINE]

2754. *Pediatr Diabetes*. 2012 Sep;13(6):510-3. doi: 10.1111/j.1399-5448.2012.00866.x. Epub 2012 Apr 5.

Concurrent protracted febrile myalgia syndrome in a child with diabetic ketoacidosis.

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Familial Mediterranean Fever (FMF), characterized by recurrent attacks of inflammation in predominantly serosal and synovial membranes, is caused by MEFV gene mutations resulting in abnormal pyrin. Protracted febrile myalgia syndrome (PFMS), a kind of vasculitis requiring corticosteroid treatment, is associated with M694V mutation of MEFV gene. Here, we report a case where the patient developed PFMS leading to the diagnosis of FMF concurrently at the time of treatment for diabetic ketoacidosis (DKA) of new-onset type 1 diabetes mellitus and discuss the possible mechanisms of simultaneous DKA and FMF-associated PFMS. DKA-associated cytokine release may be a predisposing factor or trigger for FMF-associated PFMS.

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DOI: 10.1111/j.1399-5448.2012.00866.x

PMID: 22487161 [Indexed for MEDLINE]

2755. *Oncologist*. 2012;17(4):525-35. doi: 10.1634/theoncologist.2011-0404. Epub 2012 Apr 3.

Hypophysitis induced by monoclonal antibodies to cytotoxic T lymphocyte antigen 4: challenges from a new cause of a rare disease.

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Specific human monoclonal antibodies antagonize cytotoxic T-lymphocyte antigen 4 (anti-CTLA-4 mAbs), a negative regulator of the immune system, inducing unrestrained T-cell activation. In patients with advanced or metastatic melanoma, one of these agents, ipilimumab, produced considerable disease control rates and, for the first time, a clear improvement in overall survival outcomes. However, accumulating clinical experience with anti-CTLA-4 mAbs identified a novel syndrome of autoimmune and autoinflammatory side effects, designated as "immune-related adverse events," including mainly rash, colitis, and hepatitis. Autoimmune hypophysitis has emerged as a distinctive side effect induced by anti-CTLA-4 mAbs. This condition may be life threatening because of adrenal insufficiency if not promptly recognized, but it may easily be diagnosed and treated if clinically suspected. Hypopituitarism caused by these agents is rarely reversible and prolonged or life-long substitutive hormonal treatment is often required. The precise mechanism of injury to the pituitary triggered by anti-CTLA-4 mAbs is yet to be fully elucidated.

DOI: 10.1634/theoncologist.2011-0404

PMCID: PMC3336822

PMID: 22477725 [Indexed for MEDLINE]

2756. *Pediatr Dermatol*. 2013 Nov-Dec;30(6):758-60. doi:

10.1111/j.1525-1470.2012.01725.x. Epub 2012 Apr 4.

Deficiency of interleukin-1 receptor antagonist responsive to anakinra.

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We describe a 3-month-old infant who presented to our institution with interleukin (IL)-1 receptor antagonist deficiency (DIRA), which consists of neutrophilic pustular dermatosis, periostitis, aseptic multifocal osteomyelitis, and persistently high acute-phase reactants. Skin findings promptly improved upon initiation of treatment with anakinra (recombinant human IL-1 receptor antagonist), and the bony lesions and systemic inflammation resolved with continued therapy.

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DOI: 10.1111/j.1525-1470.2012.01725.x

PMCID: PMC3548019

PMID: 22471702 [Indexed for MEDLINE]

2757. J Rheumatol. 2012 Apr;39(4):875-7. doi: 10.3899/jrheum.110700.

Clinical relevance of MEFV gene mutations in Japanese patients with unexplained fever.

Migita K, Ida H, Moriuchi H, Agematsu K.

DOI: 10.3899/jrheum.110700

PMID: 22467954 [Indexed for MEDLINE]

2758. Dig Liver Dis. 2012 Aug;44(8):636-42. doi: 10.1016/j.dld.2012.02.013. Epub 2012 Apr 1.

Prevalence and clinical relevance of enteropathy associated with systemic autoimmune diseases.

Vives MJ(1), Esteve M, Mariné M, Fernández-Bañares F, Alsina M, Salas A, Loras C, Carrasco A, Almagro P, Viver JM, Rodriguez-Carballeira M.

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**OBJECTIVE:** To assess whether systemic autoimmune diseases are a risk group for coeliac disease and if there is a systemic autoimmune diseases-associated enteropathy.

**METHODS:** 183 patients with systemic autoimmune diseases were included. Duodenal biopsy was carried out on patients with positive coeliac genetics (HLA-DQ2-DQ8) and/or serology and/or symptoms of the coeliac disease spectrum. When enteropathy was found, causes, including gluten sensitivity, were investigated and categorized according to a sequentially applied treatment. Results were analysed with Chi-square or Fisher exact tests.

**RESULTS:** The prevalence of coeliac disease with atrophy was 0.55% (1 of 183 patients). Thirty-eight of the 109 patients (34.8%) who underwent duodenal biopsy had lymphocytic enteropathy (8 infectious, 5 due to gluten sensitive enteropathy, 5 HLA-DQ2/DQ8 who did not accept gluten-free diet and 20 of unknown aetiology). Lymphocytic enteropathy was unrelated to disease activity or immunosuppressants. HLA-DQ2 was more frequent in connective tissue disease (41.5%) compared with systemic vasculitis and autoinflammatory diseases (17.9%) ( $p=0.02$ ), whereas a lower percentage of lymphocytic enteropathy was observed in the former (20.2% vs. 41.6%). Lymphocytic enteropathy was clinically irrelevant in cases with no definite aetiology.

**DISCUSSION:** One third of systemic autoimmune diseases patients had enteropathy of uncertain clinical meaning in the majority of cases, which was rarely due to gluten sensitive enteropathy.

DOI: 10.1016/j.dld.2012.02.013

PMID: 22465228 [Indexed for MEDLINE]

2759. Int J Rheum Dis. 2012 Apr;15(2):e37-9. doi: 10.1111/j.1756-185X.2011.01686.x. Epub 2011 Dec 18.

The medical odyssey of a boy with arthritis of familial Mediterranean fever.

Conca W, Ghatasheh G, Al-Salam S, Neidl Van Gorkom K.

DOI: 10.1111/j.1756-185X.2011.01686.x

PMID: 22462434 [Indexed for MEDLINE]

2760. Int J Hematol. 2012 Apr;95(4):380-5. doi: 10.1007/s12185-012-1061-6. Epub 2012 Mar 28.

High frequency of inherited variants in the MEFV gene in patients with hematologic neoplasms: a genetic susceptibility?

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Familial Mediterranean fever is an autosomal recessive disease occurring in populations originating from the Mediterranean basin. This autoinflammatory syndrome is caused by mutations in the Mediterranean FeVer (MEFV) gene. MEFV encodes a 781 amino acid protein known as pyrin. Pyrin is an important modulator of apoptosis, inflammation, and cytokine processing. In more recent pilot studies, inherited variant analysis of the MEFV gene in patients with hematologic neoplasm showed an unexpectedly high frequency of these variants in the gene. Here, we summarize the current state of knowledge of the relationship between inherited variants in the MEFV gene and hematologic neoplasms. Although no single

underlying defect could be targeted in all hematologic neoplasms, it will be important to fully exploit the mechanisms underlying the neoplasm promoting role of inherited variants in MEFV. However, it is unclear how inherited variants in the MEFV gene are associated with tumor susceptibility or promotion in hematologic neoplasms. Further investigations are needed to determine the actual role of the MEFV gene in pathogenesis of these neoplasms.

DOI: 10.1007/s12185-012-1061-6

PMID: 22453916 [Indexed for MEDLINE]

2761. Rheumatol Int. 2013 Feb;33(2):377-80. doi: 10.1007/s00296-012-2400-x. Epub 2012 Mar 27.

Prevalence and significance of the MEFV gene mutations in childhood Henoch-Schönlein purpura without FMF symptoms.

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Familial Mediterranean fever (FMF) has been reported more frequently in patients presenting with Henoch-Schönlein purpura (HSP) than in the general population. But, there is no clear knowledge about MEFV mutations in patients with HSP. We investigated the prevalence of MEFV mutations in children with HSP and without FMF whether these mutations have any effect on the disease course or complications. A total of 76 children with HSP who had no typical symptoms of FMF were screened for the mutations in exon 2 and exon 10 of the MEFV gene. Eleven of 76 patients (14.4 %) were heterozygous (E148Q in 5, M694V in 4, M680I in 1, E148V in 1), 5 (6.6 %) were homozygous (M694V/M694V in 4, V726A/V726A in 1), and 2 (2.6 %) were compound heterozygous (E148Q/M694V mutations in 1 and L110P/E148Q mutations in 1). Altogether, 7 patients carried 2 mutated MEFV alleles (9.2 %), which was higher than that observed in the general Turkish population (1 %). No significant differences in joint, gastrointestinal, renal involvement, or subcutaneous edema, and also acute phase reactants including leukocyte count, erythrocyte sedimentation rate, and serum C-reactive protein concentration were found between the groups. The prevalence of the two allele-MEFV mutations in

patients with HSP was found higher than that of the general population. However, it seems that MEFV gene mutations may not have any effect on the clinical presentation of HSP.

DOI: 10.1007/s00296-012-2400-x

PMID: 22451026 [Indexed for MEDLINE]

2762. Allergol Int. 2012 Jun;61(2):197-206. doi: 10.2332/allergolint.11-RAI-0416. Epub 2012 Mar 25.

Nakajo-Nishimura syndrome: an autoinflammatory disorder showing pernio-like rashes and progressive partial lipodystrophy.

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Nakajo-Nishimura syndrome (ORPHA2615; also registered as Nakajo syndrome in OMIM#256040) is a distinct inherited inflammatory and wasting disease, originally reported from Japan. This disease usually begins in early infancy with a pernio-like rash, especially in winter. The patients develop periodic high fever and nodular erythema-like eruptions, and gradually progress lipomuscular atrophy in the upper body, mainly the face and the upper extremities, to show the characteristic thin facial appearance and long clubbed fingers with joint contractures. So far about 30 cases have been reported from Kansai, especially Wakayama and Osaka, Tohoku and Kanto areas. At present, about 10 cases are confirmed to be alive only in the Kansai area, including one infant case in Wakayama. However, more cases are expected to be added in the near future. Although cause of the disease has long been undefined, a homozygous mutation of the PSMB8 gene, which encodes the  $\beta 5i$  subunit of immunoproteasome, has been identified to be responsible in 2011. By analyses of the patients-derived cells and tissues, it has been suggested that accumulation of ubiquitinated and oxidated proteins due to immunoproteasome dysfunction causes hyperactivation of p38 mitogen-activated protein kinase and interleukin-6 overproduction. Since similar diseases with PSMB8 mutations have recently been reported from Europe and the United States, it is becoming clear that Nakajo-Nishimura syndrome and

related disorders form proteasome disability syndromes, a new category of autoinflammatory diseases distributed globally.

DOI: 10.2332/allergolint.11-RAI-0416

PMID: 22441638 [Indexed for MEDLINE]

2763. Ned Tijdschr Geneeskd. 2012;156(12):A4196.

[Colchicine has no negative effect on fertility and pregnancy].

[Article in Dutch]

Both T(1), van Laar JA, Bonte-Mineur F, van Hagen PM, van Daele PL.

Author information:

(1)Erasmus MC, afd. Interne Geneeskunde, Rotterdam, the Netherlands.

**OBJECTIVE:** To inventorise the possible development of infertility and pregnancy complications in patients with Familial Mediterranean Fever (FMF), on treatment with colchicine.

**DESIGN:** Systematic review.

**METHOD:** PubMed was searched for articles in English, describing the effects of colchicine on fertility and pregnancy in animals or humans.

**RESULTS:** We found 73 articles, 13 of which matched the inclusion criteria. We selected another 12 articles via cross references and after evaluation by the co-authors. From these articles it appeared that colchicine inhibits the clinical symptoms of FMF and the development of amyloid deposits. No statistically significant effect was found of colchicine treatment on semen quality or hormone levels. Treatment with colchicine during pregnancy did not lead to severe complications. Both male and female patients who were treated with colchicine had a better prospect of maintaining fertility, compared with patients without this treatment.

**CONCLUSION:** According to the literature selected, colchicine use has no demonstrable negative effect on fertility. If untreated, FMF itself can lead to amyloid deposits in the testis and ovary, resulting in infertility. Patients with FMF may safely continue to use colchicine throughout the reproductive phase of their life.



PMID: 22436523 [Indexed for MEDLINE]

2764. Arch Dermatol. 2012 Mar;148(3):381-4. doi: 10.1001/archdermatol.2011.3014.

DIRA, DITRA, and new insights into pathways of skin inflammation: what's in a name?

Cowen EW, Goldbach-Mansky R.

Comment on

Arch Dermatol. 2012 Mar;148(3):301-4.

DOI: 10.1001/archdermatol.2011.3014

PMCID: PMC3464919

PMID: 22431779 [Indexed for MEDLINE]

2765. Arch Dermatol. 2012 Mar;148(3):301-4. doi: 10.1001/archdermatol.2011.2857.

Chronic cutaneous pustulosis due to a 175-kb deletion on chromosome 2q13: excellent response to anakinra.

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Comment in

Arch Dermatol. 2012 Mar;148(3):381-4.

DOI: 10.1001/archdermatol.2011.2857

PMCID: PMC3313085

PMID: 22431772 [Indexed for MEDLINE]

2766. Arch Dermatol. 2012 Jun;148(6):747-52. doi: 10.1001/archdermatol.2011.3208.

Interleukin 1 receptor antagonist deficiency presenting as infantile pustulosis mimicking infantile pustular psoriasis.

Minkis K(1), Aksentijevich I, Goldbach-Mansky R, Magro C, Scott R, Davis JG, Sardana N, Herzog R.

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**BACKGROUND:** Deficiency of interleukin 1 receptor antagonist (DIRA) is a recently described autoinflammatory syndrome of skin and bone caused by recessive mutations in the gene encoding the interleukin 1 receptor antagonist. Few studies have been published about this debilitating condition. Early identification is critical for targeted lifesaving intervention.

**OBSERVATIONS:** A male infant, born to nonconsanguineous Puerto Rican parents, was referred for management of a pustular eruption diagnosed as pustular psoriasis. At 2 months of age, the infant developed a pustular eruption. After extensive evaluation, he was confirmed to be homozygous for a 175-kb genomic deletion on chromosome 2 that includes the IL1RN gene, commonly found in Puerto Ricans. Therapy with anakinra was initiated, with rapid clearance of skin lesions and resolution of systemic inflammation.

**CONCLUSIONS:** Recent identification of DIRA as a disease entity, compounded by the limited number of reported cases, makes early identification difficult. It is critical to consider this entity in the differential diagnosis of infantile pustulosis. Targeted therapy with the recombinant human interleukin 1 receptor antagonist anakinra can be lifesaving if initiated early. A high carrier frequency of the 175-kb DIRA-associated genomic deletion in the Puerto Rican population strongly supports testing infants presenting with unexplained pustulosis in patients from this geographic region.

DOI: 10.1001/archdermatol.2011.3208

PMCID: PMC3474848

PMID: 22431714 [Indexed for MEDLINE]

2767. Nat Immunol. 2012 Mar 19;13(4):325-32. doi: 10.1038/ni.2231.

Sensing and reacting to microbes through the inflammasomes.

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Inflammasomes are multiprotein complexes that activate caspase-1, which leads to maturation of the proinflammatory cytokines interleukin 1 $\beta$  (IL-1 $\beta$ ) and IL-18 and the induction of pyroptosis. Members of the Nod-like receptor (NLR) family, including NLRP1, NLRP3 and NLRC4, and the cytosolic receptor AIM2 are critical components of inflammasomes and link microbial and endogenous danger signals to the activation of caspase-1. In response to microbial infection, activation of the inflammasomes contributes to host protection by inducing immune responses that limit microbial invasion, but deregulated activation of inflammasomes is associated with autoinflammatory syndromes and other pathologies. Thus, understanding inflammasome pathways may provide insight into the mechanisms of host defense against microbes and the development of inflammatory disorders.

DOI: 10.1038/ni.2231

PMCID: PMC3449002

PMID: 22430785 [Indexed for MEDLINE]

2768. Best Pract Res Clin Rheumatol. 2012 Feb;26(1):119-33. doi: 10.1016/j.berh.2012.01.004.

Neurologic and other systemic manifestations in FMF: published and own experience.

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**OBJECTIVE:** Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disease, presenting with recurrent episodes of fever and polyserositis. Neurologic involvement in FMF is rare and usually considered

fortuitous. The aim of this article is to review the spectrum of possible neurologic manifestations, which can be encountered in FMF patients, and to establish their relation to FMF.

**METHODS:** We reviewed the literature based on Pubmed search to find neurologic manifestations, which were reported in FMF patients. To that we added our own experience on the subject, abstracted from our computerised FMF registry of 12000 FMF patients of the National FMF Center and the computerised database of Sheba Medical Center.

**RESULTS:** A wide range of neurologic manifestations involving FMF patients was noted. A large part of these manifestations could be directly related to FMF, its complications, associated diseases and treatment adverse effects. The remaining were incidental, or of uncertain association to FMF.

**CONCLUSION:** A physician, taking care of an FMF patient, can face various neurologic manifestations and should be aware of their origin. The current chapter provides an insight to this association of FMF.

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DOI: 10.1016/j.berh.2012.01.004

PMID: 22424198 [Indexed for MEDLINE]

2769. Rheumatol Int. 2013 Jun;33(6):1653. doi: 10.1007/s00296-012-2362-z. Epub 2012 Mar 16.

About the manuscript Arıca et al.

Makay B.

Comment on

Rheumatol Int. 2012 Nov;32(11):3559-63.

DOI: 10.1007/s00296-012-2362-z

PMID: 22422216 [Indexed for MEDLINE]

2770. J Cutan Med Surg. 2012 Jan-Feb;16(1):50-3.

Mycophenolate mofetil and erythromycin for bullous lupus erythematosus of

childhood.

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Author information:

(1)McGill University-SMBD Jewish General Hospital, Montreal, QC, Canada.

**BACKGROUND:** Bullous lupus erythematosus is a rare disease that is extremely rare in childhood (with only seven previous reports) and difficult to control.

**OBJECTIVE:** Herein is presented the youngest patient reported with this condition, and a novel, safe, and effective treatment regimen is described.

**METHODS:** Through study, perseverance, serendipity, and creativity, a safe and effective regimen was developed.

**RESULTS:** The combination of mycophenolate mofetil and erythromycin (plus sun protection) was found to be efficacious.

**CONCLUSION:** It is proposed that the two medications act synergistically, with the "antibiotic" acting as a antiinflammatory agent, but at a different point in the inflammatory cascade than mycophenolate mofetil. This suggests the approach of using common, inexpensive, and benign antibiotics to potentiate, and perhaps decrease the use of, immunomodulatory agents in autoimmune and autoinflammatory diseases.

DOI: 10.1177/120347541201600110

PMID: 22417996 [Indexed for MEDLINE]

2771. Clin Exp Rheumatol. 2011 Nov-Dec;29(6 Suppl 69):S127-32. Epub 2012 Jan 3.

Frequency of juvenile fibromyalgia syndrome in children with familial Mediterranean fever: effects on depression and quality of life.

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**OBJECTIVES:** To determine the prevalence of juvenile fibromyalgia syndrome (JFMS) in children with familial Mediterranean fever (FMF) and to evaluate quality of

life (QoL) and depression.

**METHODS:** Ninety-one FMF patients (M/F: 44/47) who fulfilled the Livneh criteria and 60 healthy children (M/F: 27/33) were enrolled in the study. Yunus and Masi's criteria were used for diagnosis of JFMS. Depression was assessed with Children's Depression Inventory (CDI) and QoL was evaluated with child and parent reports of Paediatric Quality of Life Inventory 4.0 (PedsQL™).

**RESULTS:** While 20 (21.9%) of 91 FMF patients fulfilled JFMS criteria, 2 (3.3%) of the control group met the diagnostic criteria of JFMS ( $p=0.002$ ). PedsQL™ scores (child self-report and parent-report) of the FMF patients were significantly lower and the depression scores were significantly higher than the healthy controls ( $p<0.001$  for all). When the FMF patients were assigned to two groups as FMF with or without JFMS, patients with JFMS were found to have a higher depression score ( $p=0.007$ ) and child and parent reports of PedsQL™ 4.0 were lower in the children with JFMS than in the patients without JFMS ( $p=0.001$ ,  $p=0.003$ , respectively).

**CONCLUSIONS:** We have determined that JFMS frequency was higher in children with FMF and patients with FMF and JFMS had a poor QoL and were more susceptible to depression. FMF patients with widespread and persistent pain should be evaluated for JFMS in order to avoid unnecessary investigations and inappropriate treatment.

PMID: 22243560 [Indexed for MEDLINE]

2772. Med Hypotheses. 2012 Jun;78(6):717-20. doi: 10.1016/j.mehy.2012.02.017. Epub 2012 Mar 10.

The possible underlying pathophysiological mechanisms for development of multiple sclerosis in familial Mediterranean fever.

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Patients with familial Mediterranean fever (FMF) have a susceptibility to the development of multiple sclerosis (MS). Here, we will propose the possible

underlying pathophysiological mechanisms of this predisposition. Inflammation, disruption of blood-brain barrier (BBB), mitochondrial energy deficit, demyelination, and axonal damage, which play an important role in the pathogenesis of MS, may occur during the course of FMF. Most FMF patients have homozygous mutations in the MEFV gene that codes for the protein pyrin. Also, pyrin mutations were found about 3.5 times higher in the MS patients than the healthy control group. Pyrin is implicated in the maturation and secretion of the proinflammatory cytokine IL-1 $\beta$ . IL-1 $\beta$  is a major mediator of fever and systemic inflammation, and mononuclear cells from FMF patients release higher levels of IL-1 $\beta$ . Moreover, IL-1 plays a significant role in the regulation of the T-cells, and it is considered an essential cytokine for the Th cell differentiation that implicated in the MS pathogenesis. In addition, endothelial dysfunction and vasculitis in FMF may cause BBB breakdown that is the first step in the development of MS lesions. Apart from this, damage can occur in myelin and mitochondria proteins due to high body temperature that arises during the FMF attacks. Whereas the protein damage in myelin results in demyelination, and the protein damage in mitochondria causes lack of energy. Both situations play a part in the pathogenesis of MS. Due to mitochondrial energy deficit, remyelination may not be achieved, and therefore, axonal damage increases. Thus, at the end of these pathophysiological processes, MS findings may occur in the FMF patients especially with irregular use of colchicine.

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DOI: 10.1016/j.mehy.2012.02.017

PMID: 22406096 [Indexed for MEDLINE]

2773. Am J Transplant. 2012 Jun;12(6):1627-31. doi: 10.1111/j.1600-6143.2011.03989.x. Epub 2012 Mar 8.

Liver transplantation followed by allogeneic hematopoietic stem cell transplantation for atypical mevalonic aciduria.

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Mevalonic aciduria because of mutations of the gene for mevalonate kinase causes limited synthesis of isoprenoids, the effects of which are widespread. The outcome for affected children is poor. A child with severe multisystem manifestations underwent orthotopic liver transplantation at age 50 months for the indication of end-stage liver disease. This procedure corrected liver function and eliminated portal hypertension, and the patient showed substantial improvement in neurological function. However, autoinflammatory episodes continued unabated until hematopoietic stem cell transplantation was performed at 80 months. Through this complex therapy, the patient now enjoys a high quality of life without significant disability.

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DOI: 10.1111/j.1600-6143.2011.03989.x

PMID: 22405037 [Indexed for MEDLINE]

2774. Rheumatology (Oxford). 2012 Jun;51(6):1041. doi: 10.1093/rheumatology/kes021. Epub 2012 Mar 7.

Canakinumab induces remission in a patient with resistant familial Mediterranean fever.

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DOI: 10.1093/rheumatology/kes021

PMID: 22403182 [Indexed for MEDLINE]

2775. J Autoimmun. 2012 May;38(2-3):J223-38. doi: 10.1016/j.jaut.2011.11.018. Epub 2012 Mar 7.



## Neonatal autoimmune diseases: a critical review.

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Neonatal autoimmune diseases are distinctly rare. Most neonatal autoimmune diseases result from the transplacental transfer of maternal antibodies directed against fetal or neonatal antigens in various tissues. In neonatal lupus, the heart seems to be particularly susceptible. Primary autoimmunity in newborns, with the exception of familial autoinflammatory diseases, is virtually non-existent. The pathophysiologic basis for the development of neonatal autoimmunity is not entirely clear, but differences in the neonatal immune system compared with the adult immune system, as well as unique characteristics of target antigens in the newborn period may be important factors. Neonatal lupus is the most common presentation of autoimmunity in the newborn. But the characteristics defining neonatal lupus are not well defined and the presentation of neonatal lupus differs from that of classical lupus. Other neonatal autoimmune diseases involving the interaction between maternal antibodies and fetal/neonatal antigens include neonatal anti-phospholipid syndrome, Behcet's disease, neonatal autoimmune thyroid disease, neonatal polymyositis and dermatomyositis, neonatal scleroderma and neonatal type I diabetes mellitus. While autoantibodies have been detected in patients with neonatal autoimmune disease, the pathogenic role of autoantibodies has not been well defined. Other mechanisms may play a role in the development of neonatal autoimmunity, including fetal/maternal microchimerism and aberrant apoptosis of fetal cells. The autoinflammatory syndromes are a completely different category, but are also included in discussion of neonatal autoimmune diseases. The autoinflammatory syndromes include the cryopyrin associated periodic syndromes (CAPS) - familial cold autoinflammatory syndrome (FCAS), neonatal onset multisystem inflammatory disease (NOMID) and Muckle-Wells syndrome, which all share a common pathophysiologic mechanism.

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DOI: 10.1016/j.jaut.2011.11.018

PMID: 22402339 [Indexed for MEDLINE]

2776. Autoimmune Dis. 2012;2012:736384. doi: 10.1155/2012/736384. Epub 2012 Feb 15.

Spondyloarthropathies in autoimmune diseases and vice versa.

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Polyautoimmunity is one of the major clinical characteristics of autoimmune diseases (ADs). The aim of this study was to investigate the prevalence of ADs in spondyloarthropathies (SpAs) and vice versa. This was a two-phase cross-sectional study. First, we examined the presence of ADs in a cohort of patients with SpAs (N = 148). Second, we searched for the presence of SpAs in a well-defined group of patients with ADs (N = 1077) including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and Sjögren's syndrome (SS). Among patients with SpAs, ankylosing spondylitis was observed in the majority of them (55.6%). There were two patients presenting with SS in the SpA group (1.4%) and 5 patients with autoimmune thyroiditis (3.5%). The global prevalence of ADs in SpAs was 4.86%. In the ADs group, there were 5 patients with SpAs (0.46%). Our results suggest a lack of association between SpAs and ADs. Accordingly, SpAs might correspond more to autoinflammatory diseases rather than to ADs.

DOI: 10.1155/2012/736384

PMCID: PMC3286883

PMID: 22400103

2777. Adv Exp Med Biol. 2012;738:60-78. doi: 10.1007/978-1-4614-1680-7\_5.

Intracellular inflammatory sensors for foreign invaders and substances of self-origin.

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In order to survive, all organisms must recognize and eliminate foreign invaders such as infectious pathogens, chemicals, ultraviolet rays, metabolites and damaged or transformed self-tissues, as well as allogenic organs in cases of transplantation. Recent research in innate immunity has elucidated that there are versatile inflammatory sensors on spatiotemporal 'sentry duty' that recognize substances derived from both 'nonself' and 'self', e.g., Toll-like receptors, retinoic acid-inducible gene-I-like receptors, nucleotide oligomerization domain-like receptors and c-type lectin receptors. Having acquired high-level functions through the development of multiple molecules, higher organisms have established both extracellular and intracellular sensors that can discriminate danger-associated molecular patterns from promiscuous, but biologically similar, molecular patterns. In addition, 'loss-of-function' or 'gain-of-function' mutations in these inflammatory sensors have been linked (at least in part) with the etiology and severity of autoimmune diseases, autoinflammatory diseases and immunocompromised diseases in humans. Further studies focusing on the role of these inflammatory sensors in the development of immune disorders would highlight new avenues for the development of novel diagnostic and therapeutic applications with regard to these diseases.

DOI: 10.1007/978-1-4614-1680-7\_5

PMID: 22399374 [Indexed for MEDLINE]

2778. Clin Pharmacol Ther. 2012 Apr;91(4):739-42. doi: 10.1038/clpt.2012.5. Epub 2012 Mar 7.

Regulatory aspects of new medicines targeted at treatment of autoimmune diseases.

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Autoimmune diseases comprise a diverse group of clinical disorders that result from the body's adaptive immune system reacting against its own tissues.(1) Conversely, autoinflammatory disorders encompass a more limited group of diseases distinguished by recurrent episodes of inflammation but in the absence of high-titer autoantibodies and antigen-specific T cells.(2) The past 15 years have seen a tremendous growth in the development of highly effective treatments for these diseases.

DOI: 10.1038/clpt.2012.5

PMID: 22398965 [Indexed for MEDLINE]

2779. Biochem Med (Zagreb). 2012;22(1):109-13.

Relationship between serum interleukin-1beta levels and acute phase response proteins in patients with familial Mediterranean fever.

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**INTRODUCTION:** The aim of this study was to investigate whether serum levels of interleukin-1beta (IL-1beta) has any possible correlation on inflammatory parameters such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and fibrinogen concentration in patients with familial Mediterranean fever (FMF) patients during attack-free period.

**MATERIALS AND METHODS:** The serum levels of IL-1beta, as an indicator of cytokines status, and the acute phase response proteins, CRP, ESR and fibrinogen levels were evaluated in 35 attack-free patients with FMF and 25 healthy volunteers.

**RESULTS:** Serum IL-1beta levels were significantly higher in patients with FMF than control subjects ( $P = 0.018$ ). There was no statistically significant difference in the serum levels of ESR, CRP and fibrinogen between two groups ( $P = 0.181$ ,  $P = 0.816$ ,  $P = 0.686$ , respectively). There was a significant correlation between IL-1beta and CRP ( $r = 0.513$ ,  $P = 0.002$ ) values of FMF group.

**CONCLUSIONS:** In conclusion, our results confirm the presence of increased IL-1beta levels in FMF patients during attack-free period. Serum IL-1beta values seems to correlate with CRP levels. The elevation of IL-1beta levels may be

important in monitoring subclinical inflammation of attack free period in FMF patients.

PMCID: PMC4062326

PMID: 22384525 [Indexed for MEDLINE]

2780. Acta Derm Venereol. 2012 Jul;92(4):395-8. doi: 10.2340/00015555-1322.

Cryopyrin-associated periodic syndrome: a case report and review of the Japanese literature.

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Cryopyrin-associated periodic syndrome is an autoinflammatory syndrome caused by mutations of the CIAS1 gene (currently named NLRP3), and is characterized by periodic attacks of an urticaria-like rash, fever, head-ache, conjunctivitis and arthralgia. We report here a case of a 1-year-old boy with cryopyrin-associated periodic syndrome, which manifested as a recurrent skin rash in the postnatal period. Genetic analysis revealed a missense mutation of the CIAS1 gene in the mother and infant.

DOI: 10.2340/00015555-1322

PMID: 22377911 [Indexed for MEDLINE]

2781. Ann Rheum Dis. 2012 Jul;71(7):1177-82. doi: 10.1136/annrheumdis-2011-200549. Epub 2012 Feb 29.

An international registry on autoinflammatory diseases: the Eurofever experience.

Toplak N(1), Frenkel J, Ozen S, Lachmann HJ, Woo P, Koné-Paut I, De Benedetti F, Neven B, Hofer M, Dolezalova P, Kümmerle-Deschner J, Touitou I, Hentgen V, Simon A, Girschick H, Rose C, Wouters C, Vesely R, Arostegui J, Stojanov S, Ozgodan H,

Martini A, Ruperto N, Gattorno M; Paediatric Rheumatology International Trials Organisation (PRINTO), Eurotraps and Eurofever Projects.

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**OBJECTIVE:** To report on the demographic data from the first 18 months of enrollment to an international registry on autoinflammatory diseases in the context of the Eurofever project.

**METHODS:** A web-based registry collecting baseline and clinical information on autoinflammatory diseases and related conditions is available in the member area of the PRINTO web-site. Anonymised data were collected with standardised forms.

**RESULTS:** 1880 (M:F=916:964) individuals from 67 centers in 31 countries have been entered in the Eurofever registry. Most of the patients (1388; 74%), reside in western Europe, 294 (16%) in the eastern and southern Mediterranean region (Turkey, Israel, North Africa), 106 (6%) in eastern Europe, 54 in Asia, 27 in South America and 11 in Australia. In total 1049 patients with a clinical diagnosis of a monogenic autoinflammatory diseases have been enrolled; genetic analysis was performed in 993 patients (95%): 703 patients have genetically confirmed disease and 197 patients are heterozygous carriers of mutations in genes that are mutated in patients with recessively inherited autoinflammatory diseases. The median diagnosis delay was 7.3 years (range 0.3-76), with a clear reduction in patients born after the identification of the first gene associated with autoinflammatory diseases in 1997.

**CONCLUSIONS:** A shared online registry for patients with autoinflammatory diseases is available and enrollment is ongoing. Currently, there are data available for analysis on clinical presentation, disease course, and response to treatment, and to perform large scale comparative studies between different conditions.

DOI: 10.1136/annrheumdis-2011-200549

PMID: 22377804 [Indexed for MEDLINE]

2782. Nihon Rinsho Meneki Gakkai Kaishi. 2012;35(1):23-9.

[An approach to the patients with cryopyrin-associated periodic syndrome (CAPS) : a new biologic response modifier, canakinumab].

[Article in Japanese]

Yokota S(1), Kikuchi M, Nozawa T, Kizawa T, Kanetaka T, Miyamae T, Mori MA, Nishikomori R, Takata H, Heike T, Hara T, Imagawa T.

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Cryopyrin-associated periodic syndrome (CAPS) comprises a group of rare, but severe, autoinflammatory syndrome, and includes 3 distinct conditions, familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (MONID). These syndromes are characterized by urticarial-like rash, periodic fever, central nervous system inflammation, an arthropathy, and the risk of amyloidosis. About 20% die by age 20 years in the most severe cases. The disease is associated with mutations in the NLRP3 gene that encodes for the protein cryopyrin, a component of the inflammasome complex that regulates the production and secretion of IL-1 $\beta$ . Canakinumab is a human IgG monoclonal antibody targeting IL-1 $\beta$ . The clinical trials of canakinumab for patients with CAPS in both western countries and Japan were well-tolerated in most patients, and provided significant advantages over existing competitive therapies. Although no serious adverse effects have been reported, the frequencies of common infectious diseases including nasopharyngitis, upper respiratory tract infections, and gastroenteritis were reported presumably due to the blockade of proinflammatory cytokine, IL-1 $\beta$ . For us pediatrician, it will be important to be more careful for infectious diseases to provide the maximum safety of canakinumab for these patients.

PMID: 22374439 [Indexed for MEDLINE]

2783. Curr Pharm Des. 2012;18(11):1478-93.

Inflammation-induced thrombosis: mechanisms, disease associations and management.

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Although inflammation-induced thrombosis is a well-known entity, its pathogenesis remains complicated. There are complex interactions between inflammation and hemostasis, involving proinflammatory cytokines, chemokines, adhesion molecules, tissue factor expression, platelet and endothelial activation, and microparticles. Inflammation increases procoagulant factors, and also inhibits natural anticoagulant pathways and fibrinolytic activity, causing a thrombotic tendency. Besides, chronic inflammation may cause endothelial damage, resulting in the loss of physiologic anticoagulant, antiaggregant and vasodilatory properties of endothelium. However, inflammation-induced venous thrombosis may develop even in the absence of vessel wall damage. On the other hand, coagulation also augments inflammation, causing a vicious cycle. This is mainly achieved by means of thrombin-induced secretion of proinflammatory cytokines and growth factors. Platelets may also trigger inflammation by activating the dendritic cells. There are many systemic inflammatory diseases characterized by thrombotic tendency, including Behçet disease (BD), antineutrophilic cytoplasmic antibody-associated vasculitides, Takayasu arteritis, rheumatoid arthritis, systemic lupus erythematosus, antiphospholipid syndrome, familial Mediterranean fever, thromboangiitis obliterans (TAO) and inflammatory bowel diseases. Inflammation-induced thrombosis may respond to immunosuppressive (IS) treatment, as in the case of BD. However effectiveness of this treatment can not be generalized to all other inflammatory diseases. For instance, IS agents do not have any beneficial role in the management of TAO. Heparin, antiplatelet agents such as aspirin and clopidogrel, colchicine and statins also have some antiinflammatory activity. However, decreased responsiveness to aspirin and clopidogrel treatments may be observed in inflammatory diseases, due to antiplatelet resistance caused by systemic inflammation. In the present review, we aimed to discuss the details of the complex crosstalk between inflammation and hemostasis in the context of available data. We also intended to overview the major inflammatory diseases with thrombotic tendency, as well as to discuss the general principles of the management of inflammation-induced thrombosis.

PMID: 22364132 [Indexed for MEDLINE]

2784. Rev Med Interne. 2012 Apr;33(4):235-7. doi: 10.1016/j.revmed.2012.01.012. Epub 2012 Feb 22.



[Update in interleukin-1 inhibition].

[Article in French]

de Boysson H(1).

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DOI: 10.1016/j.revmed.2012.01.012

PMID: 22360831 [Indexed for MEDLINE]

2785. Harefuah. 2011 Dec;150(12):926.

[Scientific forum on systemic autoinflammatory diseases].

[Article in Hebrew]

Kessel A.

PMID: 22352288 [Indexed for MEDLINE]

2786. Int J Hematol. 2012 Mar;95(3):285-90. doi: 10.1007/s12185-012-1022-0. Epub 2012 Feb 18.

Frequency of inherited variants in the MEFV gene in myelodysplastic syndrome and acute myeloid leukemia.

Celik S(1), Oktenli C, Kilicaslan E, Tangi F, Sayan O, Ozari HO, Ipcioglu O, Sanisoglu YS, Terekeci MH, Erikci AA.

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We investigated the frequency of inherited variants in the MEFV gene, which is mutated in familial Mediterranean fever (FMF), in patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). Eight MEFV gene variants (M694I, M694V, M680I (G/C-A), V726A, R761H, E148Q and P369S) were analyzed in 33 MDS patients, 47 AML patients and 65 healthy controls; none had a history or family history compatible with FMF. We identified two homozygous (E148Q/E148Q), one compound heterozygous (M694V/E148Q) and five heterozygous inherited variants in the MEFV gene in AML patients. We also identified nine heterozygous variants in MDS patients, while we found 11 heterozygous variants in controls. The mean overall frequency of inherited variants in the MEFV gene rate was higher in MDS ( $\chi^2 = 4.241$ ;  $P = 0.039$ ) and AML ( $\chi^2 = 3.870$ ;  $P = 0.043$ ) patients than in healthy controls. In conclusion, this study reports high frequency of inherited variants in the MEFV gene in patients with MDS and AML. However, the hypothesis that MEFV is a cancer susceptibility gene at this point remains speculative. Additional evidence from future studies is needed to allow a more thorough evaluation of this hypothesis.

DOI: 10.1007/s12185-012-1022-0

PMID: 22351163 [Indexed for MEDLINE]

2787. Nihon Rinsho Meneki Gakkai Kaishi. 2011;34(5):327-8.

[Recent new findings in autoinflammatory syndrome].

[Article in Japanese]

Nishikomori R.

PMID: 22348214 [Indexed for MEDLINE]

2788. J Pediatr Gastroenterol Nutr. 2013 Apr;56(4):e22-3. doi: 10.1097/MPG.0b013e31824f2017.

Tumor necrosis factor receptor-associated periodic syndrome as a cause of recurrent abdominal pain in identical twins and description of a novel mutation of the TNFRSF1A gene.

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DOI: 10.1097/MPG.0b013e31824f2017

PMID: 22343913 [Indexed for MEDLINE]

2789. Mult Scler. 2012 Sep;18(9):1229-38. doi: 10.1177/1352458512437813. Epub 2012 Feb 15.

Familial Mediterranean fever-associated mutation pyrin E148Q as a potential risk factor for multiple sclerosis.

Kümpfel T(1), Gerdes LA, Wacker T, Blaschek A, Havla J, Krumbholz M, Pöhlmann W, Feneberg W, Hohlfeld R, Lohse P.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is an inherited autoinflammatory disease caused by mutations in the MEFV gene and characterized by recurrent febrile polyserositis. A possible association of FMF and multiple sclerosis (MS) has been suggested in cohorts from Turkey and Israel.

**OBJECTIVE:** The objective of this study was to investigate the prevalence of MEFV mutations in subjects with MS and in controls in Germany.

**METHODS:** One-hundred and fifty seven MS patients with at least one symptom or without symptoms suggestive of FMF from our outpatient clinic were investigated for mutations in exons 2, 3, and 10 of the MEFV gene (group 1). 260 independent MS patients (group 2) and 400 unrelated Caucasian controls (group 3) were screened selectively for the low-penetrance pyrin mutations E148Q and K695R

**RESULTS:** In group 1, 19 MS patients (12.1%) tested positive for a mutation in the MEFV gene, mainly the E148Q (n=7) substitution. Fifteen of the 19 mutation-positive individuals reported at least one symptom suggestive of FMF. In three cases, we could identify additional family members with MS. In these

pedigrees, the E148Q exchange co-segregated with MS ( $p=0.026$ ). Frequencies of the pyrin E148Q and K695R mutations were not statistically different between MS group 2 and controls but they occurred with a surprisingly high frequency in the German population.

CONCLUSION: The MEFV gene appears to be another immunologically relevant gene locus which contributes to MS susceptibility. In particular, the pyrin E148Q mutation, which co-segregated with disease in three MS families, is a promising candidate risk factor for MS that should be further explored in larger studies.

DOI: 10.1177/1352458512437813

PMID: 22337722 [Indexed for MEDLINE]

2790. J Dermatol Sci. 2012 Jun;66(3):183-9. doi: 10.1016/j.jdermsci.2012.01.004. Epub 2012 Jan 18.

Rare hereditary autoinflammatory disorders: towards an understanding of critical in vivo inflammatory pathways.

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Hereditary autoinflammatory syndromes are monogenic disorders with an inborn error of innate immunity, and include periodic fever syndromes such as familial Mediterranean fever (FMF), tumor necrosis factor receptor-associated periodic syndrome and cryopyrin-associated periodic syndromes (CAPS), pyogenic diseases such as pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPAS), and granulomatous diseases such as Blau syndrome. By identifying the genetic abnormalities and subsequent analyses of the molecular mechanisms underlying these disorders, several critical in vivo pathways for inflammatory processes have been discovered. In this review, three categories of autoinflammatory disorders are discussed: inflammasomopathies, receptor antagonist deficiencies and proteasome disability syndromes. Inflammasomopathies are diseases with dysregulated NLRP3 inflammasome activation, and include CAPS with NLRP3, FMF with MEFV, and PAPAS with PSTPIP1 mutations. Analyses of these diseases have clarified some critical pathways regulating NLRP3 inflammasome signaling. Receptor

antagonist deficiencies include the newly defined deficiency for interleukin-1 receptor antagonist resulting in sterile multifocal osteomyelitis with periostosis and pustulosis, and deficiency for interleukin-36 receptor antagonist resulting in generalized pustular psoriasis. The identification of these genetic abnormalities has revealed a critical role for receptor antagonists of IL-1 family cytokines in regulating neutrophil activation/recruitment. Finally, proteasome disability syndromes with PSMB8 mutations include Nakajo-Nishimura syndrome and related disorders distributed globally. Analyses of these diseases have unexpectedly shown a critical role of the ubiquitin-proteasome system in the regulation or homeostasis of inflammation/metabolism. Since there still remain a number of predicted but undefined hereditary autoinflammatory syndromes, further clinical and genetic approaches are required to discover novel in vivo critical inflammatory pathways.

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DOI: 10.1016/j.jdermsci.2012.01.004

PMID: 22336993 [Indexed for MEDLINE]

2791. Paediatr Drugs. 2012 Apr 1;14(2):109-17. doi: 10.2165/11595040-000000000-00000.

Cryopyrin-associated periodic syndromes: diagnosis and management.

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Cryopyrin-associated periodic syndromes (CAPS) are a group of rare autoinflammatory disorders; many cases of CAPS are caused by mutations in the NLRP3 gene. In these conditions, interleukin (IL)-1 is overproduced, and this overproduction plays a major role in disease onset and progression. CAPS include three variants, ranging in order of increasing severity from familial cold autoinflammatory syndrome, previously termed familial cold urticaria, through Muckle-Wells syndrome, to chronic infantile neurologic cutaneous articular syndrome, also known as neonatal onset multisystemic inflammatory disease.

Diagnosis of CAPS is initially based on clinical manifestations and medical history, and later confirmed genetically. CAPS should be suspected when characteristic skin lesions, typical periodic fever episodes, bone/joint manifestations, and CNS involvement are recognized. CAPS are life-long diseases, and early diagnosis and early treatment with IL-1-targeted therapies may improve prognosis.

DOI: 10.2165/11595040-000000000-00000

PMID: 22335455 [Indexed for MEDLINE]

2792. Dig Liver Dis. 2012 Aug;44(8):689-93. doi: 10.1016/j.dld.2012.01.003. Epub 2012 Feb 12.

Liver involvement in children with Familial Mediterranean fever.

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AIM: Familial Mediterranean fever is characterised by recurrent, febrile, inflammatory attacks of the serosal membranes. Prolonged inflammatory response is triggered secondary to cytokine stimulation due to reduced activity of pyrin. Inflammatory cytokines play major role in the pathogenesis of acute liver injury; and chronic, recurrent cytokine production may cause chronic hepatitis/cirrhosis. We aimed to analyse liver involvement in children with Familial Mediterranean fever.

PATIENTS: The study included 58 patients with Familial Mediterranean fever. Patients with liver involvement were examined in detail.

RESULTS: Liver involvement was seen in 11 of 58 patients (18.9%). Two patients (3.4%) had abnormal liver enzymes during the diagnostic evaluation, whilst 9 patients (15.5%) were admitted with the features of liver diseases, and had final diagnosis of Familial Mediterranean fever (2 had Budd-Chiari syndrome, 5 had chronic hepatitis/cirrhosis, 2 had acute hepatitis). None of the demographic factors or laboratory findings was different between the patients with or without liver involvement M694V allele was more common in patients with liver involvement but did not reach significant difference (50% vs. 33.6%,  $p=0.21$ ). All the

patients showed clinical and laboratory improvement after colchicine.

**CONCLUSION:** Paediatric hepatologists must keep Familial Mediterranean fever in mind in the patients with cryptogenic hepatitis/cirrhosis especially in regions where hereditary inflammatory diseases are common.

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DOI: 10.1016/j.dld.2012.01.003

PMID: 22333476 [Indexed for MEDLINE]

2793. Clin Exp Rheumatol. 2012 Mar-Apr;30(2):269-71. Epub 2012 Apr 13.

Diagnosis of PFAPA syndrome applied to a cohort of 17 adults with unexplained recurrent fevers.

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**BACKGROUND:** The pathophysiology of PFAPA syndrome, mainly characterised by regularly recurring periodic fevers associated with aphthous stomatitis, pharyngitis and/or lymphadenitis, and mostly occurring in the paediatric setting, resembles an acquired autoinflammatory disease. The description of PFAPA syndrome in adult patients is largely increasing.

**OBJECTIVES:** To recognise PFAPA syndrome in a group of adult patients evaluated for recurrent fevers in our Rheumatology Unit.

**METHODS:** To apply current diagnostic criteria for PFAPA syndrome in a group of 359 adults with unexplained recurrent fevers monitored in our Unit between January 2007 and June 2011.

**RESULTS:** We have found 17 out of 359 patients fulfilling the diagnosis of PFAPA syndrome: these patients (10 males, 7 females) were Caucasian with a mean age of  $33.3 \pm 9.5$  years, had recurrent febrile episodes begun at a mean age of  $25.9 \pm 8.3$  years and a mean number of episodes of  $8.3 \pm 5.2$  per year with a mean duration of  $5.5 \pm 1.8$  days. In particular, 7/17 patients had the 3 cardinal signs, the other 10 had a combination of 2 signs. Corticosteroids were given in 14/17 patients;

tonsillectomy was performed in 9/17 patients: corticosteroid responsiveness and tonsillectomy efficacy were observed respectively in 11 and 2 patients.

CONCLUSIONS: Our case highlights the importance of considering PFAPA syndrome in adults presenting with unexplained recurrent fevers and symptoms commonly encountered in general medical practice.

PMID: 22325152 [Indexed for MEDLINE]

2794. Amyloid. 2012 Mar;19(1):28-32. doi: 10.3109/13506129.2012.654530. Epub 2012 Feb 10.

The relation between urinary angiotensinogen and proteinuria in renal AA amyloidosis patients.

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OBJECTIVE: The aim of this study was to evaluate the relationship of local intrarenal renin angiotensin system (RAS) with proteinuria in patients with renal AA amyloidosis.

METHODS: Thirty-two patients with renal AA amyloidosis (19 male, mean age:  $45 \pm 13$  years) and sixteen healthy controls (5 male, mean age:  $32 \pm 5$  years) were included in this study. Spot urine samples were obtained to measure urinary angiotensinogen (AGT) using human AGT-ELISA, urinary creatinine and protein levels. Logarithmic transformations of urinary AGT-creatinine ratio  $\log(\text{UAGT}/\text{Ucre})$  and urinary protein-to-creatinine ratio (UPCR) were done to obtain the normal distributions of these parameters.

RESULTS:  $\log(\text{UAGT}/\text{Ucre})$  was significantly higher in patients compared with the controls ( $1.88 \pm 0.92 \mu\text{g/g}$  vs.  $1.25 \pm 0.70 \mu\text{g/g}$ ;  $p = 0.023$ ). Importantly a significantly positive correlation was found between  $\log(\text{UAGT}/\text{Ucre})$  and  $\log\text{UPCR}$  in patients ( $r = 0.595$ ,  $p = 0.006$ ).

CONCLUSIONS: Urinary AGT levels are higher in renal AA amyloidosis patients than in controls. Also, there is a significant positive correlation between urinary AGT and proteinuria in renal AA amyloidosis.



DOI: 10.3109/13506129.2012.654530  
PMID: 22320202 [Indexed for MEDLINE]

2795. Yonsei Med J. 2012 Mar;53(2):454-8. doi: 10.3349/ymj.2012.53.2.454.

The first case of familial Mediterranean fever associated with renal amyloidosis in Korea.

Koo KY(1), Park SJ, Wang JY, Shin JI, Jeong HJ, Lim BJ, Lee JS.

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(1)Department of Clinical Genetics, Yonsei University College of Medicine, Seoul, Korea.

Erratum in

Yonsei Med J. 2012 May;53(3):670.

Yonsei Med J. 2012 Jul 1;53(4):873.

Familial Mediterranean fever (FMF) is an auto-inflammatory disease characterized by periodic episodes of fever and recurrent polyserositis. It is caused by a dysfunction of pyrin (or marenostin) as a result of a mutation within the MEFV gene. It occurs mostly in individuals of Mediterranean origin; however, it has also been reported in non-Mediterranean populations. In this report, we describe the first case of FMF in a Korean child. An eight-year-old boy presented recurrent febrile attacks from an unknown cause, an acute scrotum and renal amyloidosis. He also showed splenomegaly, lymphadenopathy, pleural effusion, ascites and elevated acute phase reactants. After MEFV gene analysis, he was diagnosed as FMF combined with amyloidosis.

DOI: 10.3349/ymj.2012.53.2.454  
PMCID: PMC3282977  
PMID: 22318840 [Indexed for MEDLINE]

2796. Clin Res Cardiol. 2012 Jul;101(7):525-31. doi: 10.1007/s00392-012-0422-8. Epub 2012 Feb 5.

Clues to detect tumor necrosis factor receptor-associated periodic syndrome (TRAPS) among patients with idiopathic recurrent acute pericarditis: results of a multicentre study.

Cantarini L(1), Lucherini OM, Brucato A, Barone L, Cumetti D, Iacoponi F, Rigante D, Brambilla G, Penco S, Brizi MG, Patrosso MC, Valesini G, Frediani B, Galeazzi M, Cimaz R, Paolazzi G, Vitale A, Imazio M.

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**BACKGROUND:** The potential clinical expression of tumor necrosis factor receptor-associated periodic syndrome (TRAPS), in the form of idiopathic recurrent acute pericarditis (IRAP) has not been explored in the medical literature. The aim of this study was to evaluate the incidence of TRAPS mutations in patients with recurrent pericarditis and identify possible clues to TRAPS diagnosis.

**METHODS:** Therefore, 131 consecutive Caucasian IRAP patients were investigated for mutations of the TRAPS gene and prospectively evaluated.

**RESULTS:** Out of 131 patients, 8 (6.1%) carried a mutation in the TNFRSF1A gene. Compared with those without genetic mutations, patients with TRAPS mutations had more frequently a positive family history for pericarditis and periodic fever syndromes ( $p < 0.001$ ), a higher mean number of recurrences after the first year ( $p < 0.001$ ), on colchicine treatment ( $p < 0.001$ ), and a higher need of immunosuppressive therapies ( $p < 0.001$ ).

**CONCLUSION:** TRAPS is a cause of recurrent pericarditis in 6% of unselected cases with recurrent pericarditis. A positive family history for pericarditis or periodic fever syndromes, a poor response to colchicine, recurrences after the first year from the index attack or on colchicine treatment, as well as the need of immunosuppressive agents are clues of the possible presence of TNFRSF1A gene mutations in patients with recurrent pericarditis.

DOI: 10.1007/s00392-012-0422-8

PMID: 22311714 [Indexed for MEDLINE]

[Serum amyloid a protein concentrations in patients with familial Mediterranean fever].

[Article in Russian]

Dzhndoian ZT.

AIM: the determination of serum amyloid A (SAA) protein concentrations in FMF patients: the colchicine-resistant patients and the patients responded to the different doses of colchicine, and estimation of the risk of the amyloidosis development in these patients. SAA concentration was measured in 58 FMF patients: 23 colchicine-resistant patients without amyloidosis and 35 patients responded to the different doses of colchicine also without amyloidosis as a group of comparison. Serum SAA concentration was measured by ELISA (Enzyme Linked-Immuno-Sorbent-Assay) method using "ANOGEN" kit (Canada). Serum SAA concentration was the same in both groups of the patients: colchicine-resistant patients and patients responded to the different doses of colchicine. The findings of our study indicate that the risk of the amyloidosis development is the same in colchicine-resistant patients and patients responded to the different doses of colchicine.

PMID: 22306501 [Indexed for MEDLINE]

2798. Dig Dis Sci. 2012 Jun;57(6):1660-3. doi: 10.1007/s10620-012-2049-z.

Plasma ghrelin levels in patients with familial Mediterranean fever.

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BACKGROUND: Familial Mediterranean fever (FMF) is an auto-inflammatory disorder characterized by febrile attacks. Increased acute-phase reactants are characteristic during febrile attacks. Ghrelin is a natural G-protein that

decreases secretion of pro-inflammatory cytokines and acts as anti-inflammatory agent. The aim of this study was to investigate whether there is any change in ghrelin levels and whether increases in ghrelin levels can be used as a marker in these patients.

**SUBJECTS AND METHODS:** Thirty-seven male patients and 30 healthy men as a control group were included in the study. Blood samples were obtained for ghrelin measurements both before the attacks (pre-attack period; ghrelin 1 group) and during the attacks (ghrelin 2 group). Samples were kept at -80°C until the analysis was conducted and plasma ghrelin levels were measured using an immune-sorbent assay method.

**RESULTS:** Mean ghrelin levels measured during the attacks were significantly higher ( $11.01 \pm 4.78$  pg/ml) as compared to pre-attack levels ( $5.78 \pm 2.17$  pg/ml;  $p < 0.001$ ). Similarly, mean ghrelin levels measured in FMF patients during an attack were significantly different from that of the control group ( $6.57 \pm 4.13$  pg/ml;  $p < 0.001$ ).

**CONCLUSIONS:** In this study, high ghrelin levels were measured during attacks in FMF patients. This finding is in line with previous results regarding the fact that inflammatory response arising during an FMF attack is an acute inflammatory event. Our findings suggest that ghrelin levels measured during FMF attacks could be used as a biochemical indicator for the FMF attack in FMF patients and that it could be used for support of the diagnosis of the disease.

DOI: 10.1007/s10620-012-2049-z

PMID: 22297653 [Indexed for MEDLINE]

2799. Arthritis Rheum. 2012 Jul;64(7):2375-86. doi: 10.1002/art.34409.

Sustained response and prevention of damage progression in patients with neonatal-onset multisystem inflammatory disease treated with anakinra: a cohort study to determine three- and five-year outcomes.

Sibley CH(1), Plass N, Snow J, Wiggs EA, Brewer CC, King KA, Zalewski C, Kim HJ, Bishop R, Hill S, Paul SM, Kicker P, Phillips Z, Dolan JG, Widemann B, Jayaprakash N, Pucino F, Stone DL, Chapelle D, Snyder C, Butman JA, Wesley R, Goldbach-Mansky R.

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**OBJECTIVE:** Blocking interleukin-1 with anakinra in patients with the autoinflammatory syndrome neonatal-onset multisystem inflammatory disease (NOMID) reduces systemic and organ-specific inflammation. However, the impact of long-term treatment has not been established. This study was undertaken to evaluate the long-term effect of anakinra on clinical and laboratory outcomes and safety in patients with NOMID.

**METHODS:** We conducted a cohort study of 26 NOMID patients ages 0.80-42.17 years who were followed up at the NIH and treated with anakinra 1-5 mg/kg/day for at least 36 months. Disease activity was assessed using daily diaries, questionnaires, and C-reactive protein level. Central nervous system (CNS) inflammation, hearing, vision, and safety were evaluated.

**RESULTS:** Sustained improvements in diary scores, parent's/patient's and physician's global scores of disease activity, parent's/patient's pain scores, and inflammatory markers were observed (all  $P < 0.001$  at 36 and 60 months). At 36 and 60 months, CNS inflammation was suppressed, with decreased cerebrospinal fluid white blood cell counts ( $P = 0.0026$  and  $P = 0.0076$ , respectively), albumin levels, and opening pressures ( $P = 0.0012$  and  $P < 0.001$ , respectively). Most patients showed stable or improved hearing. Cochlear enhancement on magnetic resonance imaging correlated with continued hearing loss. Visual acuity and peripheral vision were stable. Low optic nerve size correlated with poor visual field. Bony lesions progressed. Adverse events other than viral infections were rare, and all patients continued to receive the medication.

**CONCLUSION:** These findings indicate that anakinra provides sustained efficacy in the treatment of NOMID for up to 5 years, with the requirement of dose escalation. Damage progression in the CNS, ear, and eye, but not bone, is preventable. Anakinra is well tolerated overall.

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DOI: 10.1002/art.34409

PMCID: PMC3474541

PMID: 22294344 [Indexed for MEDLINE]

Heparin serves as a natural stimulant of the inflammasome and exacerbates the symptoms of tumor necrosis factor receptor-associated periodic syndrome (TRAPS).

Ohmori S, Hino R, Nakamura M, Tokura Y.

DOI: 10.1016/j.jdermsci.2011.11.006

PMID: 22293543 [Indexed for MEDLINE]

2801. J Periodontol. 2012 Feb;83(2):140-2. doi: 10.1902/jop.2012.110314.

Letter to the editor: does periodontal disease cause amyloidosis?

Cengiz Mİ, Cengiz K.

Comment on

J Periodontol. 2011 Apr;82(4):566-74.

DOI: 10.1902/jop.2012.110314

PMID: 22292602 [Indexed for MEDLINE]

2802. Infect Immun. 2012 Apr;80(4):1437-44. doi: 10.1128/IAI.05680-11. Epub 2012 Jan 30.

*Toxoplasma gondii* infection inhibits Th17-mediated spontaneous development of arthritis in interleukin-1 receptor antagonist-deficient mice.

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Interleukin 1 receptor antagonist (IL-1Ra)-deficient BALB/c mice develop spontaneous arthritis resembling human rheumatoid arthritis. We herein report that infection with *Toxoplasma gondii*, an intracellular protozoan, is capable of ameliorating the spontaneous development of arthritis in IL-1Ra-deficient mice. The onset of arthritis development was delayed and the severity score of

arthritis was significantly suppressed in *T. gondii*-infected mice. Expression of IL-12p40 mRNA from CD11c(+) cells of mesenteric lymph nodes (mLN) and spleen markedly increased at 1 week after peroral infection. While CD11c(+) cells also produced IL-10, IL-1 $\beta$ , and IL-6, CD4(+) T cells from *T. gondii*-infected mice expressed significantly high levels of T-bet and gamma interferon (IFN- $\gamma$ ) mRNA in both mLN and spleen. Levels of GATA-3/IL-4 mRNA or ROR $\gamma$ t/IL-17 mRNA decreased in the infected mice, indicating Th1 cell polarization and the reduction of Th2 and Th17 cell polarization. The severity of arthritis was related to Th1 cell polarization accompanied by Th17 cell reduction, demonstrating the protective role of the *T. gondii*-derived Th1 response against Th17 cell-mediated arthritis in IL-1Ra-deficient mice.

DOI: 10.1128/IAI.05680-11

PMCID: PMC3318428

PMID: 22290145 [Indexed for MEDLINE]

2803. Clin Exp Immunol. 2012 Mar;167(3):391-404. doi: 10.1111/j.1365-2249.2011.04533.x.

Immunology in clinic review series; focus on autoinflammatory diseases: update on monogenic autoinflammatory diseases: the role of interleukin (IL)-1 and an emerging role for cytokines beyond IL-1.

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OTHER THEMES PUBLISHED IN THIS IMMUNOLOGY IN THE CLINIC REVIEW SERIES Allergy, Host Responses, Cancer, Type 1 diabetes and viruses, Metabolic diseases.SUMMARY: The disease-based discovery of the molecular basis for autoinflammatory diseases has led not only to a rapidly growing number of clinically and genetically identifiable disorders, but has unmantled key inflammatory pathways such as the potent role of the alarm cytokine interleukin (IL)-1 in human disease. Following its initial failures in the treatment of sepsis and the moderate success in the treatment of rheumatoid arthritis, IL-1 blocking therapies had a renaissance in the treatment of a number of autoinflammatory conditions, and IL-1 blocking

therapies have been Food and Drug Administration (FDA)-approved for the treatment of the autoinflammatory conditions: cryopyrin-associated periodic syndromes (CAPS). CAPS and deficiency of the IL-1 receptor antagonist (DIRA), both genetic conditions with molecular defects in the IL-1 pathway, have provided a pathogenic rationale to IL-1 blocking therapies, and the impressive clinical results confirmed the pivotal role of IL-1 in human disease. Furthermore, IL-1 blocking strategies have shown clinical benefit in a number of other genetically defined autoinflammatory conditions, and diseases with clinical similarities to the monogenic disorders and not yet identified genetic causes. The discovery that IL-1 is not only triggered by infectious danger signals but also by danger signals released from metabolically 'stressed' or even dying cells has extended the concept of autoinflammation to disorders such as gout, and those that were previously not considered inflammatory, such as type 2 diabetes, coronary artery disease, obesity and some degenerative diseases, and provided the conceptual framework to target IL-1 in these diseases. Despite the tremendous success of IL-1 blocking therapy, the use of these agents in a wider spectrum of autoinflammatory conditions has uncovered disease subsets that are not responsive to IL-1 blockade, including the recently discovered proteasome-associated autoinflammatory syndromes such as chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperatures (CANDLE), Japanese autoinflammatory syndrome with lipodystrophy (JASL), Nakajo-Nishimura syndrome (NNS) and joint contractures, muscle atrophy, panniculitis induced lipodystrophy (JMP), and urge the continued quest to characterize additional dysregulated innate immune pathways that cause autoinflammatory conditions.

Published 2011. This article is a U.S. Government work and is in the public domain in the USA.

DOI: 10.1111/j.1365-2249.2011.04533.x

PMCID: PMC3374271

PMID: 22288582 [Indexed for MEDLINE]

2804. Clin Exp Immunol. 2012 Mar;167(3):382-90. doi: 10.1111/j.1365-2249.2011.04535.x.

Immunology in clinic review series; focus on autoinflammatory diseases: role of inflammasomes in autoinflammatory syndromes.

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OTHER THEMES PUBLISHED IN THIS IMMUNOLOGY IN THE CLINIC REVIEW SERIES Allergy, Host Responses, Cancer, Type 1 diabetes and viruses, Metabolic diseases.SUMMARY: Autoinflammatory syndromes are disorders characterized by the hyperactivation of the innate immune system in the absence of microbial infection or autoantibody production. Some autoinflammatory syndromes are associated with recurrent episodes of fever and systemic inflammation that are caused by dysregulated activation of inflammasomes, molecular platforms responsible for the activation of caspase-1 and the production of interleukin (IL)-1 $\beta$ . In this review we will discuss the role of IL-1 $\beta$  and the inflammasomes in host defence and how mutations of two genes, NLRP3 and PYRIN, leads to the autoinflammatory syndromes, cryopyrin-associated periodic syndromes (CAPS) and familial Mediterranean fever (FMF). Both CAPS and FMF are characterized by increased inflammasome activity and overproduction of IL-1 $\beta$  which is ultimately responsible for disease manifestations. Importantly, understanding the molecular mechanisms of these syndromes has led to effective treatment for these rare diseases with biological drugs that target IL-1 $\beta$ -mediated signalling.

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DOI: 10.1111/j.1365-2249.2011.04535.x

PMCID: PMC3374270

PMID: 22288581 [Indexed for MEDLINE]

2805. Clin Exp Immunol. 2012 Mar;167(3):369-81. doi: 10.1111/j.1365-2249.2011.04534.x.

Immunology in clinic review series; focus on autoinflammatory diseases: inflammasomes: mechanisms of activation.

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Biochemistry, University Hospital, University of Bonn, Bonn, Germany.

OTHER THEMES PUBLISHED IN THIS IMMUNOLOGY IN THE CLINIC REVIEW SERIES Allergy, Host Responses, Cancer, Type 1 diabetes and viruses, Metabolic diseases.

**SUMMARY:** Initiation of a successful immune response requires a working set of sensors that detect any noxious agent within the cellular microenvironment and molecular platforms that process this signal to trigger an appropriate effector response. Pattern recognition receptors can engage different signalling cascades that lead to proinflammatory gene expression. At the same time, transcription-independent events such as activation of proteases and/or phagocytosis are also initiated. The inflammasome pathway constitutes a signalling platform that leads to the activation of so-called inflammatory caspases, most notably caspase-1, which plays a pivotal role in the cleavage and thus maturation of proinflammatory cytokines, but also in the induction of pyroptosis, a special type of cell death. In this review we elaborate on the currently known inflammasome complexes with a special focus on the mechanism behind their activation. Understanding these mechanisms could provide important information regarding the potential signalling nodes that might be targeted for therapeutic intervention.

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DOI: 10.1111/j.1365-2249.2011.04534.x

PMCID: PMC3374269

PMID: 22288580 [Indexed for MEDLINE]

2806. Rev Prat. 2011 Dec;61(10):1349-50.

[Why not familial Mediterranean fever?].

[Article in French]

Grateau G(1), Hentgen V, Stojanovic KS.

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PMID: 22288341 [Indexed for MEDLINE]

2807. Clin Rheumatol. 2012 May;31(5):829-34. doi: 10.1007/s10067-012-1942-3. Epub 2012 Jan 28.

Clinical and genetic features of hereditary periodic fever syndromes in Hispanic patients: the Chilean experience.

Vergara C(1), Borzutzky A, Gutierrez MA, Iacobelli S, Talesnik E, Martinez ME, Stange L, Basualdo J, Maluje V, Jimenez R, Wiener R, Tinoco J, Jarpa E, Aróstegui JI, Yagüe J, Alvarez-Lobos M.

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Hereditary periodic fever syndromes (HPFS) are rare genetic diseases characterized by recurrent episodes of inflammation. Little information is available concerning HPFS in Latin American Hispanic population. The purpose of this study was to determine the clinical and genetic features of HPFS in Chilean population. A multicenter retrospective study of Hispanic Chilean patients with genetically confirmed HPFS was performed. We included 13 patients, 8 with familial Mediterranean fever (FMF) and 5 with TNF receptor-associated periodic syndrome (TRAPS), evaluated at rheumatology or pediatric rheumatology clinics between January 2007 and December 2010. Median age of symptoms onset was 8 years (range 1-35) and 8 years (range 0.3-21) for FMF and TRAPS, respectively. Median duration of fever was 3 days (range 2.5-15) for FMF and 21 days (range 9.5-30) for TRAPS. Genotyping of the MEFV gene in FMF patients revealed a homozygous M694V missense mutation in one patient, and heterozygous missense mutations in seven patients: M694V (n = 3), E148Q, R717H, A744S, and A511V. Sequencing of the TNFRSF1A gene in TRAPS patients revealed heterozygous missense mutations in four patients: T50M, C30R, R92Q, and IVS3+30:G→A, and a two-base pair deletion (IVS2-17\_18del2bpCT) in one patient. Mutation in MEFV R717H and mutations in TNFRSF1A IVS2-17\_18del2bpCT and IVS3+30:G→A are novel and have not been described previously. This study reports the largest series of genetically confirmed HPFS

in Latin America, and adds evidence regarding the clinical and genetic characteristics of patients with FMF and TRAPS in Hispanic population. Mutations identified in MEFV and TNFRSF1A genes include defects reported in other ethnicities and novel mutations.

DOI: 10.1007/s10067-012-1942-3

PMID: 22281876 [Indexed for MEDLINE]

2808. Clin Immunol. 2012 Mar;142(3):362-72. doi: 10.1016/j.clim.2011.12.008. Epub 2011 Dec 28.

Alternative activation in systemic juvenile idiopathic arthritis monocytes.

Macaubas C(1), Nguyen KD, Peck A, Buckingham J, Deshpande C, Wong E, Alexander HC, Chang SY, Begovich A, Sun Y, Park JL, Pan KH, Lin R, Lih CJ, Augustine EM, Phillips C, Hadjinicolaou AV, Lee T, Mellins ED.

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Systemic juvenile idiopathic arthritis (SJIA) is a chronic autoinflammatory condition. The association with macrophage activation syndrome, and the therapeutic efficacy of inhibiting monocyte-derived cytokines, has implicated these cells in SJIA pathogenesis. To characterize the activation state (classical/M1 vs. alternative/M2) of SJIA monocytes, we immunophenotyped monocytes using several approaches. Monocyte transcripts were analyzed by microarray and quantitative PCR. Surface proteins were measured at the single cell level using flow cytometry. Cytokine production was evaluated by intracellular staining and ELISA. CD14(++)CD16(-) and CD14(+)CD16(+) monocyte subsets are activated in SJIA. A mixed M1/M2 activation phenotype is apparent at the single cell level, especially during flare. Consistent with an M2 phenotype, SJIA monocytes produce IL-1 $\beta$  after LPS exposure, but do not secrete it. Despite the inflammatory nature of active SJIA, circulating monocytes demonstrate significant anti-inflammatory features. The persistence of some of these phenotypes during clinically inactive disease argues that this state reflects compensated inflammation.

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DOI: 10.1016/j.clim.2011.12.008

PMCID: PMC3288602

PMID: 22281427 [Indexed for MEDLINE]

2809. Isr Med Assoc J. 2011 Nov;13(11):714; author reply 714.

Pyrin protein: the structural effect of E148Q mutation.

Konstantopoulos K, Kalotychou V.

Comment on

Isr Med Assoc J. 2011 Apr;13(4):199-201.

PMID: 22279711 [Indexed for MEDLINE]

2810. DNA Res. 2012 Apr;19(2):143-52. doi: 10.1093/dnares/dsr047. Epub 2012 Jan 24.

Detection of base substitution-type somatic mosaicism of the NLRP3 gene with >99.9% statistical confidence by massively parallel sequencing.

Izawa K(1), Hijikata A, Tanaka N, Kawai T, Saito MK, Goldbach-Mansky R, Aksentijevich I, Yasumi T, Nakahata T, Heike T, Nishikomori R, Ohara O.

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Chronic infantile neurological cutaneous and articular syndrome (CINCA), also known as neonatal-onset multisystem inflammatory disease (NOMID), is a dominantly inherited systemic autoinflammatory disease and is caused by a heterozygous germline gain-of-function mutation in the NLRP3 gene. We recently found a high incidence of NLRP3 somatic mosaicism in apparently mutation-negative CINCA/NOMID patients using subcloning and subsequent capillary DNA sequencing. It is important to rapidly diagnose somatic NLRP3 mosaicism to ensure proper treatment.

However, this approach requires large investments of time, cost, and labour that prevent routine genetic diagnosis of low-level somatic NLRP3 mosaicism. We developed a routine pipeline to detect even a low-level allele of NLRP3 with statistical significance using massively parallel DNA sequencing. To address the critical concern of discriminating a low-level allele from sequencing errors, we first constructed error rate maps of 14 polymerase chain reaction products covering the entire coding NLRP3 exons on a Roche 454 GS-FLX sequencer from 50 control samples without mosaicism. Based on these results, we formulated a statistical confidence value for each sequence variation in each strand to discriminate sequencing errors from real genetic variation even in a low-level allele, and thereby detected base substitutions at an allele frequency as low as 1% with 99.9% or higher confidence.

DOI: 10.1093/dnares/dsr047

PMCID: PMC3325078

PMID: 22279087 [Indexed for MEDLINE]

2811. Clin Rheumatol. 2012 May;31(5):795-9. doi: 10.1007/s10067-011-1926-8. Epub 2012 Jan 25.

QT interval variability in familial Mediterranean fever: a study in colchicine-responsive and colchicine-resistant patients.

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The association between familial Mediterranean fever (FMF), early atherosclerosis, and electrocardiographic markers for arrhythmias remains controversial. There are conflicting results as to the occurrence of high QT dispersion in FMF. The aim of the present study was to further investigate repolarization dynamics and other repolarization-associated pro-arrhythmogenic markers in FMF patients. To explore repolarization in FMF, patients who responded well to colchicine and patients who had not responded to colchicine, yet were amyloidosis-free, were included. We aimed to evaluate whether increased

inflammatory burden, a characteristic of non-responsive patients, was specifically associated with abnormal repolarization. Included in the study were 53 FMF patients (27 colchicine non-responders) and 53 age- and sex-matched control subjects. Electrocardiograms were performed under strict standards. QT variability parameters were computed with custom-made computer software. No significant difference in any of the QT dynamic parameters was found in either FMF group compared with the healthy controls. Mean values of QT variability index, regardless of colchicine response, were similar to previously published results for healthy persons. In conclusion, patients with FMF who are continuously treated with colchicine and have not developed amyloidosis, regardless of their clinical response, have normal QT variability parameters, indicating normal repolarization dynamics and suggesting no increased risk of repolarization-associated cardiac arrhythmias.

DOI: 10.1007/s10067-011-1926-8

PMID: 22271228 [Indexed for MEDLINE]

2812. Ann Rheum Dis. 2012 May;71(5):753-60. doi: 10.1136/annrheumdis-2011-200556. Epub 2012 Jan 20.

Impact of IL-1 signalling on experimental uveitis and arthritis.

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**BACKGROUND:** Uveitis, or inflammatory eye disease, is a common extra-articular manifestation of many systemic autoinflammatory diseases involving the joints. Anakinra (recombinant interleukin (IL)-1 receptor antagonist (Ra)) is an effective therapy in several arthritic diseases; yet, few studies have investigated the extent to which IL-1 signalling or IL-1Ra influences the onset and/or severity of uveitis.

**OBJECTIVE:** To seek possible links between arthritis and uveitis pathogenesis related to IL-1 signalling.

**METHODS:** The eyes of IL-1Ra-deficient BALB/c mice were monitored histologically and by intravital videomicroscopy to determine if uveitis developed along with

the expected spontaneous arthritis in ankles and knees. Expression levels of IL-1R and its negative regulators (IL-1Ra, IL-1RII, IL-1RAcP and single Ig IL-1R-related molecule) in eye and joint tissues were compared. Differences in uveitis induced by intraocular injection of lipopolysaccharide (LPS) in mice lacking IL-1R or IL-1Ra were assessed.

RESULTS: Deficiency in IL-1Ra predisposes to spontaneous arthritis, which is exacerbated by previous systemic LPS exposure. The eye, however, does not develop inflammatory disease despite the progressive arthritis or LPS exposure.

Organ-specific expression patterns for IL-1Ra and negative regulators of IL-1 activity were observed that appear to predict predisposition to inflammation in each location in IL-1Ra knockout mice. The eye is extremely sensitive to locally administered LPS, and IL-1Ra deficiency markedly exacerbates the resulting uveitis.

CONCLUSION: This study demonstrates that IL-1Ra plays an important role in suppressing local responses in eyes injected with LPS and that there is discordance between murine eyes and joints in the extent to which IL-1Ra protects against spontaneous inflammation.

DOI: 10.1136/annrheumdis-2011-200556

PMCID: PMC3335437

PMID: 22267332 [Indexed for MEDLINE]

2813. Am J Med Genet A. 2012 Feb;158A(2):vii-viii. doi: 10.1002/ajmg.a.35225.

Genetic culprit of rare autoinflammatory disorder confirmed.

[No authors listed]

DOI: 10.1002/ajmg.a.35225

PMID: 22266958 [Indexed for MEDLINE]

2814. Int Urol Nephrol. 2013 Apr;45(2):591-4. doi: 10.1007/s11255-012-0124-1. Epub 2012 Jan 20.

Mesangial proliferative glomerulonephritis in familial Mediterranean fever patient with E148Q mutation: the first case report.



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Familial Mediterranean fever (FMF) is an autosomal recessive hereditary disease characterized by recurrent attacks of fever, usually accompanied by sterile polyserositis. Although amyloidosis is the most common renal involvement, non-amyloid renal lesions, such as glomerulonephritis, have been described in patients with FMF. In this report, we present the first case of an FMF patient with heterozygous mutation of E148Q, mesangial proliferative glomerulonephritis, and no amyloidosis. While the association of mutation E148Q with renal involvement is still obscure, colchicine treatment is useful in mesangial proliferative glomerulonephritis with FMF.

DOI: 10.1007/s11255-012-0124-1

PMID: 22261745 [Indexed for MEDLINE]

2815. Clin Exp Rheumatol. 2012 Jan-Feb;30(1):141. Epub 2012 Mar 7.

Cogan's syndrome in a patient with familial Mediterranean fever.

Zenone T, Puget M.

PMID: 22261355 [Indexed for MEDLINE]

2816. Inflammation. 2012 Jun;35(3):1191-7. doi: 10.1007/s10753-012-9428-7.

The effect of regular colchicine treatment on biomarkers related with vascular injury in newly diagnosed patients with familial Mediterranean fever.

Sari I(1), Yuksel A, Kozaci D, Selcuk S, Gokce G, Yildiz Y, Demirel H, Sop G, Alacacioglu A, Gunay N, Akkoc N.

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We aimed to evaluate some of the vascular biomarkers in newly diagnosed, colchicine naive familial Mediterranean fever (FMF) patients. Our primary aim was to investigate the effect of regular colchicine treatment on these variables. Twenty-four (12 males [M] and 12 females [F],  $33.3 \pm 13.4$  years) newly diagnosed FMF patients were included in the study. These patients were started on colchicine treatment following the initial assessment and were studied again no earlier than 2 months. Five patients were lost to follow-up, and assessment of the on-treatment patients was performed on the remaining 19 patients (8 M and 11 F,  $33.6 \pm 11.8$  years). There were 19 healthy subjects (11 M and 8 F,  $32.2 \pm 7.2$  years) who served as a control group. Cellular adhesion molecules (CAMs; soluble intercellular adhesion molecule-1 [sICAM-1] and soluble CD146 [sCD146]), plasminogen activator inhibitor-1 (PAI-1), fetuin-A and hs-CRP were studied. Examinations were performed on attack-free periods. The levels of hs-CRP, fetuin-A, sICAM-1, and PAI-1 were significantly higher in newly diagnosed patients compared to those of controls ( $P < 0.05$ ). All studied parameters were significantly downregulated after regular colchicine therapy ( $P < 0.05$ ). Comparison of on-treatment data with controls showed that the levels of the vascular biomarkers, except sCD146, were similar between the groups ( $P > 0.05$ ). On-treatment sCD146 was found significantly lower than the controls ( $P < 0.05$ ). In regression analysis, none of the independent variables in the model significantly predicted the vascular biomarkers ( $P > 0.05$ ). Administration of therapeutic doses of colchicine markedly reduces vascular injury parameters and normalizes the values in FMF.

DOI: 10.1007/s10753-012-9428-7

PMID: 22258906 [Indexed for MEDLINE]

2817. Annu Rev Med. 2012;63:233-46. doi: 10.1146/annurev-med-041610-134208.

Familial and acquired hemophagocytic lymphohistiocytosis.

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Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening syndrome in which an uncontrolled and ineffective immune response, triggered in most cases by infectious agents, leads to severe hyperinflammation. Familial forms of HLH (FHL), which are increasingly found also in adolescents and adults, are due to genetic defects leading to impaired function of natural killer cells and cytotoxic T cells. These mutations occur either in the perforin gene or in genes important for the exocytosis of cytotoxic granules. Cytotoxic granules contain perforin and granzymes, which induce apoptosis upon entering (infected) target cells. Additionally, perforin is important for the downregulation of the immune response. Acquired forms of HLH are encountered in association with (usually) viral infections, autoinflammatory/autoimmune diseases, malignant diseases, and acquired immune deficiency states (e.g., after organ transplantation). Treatment of HLH includes immune-suppressive and immune-modulatory agents, cytostatic drugs, and biological response modifiers. For patients with FHL, stem cell transplantation is indicated and can be curative.

DOI: 10.1146/annurev-med-041610-134208

PMID: 22248322 [Indexed for MEDLINE]

2818. Clin Rheumatol. 2012 May;31(5):889-93. doi: 10.1007/s10067-011-1932-x. Epub 2012 Jan 14.

Different clinical presentation of the hyperimmunoglobulin D syndrome (HIDS) (four cases from Turkey).

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Hyperimmunoglobulin D syndrome (HIDS) is one of the autoinflammatory syndromes which are characterized by febrile attacks. Duration and frequency of the febrile attacks, as well as typical organ involvements vary greatly. Recently, it is possible to reach more reliable data by the possibilities that are opened up by

molecular genetics in order to highlight the aetiopathogenesis of this group of diseases. Typical patients with HIDS have an onset of disease in the first year of life. Here, we report four Turkish HIDS cases; three of whom, the symptoms started at a later age. The diagnoses were made by relevant clinical symptoms along with MVK mutations detected by DNA sequencing method. As summarised in this article, HIDS could be presented with a broad spectrum of symptoms. Although most of the HIDS patients are reported from Europe and especially Dutch ancestry, case reports are presented from all over the world. For this reason, HIDS should be kept in mind for the differential diagnosis of periodic fever syndromes or before accepting an FMF patient as colchicine resistant. We suppose that the phenomenon of "later-onset HIDS" should shed light into unresolved clinical problems of patients with periodic fever. Especially in countries that FMF is more frequent such as Turkey, even though the symptoms start later than classic cases, HIDS should be kept in mind for differential diagnosis of periodic fever syndromes.

DOI: 10.1007/s10067-011-1932-x

PMID: 22246419 [Indexed for MEDLINE]

2819. Am J Pathol. 2012 Mar;180(3):1254-63. doi: 10.1016/j.ajpath.2011.11.028. Epub 2012 Jan 11.

Deficiency of interleukin-1 receptor antagonist promotes spontaneous femoral artery aneurysm formation in mice.

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Femoral artery aneurysms (FAAs) are very rare, and their natural history is not well understood. In this study, we sought to analyze the pathogenesis of inflammatory FAAs in interleukin-1 receptor antagonist-deficient (IL-1Ra(-/-)) B6 mice. Systolic arterial pressures and plasma lipid levels of IL-1Ra(-/-) mice and wild-type (WT) mice did not differ significantly. However, IL-1Ra(-/-) mice spontaneously developed fusiform FAAs. Real-time PCR of 9-month-old IL-1Ra(-/-) mice revealed significantly increased mRNA levels of IL-1 $\beta$  (6.6-fold), tumor

necrosis factor- $\alpha$  (TNF- $\alpha$ ) (12.4-fold), and matrix metalloproteinase-9 (6.0-fold) compared with WT mice. Histological analysis revealed numerous inflammatory cells around the FAAs in IL-1Ra(-/-) mice, and elastin staining showed destruction of both the internal and external elastic lamina in IL-1Ra(-/-) mice. Afterward, macrophage function was studied. After lipopolysaccharide (1  $\mu$ g/mL) stimulation, IL-1Ra-deficient macrophages produced much higher levels of TNF- $\alpha$  than those from WT mice. Finally, we performed bone marrow cell transplantation. FAAs with many inflammatory cells in the adventitia were detected in several WT mice that received bone marrow cells from IL-1Ra(-/-) mice (44%), but not from WT mice (0%). Our study is the first to demonstrate that IL-1Ra deficiency in inflammatory cells disrupts immune system homeostasis and induces inflammatory FAAs in IL-1Ra(-/-) B6 mice. We believe that these mice will provide much information about the natural history and management of FAAs.

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DOI: 10.1016/j.ajpath.2011.11.028

PMID: 22245214 [Indexed for MEDLINE]

2820. Semin Arthritis Rheum. 2012 Aug;42(1):84-8. doi: 10.1016/j.semarthrit.2011.12.002. Epub 2012 Jan 12.

NOD2/CARD15 gene mutations in patients with familial Mediterranean fever.

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**OBJECTIVE:** Familial Mediterranean fever (FMF) and Crohn's disease are autoinflammatory disorders, associated with genes (MEFV and NOD2/CARD15, respectively) encoding for regulatory proteins, important in innate immunity, apoptosis, cytokine processing, and inflammation. Although mutations in the MEFV gene were shown to modify Crohn's disease, the role of NOD2/CARD15 gene mutations in the FMF disease phenotype was never studied before.

**PATIENTS AND METHODS:** The cohort consisted of 103 consecutive children with FMF,

followed in a single referral center. NOD2/CARD15 genotypes were analyzed in all patients and 299 ethnically matched unaffected controls. Demographic data, clinical characteristics, and disease course of FMF patients with and without NOD2/CARD15 mutation were compared.

**RESULTS:** A single NOD2/CARD15 mutation was detected in 10 (9.7%) FMF patients and 26 (8.7%) controls. No homozygous or compound heterozygous subjects were discovered in the 2 groups. FMF patients carrying a NOD2/CARD15 mutation had a higher rate of erysipelas-like erythema and acute scrotum attacks, a trend for a higher rate of colchicine resistance and a more severe disease as compared with patients without mutations.

**CONCLUSIONS:** NOD2/CARD15 mutations are not associated with an increased susceptibility to develop FMF. Nevertheless, the presence of these mutations in FMF patients appears to be associated with a trend to a more severe disease.

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DOI: 10.1016/j.semarthrit.2011.12.002

PMID: 22244368 [Indexed for MEDLINE]

2821. J Eur Acad Dermatol Venereol. 2013 Jul;27(7):912-5. doi: 10.1111/j.1468-3083.2011.04442.x. Epub 2012 Jan 14.

Erysipelas-like erythema as the presenting feature of familial Mediterranean fever.

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**BACKGROUND:** 'Erysipelas-like' erythema (ELE) is a well recognized, although uncommon, manifestation of familial Mediterranean fever (FMF), which is frequently mistaken for infectious erysipelas, especially when forming the initial disease presentation.

**AIM:** To clinically and genetically characterize ELE as the first manifestation of FMF.

**METHODS:** FMF patients with ELE as the first disease presentation (study group), were compared with FMF patients with ELE, appearing during the disease course (control group I), and to those FMF patients who never had ELE (control group II).

**RESULTS:** Patients of the study group were comparable to patients without ELE with respect to all demographic, clinical and genetic features studied, and yet differed from patients with ELE appearing later in the disease course in disease severity score ( $1.7 \pm 0.4$  vs.  $2.4 \pm 0.6$ ,  $P = 0.01$ ), length of diagnosis delay ( $7.2 \pm 6.4$  vs.  $2.3 \pm 3.3$  years,  $P=0.037$ ), age of FMF onset ( $24.8 \pm 19.9$  vs.  $5.6 \pm 5.7$  years of age,  $P=0.014$ ) and rate of homozygosity to the M694V mutation (14.3% vs. 68.7% respectively). ELE traits in the study and control groups were alike.

**CONCLUSIONS:** FMF with ELE as the first disease manifestation form an uncommon subgroup, clinically and genetically diverging from the rest of the FMF-ELE patients.

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DOI: 10.1111/j.1468-3083.2011.04442.x

PMID: 22243424 [Indexed for MEDLINE]

2822. Curr Rheumatol Rep. 2012 Apr;14(2):150-4. doi: 10.1007/s11926-011-0233-3.

What do cytokine profiles tell us about subsets of juvenile idiopathic arthritis?

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Classification of juvenile idiopathic arthritis is an ongoing process and up to now has been predominantly based on clinical manifestations--mainly number of joints at onset of disease. In the meantime, basic studies have advanced our knowledge regarding the disease pathogenesis. Unfortunately, studies of cytokines and cytokine polymorphisms have not followed the predominantly clinical International League of Associations for Rheumatology classification in that no significant biological differences among the different disease categories have been demonstrated with robust associations. Only systemic-onset disease seems to

be quite different from other disease categories with regard to biologic mechanisms; indeed, it now seems closer to autoinflammatory than to classic autoimmune diseases. New players in the immunologic basis of juvenile idiopathic arthritis (eg, interleukin-17 and regulatory T cells) are also discussed in this review.

DOI: 10.1007/s11926-011-0233-3

PMID: 22237965 [Indexed for MEDLINE]

2823. Int J Inflam. 2012;2012:271569. doi: 10.1155/2012/271569. Epub 2011 Dec 25.

Systemic arthritis in children: a review of clinical presentation and treatment.

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Systemic juvenile idiopathic arthritis (sJIA) constitutes a small part of juvenile idiopathic arthritis (JIA), yet has a disproportionally higher rate of mortality. Despite being grouped under JIA, it is considered to be a multifactorial autoinflammatory disease. The objective of this paper is to review the epidemiology, pathogenesis, genetics, clinical manifestations, complications, therapy, prognosis, and outcome of sJIA. The presentation and clinical manifestations of sJIA have not changed much in the past several decades, but the collective understanding of the pathogenesis and the development of new targeted therapies (particularly the biologic agents) have transformed and improved the disease outcome for children with sJIA.

DOI: 10.1155/2012/271569

PMCID: PMC3253447

PMID: 22235382

2824. Lupus. 2012 Feb;21(2):190-4. doi: 10.1177/0961203311429552.



Gulf War syndrome as a part of the autoimmune (autoinflammatory) syndrome induced by adjuvant (ASIA).

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Gulf War syndrome (GWS) is a multi-symptom condition comprising a variety of signs and symptoms described in the literature, which not been fully resolved. The various symptoms of the condition include muscle fatigue and tiredness, malaise, myalgia, impaired cognition, ataxia, diarrhoea, bladder dysfunction, sweating disturbances, headaches, fever, arthralgia, skin rashes, and gastrointestinal and sleep disturbances. In addition, excessive chemical sensitivity and odour intolerance is reported. The aetiology of the condition is unclear, but many reviews and epidemiological analyses suggest association with pyridostigmine bromide (PB), certain vaccination regimes, a variety of possible chemical exposures, including smoke from oil-well fires or depleted uranium from shells, as well as physical and psychological stress. Recently, Shoenfeld et al. suggested that four conditions--siliconosis, macrophagic myofaciitis (MMF), GWS and post-vaccination phenomena--that share clinical and pathogenic resemblances, may be incorporated into common syndrome called 'Autoimmune (Autoinflammatory) Syndrome induced by Adjuvants' (ASIA). Symptoms and signs of the four conditions described by Shoenfeld et al. show that at least eight out of ten main symptoms are in correlation in all four conditions. Namely, myalgia, arthralgias, chronic fatigue, neurological cognitive impairment, gastrointestinal symptoms, respiratory symptoms, skin manifestations and appearance of autoantibodies. Regardless of the aetiology of GWS, be it exposure to environmental factors or chemical drugs, vaccinations or the adjuvants in them, GWS fits well with the definition of ASIA and is included as part of 'Shoenfeld's syndrome'.

DOI: 10.1177/0961203311429552

PMID: 22235052 [Indexed for MEDLINE]

2825. Clin Rheumatol. 2012 May;31(5):885-8. doi: 10.1007/s10067-011-1935-7. Epub 2012 Jan 11.

## The role of regulatory T cells in familial Mediterranean fever (FMF).

Rimar D(1), Rosner I, Slobodin G, Boulman N, Toubi E, Kessel A, Peri R, Rozenbaum M.

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The role of regulatory T cells (T-regs) in familial Mediterranean fever (FMF) was never evaluated. Preliminary studies that we have conducted suggested a rise in the number of regulatory T cells after FMF attacks reaching a maximal level at 7 days. The aim of this study was to evaluate the percentage and activity of regulatory T cells in FMF. Six patients with refractory FMF and six healthy controls were evaluated. The percentage of T-reg cells and forkhead box protein 3 (Foxp3) expression was evaluated and compared between four states: FMF in remission, FMF at the first day of an attack, FMF 7 days after the start of the attack, and healthy controls. Four females and two males were included. All patients had FMF with high severity score,  $2.8 \pm 0.4$  (0-3). The mean age was  $31.6 \pm 6.2$ . The mean age at onset was  $9.3 \pm 9.3$ . The mean colchicine dose was  $2.6 \text{ mg} \pm 0.4$ . The expression of Foxp3 7 days after the attacks was significantly higher than in FMF at the first day of the attack, FMF in remission, and healthy controls  $10.08 \pm 2.36$  vs.  $7.005 \pm 0.3$  vs.  $5.3 \pm 1.06$  vs.  $4.44 \pm 1.8$ ;  $p < 0.05$  (Fig.1). The percentage of T-regs in peripheral blood was not statistically different between the four groups. The expression of Foxp3 by T-regs increases 7 days after attacks of FMF. Anti-inflammatory cytokines interleukin-10 and TGF- $\beta$  are known to activate T-regs and have been reported to increase in FMF attacks in line with the present findings. It is suggested that T-regs may have a role in terminating FMF attacks.

DOI: 10.1007/s10067-011-1935-7

PMID: 22234494 [Indexed for MEDLINE]

2826. Am J Epidemiol. 2012 May 15;175(10):1054-61. doi: 10.1093/aje/kwr460. Epub 2012 Jan 10.

Triggers for attacks in familial Mediterranean fever: application of the case-crossover design.

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The etiology of recurrent attacks of serositis in familial Mediterranean fever (FMF) is not completely understood. Uncontrolled clinical case series have reported that factors associated with emotional, physiological, or physical stress precede and might trigger the attacks. This case-crossover study, conducted between July 2007 and May 2008, aimed to estimate the role of precipitating factors in attacks in a sample of Armenian FMF patients in Yerevan, Armenia, where 104 patients contributed 55 case and 189 control time periods. The authors used conditional logistic regression to compare frequency of exposure to stressful events, strenuous physical activity, menstrual periods, and high-fat food consumption prior to FMF attacks and on attack-free random days. Multiple stressful life events predicted FMF attacks 2 days following the event. After adjustment for treatment, an additional stressful event was associated with an estimated 70% increase in the odds of having an FMF attack on the second day (95% confidence interval: 1.04, 2.79). High levels of perceived stress were also associated with FMF attacks. Physical exertion and high-fat diet did not increase the likelihood of FMF attacks. The possibility of prevention of attacks in FMF needs to be tested through stress-reduction interventions.

DOI: 10.1093/aje/kwr460

PMID: 22234484 [Indexed for MEDLINE]

2827. Int J Immunopathol Pharmacol. 2011 Oct-Dec;24(4):827-36.

Bridging the gap between the clinician and the patient with cryopyrin-associated periodic syndromes.

Cantarini L, Lucherini OM, Frediani B, Brizi MG, Bartolomei B, Cimaz R, Galeazzi M, Rigante D.

Cryopyrin-associated periodic syndromes are categorized as a spectrum of three

autoinflammatory diseases, namely familial cold auto-inflammatory syndrome, Muckle-Wells syndrome and chronic infantile neurological cutaneous articular syndrome. All are caused by mutations in the NLRP3 gene coding for cryopyrin and result in active interleukin-1 release: their rarity and shared clinical indicators involving skin, joints, central nervous system and eyes often mean that correct diagnosis is delayed. Onset occurs early in childhood, and life-long therapy with interleukin-1 blocking agents usually leads to tangible clinical remission and inflammatory marker normalization in a large number of patients, justifying the need to facilitate early diagnosis and thus avoid irreversible negative consequences for tissues and organs.

DOI: 10.1177/039463201102400402

PMID: 22230390 [Indexed for MEDLINE]

2828. Int J Inflam. 2012;2012:819467. doi: 10.1155/2012/819467. Epub 2011 Nov 15.

Th17 response and inflammatory autoimmune diseases.

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The proinflammatory activity of T helper 17 (Th17) cells can be beneficial to the host during infection. However, uncontrolled or inappropriate Th17 activation has been linked to several autoimmune and autoinflammatory pathologies. Indeed, preclinical and clinical data show that Th17 cells are associated with several autoimmune diseases such as arthritis, multiple sclerosis, psoriasis, and lupus. Furthermore, targeting the interleukin-17 (IL-17) pathway has attenuated disease severity in preclinical models of autoimmune diseases. Interestingly, a recent report brings to light a potential role for Th17 cells in the autoinflammatory disorder adult-onset Still's disease (AOSD). Whether Th17 cells are the cause or are directly involved in AOSD remains to be shown. In this paper, we discuss the biology of Th17 cells, their role in autoimmune disease development, and in AOSD in particular, as well as the growing interest of the pharmaceutical industry in their use as therapeutic targets.

DOI: 10.1155/2012/819467

PMCID: PMC3249891

PMID: 22229105

2829. Int J Pediatr Otorhinolaryngol. 2012 Mar;76(3):379-81. doi: 10.1016/j.ijporl.2011.12.015. Epub 2012 Jan 9.

Evaluation of cochlear function using transient evoked otoacoustic emission in children with Familial Mediterranean Fever.

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**OBJECTIVE:** The aim of this study was to investigate cochlear functions in children with Familial Mediterranean Fever (FMF).

**METHODS:** Fifty-six FMF patients (112 ears) and 30 healthy control subjects (60 ears) were included in the study. Transient evoked otoacoustic emission (TEOAE) was investigated. Numerical measurements of TEOAE, except the correlation percentage (%), included response amplitude (dB) and signal/noise (SN) ratio.

**RESULTS:** There was no statistically significant difference in age and sex in the two groups. Mean TEOAE correlation percentage, signal/noise ratio, TEOAE amplitudes in 1, 1.5, 2, 3 and 4 Hz frequency values were not different between the two groups ( $p>0.05$ ).

**CONCLUSIONS:** In this study using the TEOAE test, we found that FMF did not cause outer cell hair damage in children. In the literature, there is no study on outer cell hair damage in children or adults with FMF, so this is the first investigational study.

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DOI: 10.1016/j.ijporl.2011.12.015

PMID: 22227121 [Indexed for MEDLINE]

2830. Annu Rev Immunol. 2012;30:531-64. doi: 10.1146/annurev.immunol.25.022106.141623.

Epub 2012 Jan 6.

Regulatory T cells: mechanisms of differentiation and function.

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The immune system has evolved to mount an effective defense against pathogens and to minimize deleterious immune-mediated inflammation caused by commensal microorganisms, immune responses against self and environmental antigens, and metabolic inflammatory disorders. Regulatory T (Treg) cell-mediated suppression serves as a vital mechanism of negative regulation of immune-mediated inflammation and features prominently in autoimmune and autoinflammatory disorders, allergy, acute and chronic infections, cancer, and metabolic inflammation. The discovery that Foxp3 is the transcription factor that specifies the Treg cell lineage facilitated recent progress in understanding the biology of regulatory T cells. In this review, we discuss cellular and molecular mechanisms in the differentiation and function of these cells.

DOI: 10.1146/annurev.immunol.25.022106.141623

PMCID: PMC6066374

PMID: 22224781 [Indexed for MEDLINE]

2831. Ann Dermatol Venereol. 2011 Dec;138 Suppl 4:S233-40. doi: 10.1016/S0151-9638(11)70096-5.

[What's new in dermatological research?].

[Article in French]

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Dermatological research has been very active this year. Most of the numerous fields investigated involve the mechanisms of cutaneous regeneration and barrier function. A novel target of early ultraviolet-induced skin photodamage, the Syk kinase, has been recently identified. Synergistic relationship between telomere damage and cutaneous progerin production during cell senescence may also participate in the natural skin aging process. Interestingly, ultraviolet radiation induces an inhibitory effect on subcutaneous lipogenesis. Androgenetic alopecia or common baldness is not characterized by loss of hair follicle stem cells but by a defect in the conversion of hair follicle stem cells into active progenitor cells. It has been shown that the cornified envelope functions not only as a physicochemical barrier, but also as both a biochemical line of antioxidant defense and an immunological line of defense. Like human papillomaviruses, Merkel cell polyomavirus belongs to the skin microbiome and different studies have demonstrated the protective role of epidermal resident microflora through the activation of innate immunity. Production of antimicrobial peptides and the activation of inflammasome and plasmacytoid dendritic cells are involved in the modulation of the cutaneous barrier function. Results from different studies suggest that IL-22 and IL-36 may be common mediators of both innate and adaptive immune responses. All these pathways interact not only to maintain cutaneous homeostasis and integrity (wound healing) but also to regulate autoinflammatory and autoimmune dermatoses (psoriasis, lupus, rosacea, atopic dermatitis, etc...). In addition, molecular mechanisms that regulate T helper type 2 differentiation and the retention at the site of inflammation of Th2 cells have been identified. New promising therapeutic targets for different chronic dermatosis are thus suggested. Mechanobiology and mechanotransduction are also emerging fields that investigate mechanical interactions between living cells and their environment and the conversion of mechanical cues into biochemical signals. Electronic second skin is now a current concept through bio-integrated epidermal electronics platforms used for different monitoring and stimulations of body functions.

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DOI: 10.1016/S0151-9638(11)70096-5

PMID: 22202644 [Indexed for MEDLINE]

2832. Mol Biol Rep. 2012 May;39(5):6193-6. doi: 10.1007/s11033-011-1437-3. Epub 2011 Dec 30.

Evaluating MEFV mutation frequency in Turkish familial Mediterranean fever suspected patients and gender correlation: a retrospective study.

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Familial Mediterranean fever (FMF) is the most frequent hereditary inflammatory disease. FMF causes different clinical manifestations in different ethnic groups and countries. In this study, we retrospectively reviewed the records of 1,152 FMF suspected patients (673 female and 479 male) from November 2006 to December 2010. A commercial kit assay for the identification of MEFV (Mediterranean fever) gene mutations based on PCR and reverse-hybridization was used to investigate 12 mutations of the MEFV gene. 52.17% of 1,152 FMF suspected patients had MEFV mutation and 45.25% of them were male. The rate of MEFV mutation among male and female patients were 56.78 and 48.88%, respectively. These results were statistically significant and might support the suggestion that FMF had much more penetrance in male patients ( $P = 0.009$ ). Not any significant difference was observed between the male and female patients in terms of heterozygote and homozygote mutation carriage rate ( $P = 0.071$ ). Also not any significant difference was observed between the male and female patients in terms of compound heterozygote mutation carriage rate ( $P = 0.058$ ).

DOI: 10.1007/s11033-011-1437-3

PMID: 22207183 [Indexed for MEDLINE]

2833. Autoimmun Rev. 2012 Aug;11(10):687-98. doi: 10.1016/j.autrev.2011.11.026. Epub 2011 Dec 11.

New insights into the pathogenesis of Behçet's disease.

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Behçet's disease (BD) is a recurrent systemic inflammatory disorder of unknown origin characterized by oral and genital mucous ulcer, uveitis, and skin lesions. Involvement of large vessels, central nervous system (CNS), gastrointestinal tract and thrombotic events are less frequent but can be life threatening. The aim of this review is to provide new insights into the pathogenesis of BD. Over the past year substantial advances have been done in the understanding of the genetic [1,2] and immunology [3] of BD. BD is at the crossroad between autoimmune and autoinflammatory syndromes. In common with autoimmune diseases BD shares class I MHC association. However, in contrast to autoimmune disorders, BD has clinical features that seem to be mostly autoinflammatory. The pathogenesis of BD is still unknown, but major determinants of the genetic and immune system abnormalities have been reported recently. Triggering infectious factors are supposed to participate in the outbreak of BD in genetically predisposed patients. Two recent large genome-wide association study (GWAS) conducted in Turkey and Japan reported association between single nucleotide polymorphism (SNP) of interleukin (IL)-10 and IL-23R/IL-12RB2 genes and BD. New insights into the perturbations of T cell homeostasis of BD recently emerged. We have recently demonstrated the promotion of Th17 responses and the suppression of regulatory T cells (Tregs) that were driven by interleukin (IL)-21 production and that correlates with BD activity. Inflammatory cells within BD inflammatory lesions included mostly neutrophils, Th1 and Th17 cells, and cytotoxic CD8+ and  $\gamma\delta$  T cells. Altogether, the recent progresses in the knowledge of BD pathogenesis pave the way for innovative therapy.

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DOI: 10.1016/j.autrev.2011.11.026

PMID: 22197900 [Indexed for MEDLINE]

2834. Genet Mol Res. 2011 Dec 14;10(4):3411-20. doi: 10.4238/2011.December.14.7.

Analysis of common MDR1 (ABCB1) gene C1236T and C3435T polymorphisms in Turkish patients with familial Mediterranean fever.

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The multidrug resistance (MDR1) gene encodes a P-glycoprotein that plays a key role in drug bioavailability and response to drugs in different human populations. More than 50 SNPs have been described for the MDR1 gene. Familial Mediterranean fever (FMF) is considered an autosomal recessive hereditary disease, associated with a single gene named the Mediterranean fever gene (MEFV). However, about one-third of FMF patients have only one mutated allele, suggesting that this disease is expressed as an autosomal dominant trait with partial penetration or an additional gene might be responsible for the disease. We made genotype and haplotype analyses of the MDR1 gene in 142 FMF patients and 130 unrelated Turkish subjects; two MDR-1 genetic markers (C1236T and C3435T) were analyzed by PCR-RFLP analysis. FMF patients had a significantly higher frequency of the 3435 CT genotype compared with the control group (59.9% in FMF patients versus 44.6% in controls; odds ratio [OR] = 1.85; 95% confidence interval [CI] = 1.14-3.00). Based on haplotype analysis, the T-C shift was significantly more frequent in controls (14.4% versus 7.1% in FMF patients). This haplotype could be protective for FMF disease (OR = 0.45; 95%CI = 0.25-0.84). The frequency of CC-CT (1236-3435) binary genotype was significantly higher in FMF patients (14.79% versus 4.61% in controls; OR = 3.59; 95%CI = 1.40-9.20).

DOI: 10.4238/2011.December.14.7

PMID: 22194207 [Indexed for MEDLINE]

2835. J Clin Immunol. 2012 Apr;32(2):221-9. doi: 10.1007/s10875-011-9629-0. Epub 2011 Dec 24.

Characterization of NLRP3 variants in Japanese cryopyrin-associated periodic syndrome patients.

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The etiology of cryopyrin-associated periodic syndrome (CAPS) is caused by germline gene mutations in NOD-like receptor family, pyrin domain containing 3 (NLRP3)/cold-induced autoinflammatory syndrome 1 (CIAS1). CAPS includes diseases with various severities. The aim of this study was to characterize patients according to the disease severity of CAPS. Five Japanese patients with four kinds of gene variations in NLRP3 were found and diagnosed as CAPS or juvenile idiopathic arthritis. Two mutations in NLRP3, Y563N and E688K, found in CAPS patients exhibit significant positive activities in the nuclear factor- $\kappa$ B reporter gene assay. Increased serum interleukin (IL)-18 levels were only observed in severe cases of CAPS. In mild cases of CAPS, the serum IL-18 levels were not increased, although lipopolysaccharide- or hypothermia-enhanced IL-1 $\beta$  and IL-18 production levels by their peripheral blood mononuclear cells were detectable. This series of case reports suggests that a combination of in vitro assays could be a useful tool for the diagnosis and characterization of the disease severity of CAPS.

DOI: 10.1007/s10875-011-9629-0

PMID: 22193915 [Indexed for MEDLINE]

2836. Rheumatol Int. 2012 Dec;32(12):3845-9. doi: 10.1007/s00296-011-2281-4. Epub 2011 Dec 23.

Low plasma vitamin D levels in patients with familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is an autosomal recessive, inherited autoinflammatory disease characterized by recurrent, self-limited attacks of fever and inflammation of serosal surfaces. There is an explosion of the data regarding inflammatory markers in FMF and clinical effects of chronic

inflammation on the disease presentation. Vitamin D (vit D) is the common denomination of a group of sterols with a crucial role in phospho-calcium metabolism. There are some data about the importance of vit D in the initiation and propagation of a range of autoimmune diseases. The aim of the present study was to determine whether vit D deficiency is present in patients with FMF compared with healthy individuals. The study group included 99 patients with diagnosis of FMF attended to our outpatient Rheumatology and Nephrology Clinics of Atatürk Education and Research Hospital. The control group comprised 51 age- and sex-matched healthy people selected from hospital staff. Serum baseline 25-hydroxy vit D levels were measured by HPLC method using an Agilent 1100 Liquid Chromatograph. We found significantly lower serum 25-hydroxy vit D levels among FMF patients compared with matched controls and a high prevalence of vit D deficiency. This study demonstrated that vit D deficiency is frequent in patients with FMF than the healthy controls. It is convenient to look for vit D deficiency and to correct vit D nutritional status in FMF patients.

DOI: 10.1007/s00296-011-2281-4

PMID: 22193220 [Indexed for MEDLINE]

2837. Rheumatology (Oxford). 2012 May;51(5):780-8. doi: 10.1093/rheumatology/ker412. Epub 2011 Dec 20.

Pro-resolution immunological networks: binding immunoglobulin protein and other resolution-associated molecular patterns.

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Appropriate regulation and subsequent resolution of acute inflammatory events is critical to the prevention of autoinflammatory diseases. Indeed, the chronic inflammation observed in diseases such as RA is at least partially consequent on the failure of endogenous immunoregulation. Current RA therapies (e.g. anti-TNF- $\alpha$  inhibitors and MTX) inhibit components of the inflammatory disease process without directly promoting the resolution of inflammation. We propose that the

next generation of RA therapeutics will complement and augment endogenous immunoregulatory and pro-resolution immunological networks, thus promoting the definitive resolution of inflammation rather than temporary immunological control. Of particular interest with respect to this therapeutic approach is binding immunoglobulin protein [BiP; also known as glucose-regulated protein-78 (GRP78)], a member of the recently defined resolution-associated molecular pattern (RAMP) family of molecules. In this review, we consider the preclinical evidence from experiments in mouse and man that suggests BiP and other members of the RAMP family have the potential to herald a new generation of immunotherapeutics.

DOI: 10.1093/rheumatology/ker412

PMID: 22190690 [Indexed for MEDLINE]

2838. Rheumatology (Oxford). 2012 Apr;51(4):743-8. doi: 10.1093/rheumatology/ker421. Epub 2011 Dec 20.

Evaluation of the current disease severity scores in paediatric FMF: is it necessary to develop a new one?

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**OBJECTIVES:** Modified adult disease severity scoring systems are being used for childhood FMF. We aim to test the clinical consistency of two common severity scoring systems and to evaluate the correlation of scores with the type of FMF mutations in paediatric FMF patients since certain mutations are prone to severe disease.

**METHODS:** Two hundred and fifty-eight children with FMF were cross-sectionally studied. Assessment of the disease severity was performed by using the modified scoring systems of Mor et al. and Pras et al. Genetic analysis was performed

using PCR and restriction endonuclease digestion methods for the presence of 15 FMF gene mutations. FMF mutations were grouped into three based on well-known genotypic-phenotypic associations. Correlation between the mutation groups and the severity scoring systems was assessed. The consistency of the severity scoring systems was evaluated.

**RESULTS:** The results of two scoring systems were not statistically consistent with each other ( $\kappa = 0.171$ ). This inconsistency persisted even in a more homogeneous subgroup of patients with only homozygote mutations of M694V, M680I and M694I ( $\kappa = 0.125$ ). There was no correlation between the mutation groups and either of the scoring systems ( $P = 0.002$ ,  $r = 0.196$  for scoring systems of Mor et al.;  $P = 0.009$ ,  $r = 0.162$  for Pras et al.).

**CONCLUSIONS:** The inconsistency of the two scoring systems and lack of correlation between the scoring systems and mutation groups raises concerns about the reliability of these scoring systems in children. There is a need to develop a scoring system in children based on a prospective registry.

DOI: 10.1093/rheumatology/ker421

PMID: 22190688 [Indexed for MEDLINE]

2839. Ann Hum Genet. 2012 Mar;76(2):159-67. doi: 10.1111/j.1469-1809.2011.00693.x. Epub 2011 Dec 21.

Estimating the allele frequency of autosomal recessive disorders through mutational records and consanguinity: the Homozygosity Index (HI).

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In principle mutational records make it possible to estimate frequencies of disease alleles ( $q$ ) for autosomal recessive disorders using a novel approach based on the calculation of the Homozygosity Index (HI), i.e., the proportion of homozygous patients, which is complementary to the proportion of compound heterozygous patients  $P(CH)$ . In other words, the rarer the disorder, the higher

will be the HI and the lower will be the P(CH). To test this hypothesis we used mutational records of individuals affected with Familial Mediterranean Fever (FMF) and Phenylketonuria (PKU), born to either consanguineous or apparently unrelated parents from six population samples of the Mediterranean region. Despite the unavailability of precise values of the inbreeding coefficient for the general population, which are needed in the case of apparently unrelated parents, our estimates of  $q$  are very similar to those of previous descriptive epidemiological studies. Finally, we inferred from simulation studies that the minimum sample size needed to use this approach is 25 patients either with unrelated or first cousin parents. These results show that the HI can be used to produce a ranking order of allele frequencies of autosomal recessive disorders, especially in populations with high rates of consanguineous marriages.

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DOI: 10.1111/j.1469-1809.2011.00693.x

PMID: 22188137 [Indexed for MEDLINE]

2840. Mol Biol Rep. 2012 May;39(5):5503-10. doi: 10.1007/s11033-011-1353-6. Epub 2011 Dec 21.

Genetic analysis of C5a receptors in neutrophils from patients with familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is an autoinflammatory disease, characterized by MEFV gene mutations and self-limited recurrent episodes of fever and localized serositis. Complement system is a key regulator of the inflammatory process. The aim of this study was to investigate the genetic alterations and mRNA expression pattern of C5aR and C5L2 genes in neutrophils from attack-free FMF patients. No mutations were observed in the two receptors' genes, while the genetic alteration

observed in the C5aR1 gene was identified as N279 K polymorphic variant. Furthermore, lower mRNA expression of C5L2 gene was observed in neutrophils from FMF patients compared to control subjects. The binding capacity of rhC5a and the ability to produce reactive oxygen species was similar in neutrophils from healthy subjects and FMF patients and independent of the presence of N279 K polymorphism or mRNA expression of C5L2.

DOI: 10.1007/s11033-011-1353-6

PMID: 22187344 [Indexed for MEDLINE]

2841. Clin Rev Allergy Immunol. 2012 Feb;42(1):1-4. doi: 10.1007/s12016-011-8298-3.

Mechanisms and pathophysiology of autoimmune disease.

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The first textbook on autoimmunity was published by Ian Mackay and McFarland Burnett in 1963. It was the first attempt to summarize existing knowledge on human autoimmunity. Since that time, there have been tens of thousands of experimental papers and numerous textbooks that focus on the diagnosis and treatment of human autoimmunity. There have been at least as many, if not more, directed at similar issues in animal models. Enormous strides have been made not only in diagnosis, but also in the pathophysiology and especially in treatment. We have gone from the era of simple HLA typing to deep sequencing and, more recently, epigenetic analysis. We have gone from the era of white blood cell differentials to detailed lymphoid phenotyping. We have gone from the era of simple antinuclear antibodies to detailed and sophisticated immunodiagnosis with recombinant autoantigens and disease-specific epitopes. We have gone from the era of using only corticosteroids to selective biologic agents. Diseases that were previously considered idiopathic are now very much understood as autoimmune. We are in the era of autoinflammatory reactions and the concept of both innate versus adaptive immunity in mediating immunopathology. In this edition of Clinical Reviews in Allergy and Immunology, we focus on key and cutting-edge issues in the pathophysiology of autoimmunity. The issues are very much oriented



and driven by hypothesis, i.e., a prediction of events expected to occur based on observations. It is not meant to be a complete summary of potential mechanisms of autoimmunity, but rather an attempt to accelerate discussion and better understanding. The primary goal is obviously to help our patients with autoimmune disease.

DOI: 10.1007/s12016-011-8298-3

PMID: 22187334 [Indexed for MEDLINE]

2842. Rheumatol Int. 2013 May;33(5):1355-7. doi: 10.1007/s00296-011-2278-z. Epub 2011 Dec 21.

Decreased vitamin D levels in patients with familial mediterranean fever.

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Familial mediterranean fever (FMF) is an autosomal recessive disorder caused by mutations in the FMF gene (MEFV). The gene causing FMF, designated MEFV, encodes a protein called pyrin or marenostrin that is expressed mainly in myeloid bone marrow precursors, neutrophils, and monocytes. Since there are several etiological factors, FMF is the most common periodic fever syndrome. However, it is still unknown what triggers or ends these periodical attacks. As a pleiotropic hormone, vitamin D has immunomodulation effects. The aim of this study was to evaluate the vitamin D levels in FMF patients. The study group was comprised of 26 patients diagnosed with FMF (men/women: 12/14), and 34 healthy control (men/women: 17/17). Vitamin D levels in FMF patients and healthy controls were  $11.05 \pm 7.11$ ,  $17.15 \pm 6.49$ , respectively. FMF patients had significantly decreased vitamin D levels compared with healthy controls ( $P < 0.001$ ). In conclusion, it is thought that vitamin D deficiency in FMF patients may trigger the attacks. Further studies with larger patient populations need to hold to investigate the vitamin D deficiency in patients with FMF and that may assist to clarify the mechanism behind the colchicines resistant cases.

2843. Int J Pediatr Otorhinolaryngol. 2012 Feb;76(2):244-7. doi: 10.1016/j.ijporl.2011.11.013. Epub 2011 Dec 15.

Cochlear involvement in Familial Mediterranean Fever: a new feature of an old disease.

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**OBJECTIVES:** In this study we first aimed to assess the cochlear functions in children with Familial Mediterranean Fever. The second aim was to investigate the correlation between the hearing levels and some clinical features of Familial Mediterranean Fever including the duration of the disease, age at onset, genetic analysis and colchicine use.

**METHODS:** Thirty-four children with Familial Mediterranean Fever and 27 age matched children were included in the study. Following otologic examination, all children underwent audiometric evaluation, including Pure Tone Average measurements and Distortion Product Otoacoustic Emission testing. Audiological results of the two groups were compared and correlation between the audiological status and clinical parameters of the disease like the duration of disease, age at onset, mutations and colchicine treatment were studied.

**RESULTS:** Pure tone audiometry hearing levels were within normal levels in both groups. Hearing thresholds of Familial Mediterranean Fever patients were found to be increased at frequencies 8000, 10,000, 12,500 and 16,000 ( $p<0.05$ ). In otoacoustic emission evaluation, distortion products and signal-noise ratio of FMF children were lower in the tested frequencies, from 1400 Hz to 4000 Hz ( $p<0.05$ ). Interaction of the disease duration and age of disease onset was found to predict hearing levels, distortion products and signal-noise ratios of children with Familial Mediterranean Fever (F value=2.034;  $p=0.033$ ).

**CONCLUSIONS:** To our knowledge this is the first study demonstrating cochlear involvement in children with Familial Mediterranean Fever which showed increased hearing thresholds at higher frequencies in audiometry together with decreased

distortion products and signal-noise ratios demonstrated by distortion product otoacoustic emission testing. Similar studies must be carried out on adult patients to see if a clinical hearing impairment develops. The possible mechanisms that cause cochlear involvement and the effect of colchicine treatment on cochlear functions must be enlightened.

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DOI: 10.1016/j.ijporl.2011.11.013

PMID: 22177320 [Indexed for MEDLINE]

2844. Gastroenterol Hepatol. 2012 Apr;35(4):259-65. doi: 10.1016/j.gastrohep.2011.11.001. Epub 2011 Dec 15.

[Systemic amyloidosis in inflammatory bowel disease].

[Article in Spanish]

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Systemic amyloidosis comprises a group of diseases that develop as a consequence of an abnormal accumulation of different proteins in several organs, altering their function. Secondary amyloidosis develops after the accumulation of serum amyloid A protein (an acute phase reactant), mainly in the course of chronic inflammatory conditions such as rheumatologic diseases, familial Mediterranean fever, or tuberculosis. Inflammatory bowel disease (IBD) may also cause secondary amyloidosis. However, little is known about the true prevalence, risk factors, and clinical outcomes of amyloidosis among IBD patients. A few studies suggest that amyloidosis is more prevalent in Crohn's disease than in ulcerative colitis, mainly occurring in patients with an extensive, long-lasting, and penetrating disease pattern. In this article we review the available data on secondary amyloidosis and IBD, focusing on prevalence, risk factors, clinical presentation and therapeutic measures.

2845. Arthritis Rheum. 2012 Jun;64(6):2022-7. doi: 10.1002/art.34332. Epub 2011 Dec 12.

Brief report: genotype, phenotype, and clinical course in five patients with PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, and acne).

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**OBJECTIVE:** To describe the genotypes, phenotypes, immunophenotypes, and treatments of PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, and acne), a rare autoinflammatory disease, in 5 patients.

**METHODS:** Clinical information was gathered from medical records and through interviews with 5 patients from 4 kindreds. PSTPIP1 (CD2BP1) exon 10 and exon 11 sequencing was performed in each patient. Neutrophil granule content and cytokine levels were determined in plasma and stimulated peripheral blood mononuclear cells (PBMCs) from patients and controls.

**RESULTS:** We identified 2 previously described PAPA syndrome-associated PSTPIP1 mutations, A230T and E250Q, and a novel change, E250K. Disease penetrance was incomplete, with variable expressivity. The cutaneous manifestations included pathergy, cystic acne, and pyoderma gangrenosum. Interleukin-1 $\beta$  (IL-1 $\beta$ ) and circulating neutrophil granule enzyme levels were markedly elevated in patients compared to those in controls. PBMC stimulation studies demonstrated impaired production of IL-10 and enhanced production of granulocyte-macrophage colony-stimulating factor. Good resolution of pyoderma gangrenosum was achieved in 3 patients with tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) blockade treatment.

**CONCLUSION:** This analysis of 5 patients demonstrates that mutations in PSTPIP1 are incompletely penetrant and variably expressed in the PAPA syndrome.

Neutrophil granule proteins are markedly elevated ex vivo and in the plasma, and elevated levels might be compatible with a diagnosis of PAPA syndrome. TNF $\alpha$

blockade appears to be effective in treating the cutaneous manifestations of PAPA syndrome.

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DOI: 10.1002/art.34332

PMCID: PMC3737487

PMID: 22161697 [Indexed for MEDLINE]

2846. Ann Saudi Med. 2012 Jan-Feb;32(1):43-8.

A retrospective review of autoinflammatory diseases in Saudi children at a rheumatology clinic.

Alenazi A(1), Al Sonbul A, Al Jumaah S, Al Mehaidib A, Al-Mayouf SM.

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**BACKGROUND AND OBJECTIVE:** Published data from Saudi Arabia regarding autoinflammatory diseases are scarce. In this study, we describe the clinical and laboratory features of autoinflammatory diseases in Saudi children.

**DESIGN AND SETTING:** Restrospective, hospital-based study conducted from January 2010 until June 2010.

**PATIENTS AND METHODS:** Patients with autoinflammatory disease treated at the Pediatric Rheumatology Clinic at King Faisal Specialist Hospital and Research Center, Riyadh, over the past 10 years were included. Autoinflammatory diseases included the following: familial Mediterranean fever (FMF); chronic recurrent multifocal osteomyelitis (CRMO); early-onset sarcoidosis (EOS); periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA); chronic infantile neurologic cutaneous and articular syndrome (CINCA); and Muckle-Wells syndrome (MWS). Demographic characteristics, diagnosis, age at onset, disease duration, follow-up duration, clinical and laboratory variables, and outcome data were compiled. Gathered laboratory data were part of patients' usual medical care.

**RESULTS:** Thirty-four patients (females, 53%) with autoinflammatory diseases were included (mean age, 151 months). Mean disease duration was 118 months; mean age

at onset was 32 months; consanguinity was present in 40%. Patients were diagnosed as follows: FMF, 50%; CRMO, 23.5%; CINCA, 8.8%; EOS, 8.8%; MWS, 6%; and PFAPA, 2.9%. The referral diagnosis was inaccurate in all patients except for FMF patients. Gene study was informative in 9 of 14 FMF patients who had molecular analyses. None of our cohort had amyloidosis. All CRMO patients had a favorable response to treatment except 1 patient, who had refractory, progressive disease. All patients with EOS had multiorgan involvement, including uveitis. All CINCA patients had a favorable response to anakinra.

**CONCLUSION:** Our report shows that autoinflammatory diseases other than FMF may be overlooked. Increased awareness among pediatricians about these conditions will help to provide better health care to patients in the form of early diagnosis and management.

PMCID: PMC6087640

PMID: 22156639 [Indexed for MEDLINE]

2847. Arthritis Res Ther. 2011;13(6):R196. doi: 10.1186/ar3526. Epub 2011 Dec 6.

NLRP3 E311K mutation in a large family with Muckle-Wells syndrome--description of a heterogeneous phenotype and response to treatment.

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**INTRODUCTION:** Muckle-Wells syndrome (MWS) is an inherited autoinflammatory disease characterized by fever, rash, arthralgia, conjunctivitis, sensorineural deafness and potentially life-threatening amyloidosis. The NLRP3/CIAS1 E311K mutation caused a heterogeneous phenotype of MWS in a large family. This study analyzes the clinical spectrum, patterns of inflammatory parameters and reports on response to treatment.

**METHODS:** A total of 42 patients and family members were screened for the presence of the NLRP3 mutation. Clinical symptoms were reviewed in all family members.

Classical (erythrocyte sedimentation rate (ESR, C-reactive protein (CRP)) and novel MWS inflammatory markers (serum amyloid A (SAA), cytokines, cytokine receptor levels) were determined. Patients were treated with the IL-1 inhibitors Anakinra or Canakinumab.

RESULTS: All 13 clinically affected patients were heterozygous carriers of the amino acid substitution p.Glu311Lys/E311K encoded by exon 3 of the NLRP3 gene, but none of the healthy family members. Disease manifestations varied widely. Except for one child, all carriers suffered from hearing loss and severe fatigue. TNF- $\alpha$ , IL-6, TNF-RI, and TNF-RII levels as well as SAA were elevated in three, two, one, six and ten patients, respectively. Both clinical and laboratory parameters responded quickly and sustainedly to treatment with Anakinra or Canakinumab.

CONCLUSION: The NLRP3 E311K mutation is associated with a heterogeneous clinical spectrum, which may expand the view on MWS presentation. The leading symptom was hearing loss. Pericarditis, a rare but severe clinical feature of MWS, was diagnosed in three patients. One patient had a severe course, which led to renal failure secondary to amyloidosis. IL-1 inhibition leads to rapid and sustained improvement of symptoms.

DOI: 10.1186/ar3526

PMCID: PMC3334646

PMID: 22146561 [Indexed for MEDLINE]

2848. Afr Health Sci. 2011 Aug;11 Suppl 1:S6-13.

Increased oxidative stress in patients with familial Mediterranean fever during attack period.

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OBJECTIVES: We aimed to investigate the status of oxidant and antioxidants during attack period (AP) and attack free periods (AFP) in Familial Mediterranean fever (FMF) patients.

METHODS: Measured the levels of malondialdehyde (MDA), protein carbonyl (PC),

glutathione (GSH) and antioxidant vitamins (A,C and E) as well as the activities of catalase (CAT) and glutathione peroxidase (GSH-Px) in serum and whole blood of FMF patients in FMF-AP and FMF-AFP.

RESULTS: Levels of MDA and PC were found significantly higher ( $p < 0.05$ ) both in serum and whole blood of FMF-AP group compared with other groups. The CAT and GSH-Px activities in FMF-AP group were found markedly lower ( $p < 0.05$ ) comparing to HC group. However, there were no statistically significant differences between the groups in terms of antioxidant vitamin levels.

CONCLUSIONS: Our study demonstrated increased oxidative stress in patients with FMF during AP. Investigations are needed to establish the effect of antioxidant supplementation on FMF attack frequency and severity. We also suggest that these increased MDA and PC levels and decreased antioxidants may be used as supportive markers to differentiate AP from AFP. These conclusions need to be validated in further multicenter studies with high number of FMF patients.

PMCID: PMC3220131

PMID: 22135646 [Indexed for MEDLINE]

2849. Arthritis Rheum. 2012 Mar;64(3):613-6. doi: 10.1002/art.33451.

Osteoarthritis as an autoinflammatory disease caused by chondrocyte-mediated inflammatory responses.

Konttinen YT, Sillat T, Barreto G, Ainola M, Nordström DC.

Comment on

Arthritis Rheum. 2012 Mar;64(3):729-39.

DOI: 10.1002/art.33451

PMID: 22130805 [Indexed for MEDLINE]

2850. Arthritis Rheum. 2011 Dec;63(12):4007-17. doi: 10.1002/art.30588.

A novel mutation of IL1RN in the deficiency of interleukin-1 receptor antagonist syndrome: description of two unrelated cases from Brazil.



Jesus AA(1), Osman M, Silva CA, Kim PW, Pham TH, Gadina M, Yang B, Bertola DR, Carneiro-Sampaio M, Ferguson PJ, Renshaw BR, Schooley K, Brown M, Al-Dosari A, Al-Alami J, Sims JE, Goldbach-Mansky R, El-Shanti H.

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**OBJECTIVE:** Monogenic autoinflammatory diseases are disorders of Mendelian inheritance that are characterized by mutations in genes that regulate innate immunity and whose typical features are systemic inflammation without high-titer autoantibodies or antigen-specific T cells. Skin and bone inflammation in the newborn period have been described in 3 of these autoinflammatory disorders: neonatal-onset multisystem inflammatory disease, Majeed syndrome, and deficiency of interleukin-1 (IL-1) receptor antagonist (DIRA) syndrome. This study was undertaken to present the characteristics of the DIRA syndrome in 2 cases from Brazil, and describe a novel mutation in IL1RN.

**METHODS:** Two unrelated Brazilian patients were evaluated for the clinical signs and symptoms of these 3 disorders, and peripheral blood samples were assessed for mutations in NLRP3, LPIN2, and IL1RN by DNA resequencing analysis. A mutation in IL1RN that encodes a mutant protein was identified, and the expression and function of this mutant protein were compared to those of the wild-type protein.

**RESULTS:** Both patients presented with pustular dermatitis resembling generalized pustular psoriasis, recurrent multifocal aseptic osteomyelitis, and elevation in the levels of acute-phase reactants, all of which are features most consistent with the DIRA syndrome. Chronic lung disease was observed in 1 of the patients, and jugular venous thrombosis was observed in the other patient. Both patients showed a partial response to corticosteroid therapy, and 1 patient experienced an initial improvement of dermatitis with the use of acitretin. Both patients were homozygous for a novel 15-bp (in-frame) deletion on the IL1RN gene. The mutated protein expressed in vitro had no affinity with the IL-1 receptor, and stimulation of the patients' cells with recombinant human IL-1 $\alpha$  or IL-1 $\beta$  led to oversecretion of proinflammatory cytokines, similar to the findings obtained in previously reported patients.

**CONCLUSION:** The presence of the same homozygous novel mutation in IL1RN in 2 unrelated Brazilian patients suggests that this genetic variant may be a founder mutation that has been introduced in the Brazilian population.

DOI: 10.1002/art.30588

PMCID: PMC3463867

PMID: 22127713 [Indexed for MEDLINE]

2851. Angle Orthod. 2012 May;82(3):552-5. doi: 10.2319/060811-375.1. Epub 2011 Nov 29.

Cephalometric evaluation of children with familial Mediterranean fever.

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**OBJECTIVE:** To test the null hypothesis that no differences exist in craniofacial morphology between patients with familial Mediterranean fever (FMF) and the healthy population.

**MATERIALS AND METHODS:** Standardized lateral cephalograms of 32 FMF patients (mean age,  $11.50 \pm 2.72$  years) and 32 healthy controls (mean age,  $11.86 \pm 2.19$  years) were obtained. Cranial and dentofacial parameters were measured using a cephalometric analysis program (Nemoceph Imaging Cephalometric and Tracing Software S.L., Spain). All statistical analyses were conducted using SPSS version 17.0.0 (SPSS Inc., Chicago, Ill). Descriptive statistics were calculated for all measurements, and the independent t-test was used to evaluate intergroup differences.

**RESULTS:** The ANB angle was significantly greater in the FMF group ( $P < .05$ ). Differences in SNA and SNB angles were insignificant. Anterior ( $P < .001$ ) and posterior ( $P < .05$ ) face heights were significantly shorter in the FMF group. Mandibular body length ( $P < .001$ ) and condylion to gnathion ( $P < .05$ ) measurements were significantly shorter in the FMF group. The upper lip was more protrusive in the FMF group ( $P < .05$ ). U1-NA (mm;  $P < .001$ ) and L1-NB (mm;  $P < .05$ ) measurements were significantly shorter in the FMF group.

**CONCLUSION:** The hypothesis is rejected. Significant differences exist between the craniofacial morphology of patients with FMF and the healthy population.

DOI: 10.2319/060811-375.1

PMID: 22126097 [Indexed for MEDLINE]

2852. Prog Retin Eye Res. 2012 Mar;31(2):182-94. doi: 10.1016/j.preteyeres.2011.11.004. Epub 2011 Nov 22.

Interplay between innate and adaptive immunity in the development of non-infectious uveitis.

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In vertebrates, the innate and adaptive immune systems have evolved seamlessly to protect the host by rapidly responding to danger signals, eliminating pathogens and creating immunological memory as well as immunological tolerance to self. The innate immune system harnesses receptors that recognize conserved pathogen patterns and alongside the more specific recognition systems and memory of adaptive immunity, their interplay is evidenced by respective roles during generation and regulation of immune responses. The hallmark of adaptive immunity which requires engagement of innate immunity is an ability to discriminate between self and non-self (and eventually between pathogen and symbiont) as well as peripheral control mechanisms maintaining immunological health and appropriate responses. Loss of control mechanisms and/or regulation of either the adaptive or the innate immune system lead to autoimmunity and autoinflammation respectively. Although autoimmune pathways have been largely studied to date in the context of development of non-infectious intraocular inflammation, the recruitment and activation of innate immunity is required for full expression of the varied phenotypes of non-infectious uveitis. Since autoimmunity and autoinflammation implicate different molecular pathways, even though some convergence occurs, increasing our understanding of their respective roles in the development of uveitis will highlight treatment targets and influence our understanding of immune mechanisms operative in other retinal diseases. Herein, we extrapolate from the basic mechanisms of activation and control of innate and adaptive immunity to how autoinflammatory and autoimmune pathways contribute to disease development in non-infectious uveitis patients.

DOI: 10.1016/j.preteyeres.2011.11.004  
PMCID: PMC3288447  
PMID: 22120610 [Indexed for MEDLINE]

2853. *Inflamm Res*. 2012 Mar;61(3):225-31. doi: 10.1007/s00011-011-0404-8. Epub 2011 Nov 26.

The NLRP3 inflammasome is active but not essential in endotoxin-induced uveitis.

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**OBJECTIVE:** The inflammasome complex involving caspase-1 and nucleotide-binding domain, leucine-rich repeat containing protein (NLRP)3, also known as NALP3 or cryopyrin is important for host responses to microbial pathogens and several autoinflammatory diseases. We investigated the extent to which NLRP3 and caspase-1 control ocular interleukin (IL)-1 $\beta$  production and severity of uveitis (intraocular inflammatory disease) in an established, acute inflammatory uveitis model, endotoxin-induced uveitis (EIU).

**METHODS:** Expression of NLRP3, its adaptor molecule ASC, also known as PYCARD (PYD and CARD domain containing), and caspase-1 were examined by immunoblotting. IL-1 $\beta$  production was measured by enzyme-linked immunosorbent assay (ELISA). Using knockout mice, roles for caspase-1 and NLRP3 were examined in uveitis induced by intraocular injection of *Escherichia coli* lipopolysaccharide (LPS).

**RESULTS:** NLRP3, ASC, and caspase-1 proteins are constitutively expressed in eye tissue. During EIU, IL-1 $\beta$  protein production increases; this requires the presence of both caspase-1 and NLRP3. However, severity of EIU is not altered by deficiency in either caspase-1 or NLRP3, as assessed by both intravital microscopy and histology.

**CONCLUSIONS:** These data identify the importance of the NLRP3 inflammasome for IL-1 $\beta$  production in the eye, yet indicate that its participation in EIU is nonessential.

DOI: 10.1007/s00011-011-0404-8

PMCID: PMC3335428

PMID: 22119862 [Indexed for MEDLINE]

2854. J Int Med Res. 2011;39(5):2006-11.

QT dispersion is not increased in familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is an autoimmune disease inherited as an autosomal recessive trait and is characterized by recurrent attacks of fever and sterile polyserositis. This study examined electrocardiographic ventricular repolarization parameters (QT interval and QT dispersion) in 38 FMF patients and 35 healthy controls. The QT interval was measured manually from the onset of QRS to the end of the T wave (return to the TP baseline). QT dispersion was defined as the difference between the maximum and minimum QT values, and corrected QT was calculated according to the Bazett formula. There were no significant differences between FMF patients and healthy control subjects in any parameter of ventricular repolarization; hence QT dispersion was not affected by FMF. Electrocardiographic assessment of QT interval and QT dispersion are, therefore, of little value for the evaluation of cardiac impairment and risk of arrhythmia in FMF patients.

DOI: 10.1177/147323001103900547

PMID: 22118005 [Indexed for MEDLINE]

2855. Thromb Haemost. 2012 Jan;107(1):88-98. doi: 10.1160/TH11-08-0556. Epub 2011 Nov 24.

Platelet soluble CD40L and matrix metalloproteinase 9 activity are proinflammatory mediators in Behçet disease patients.

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Platelets are the major source of plasma-soluble CD40L (sCD40L), an important inflammatory mediator. This study explored the impact of platelet-derived sCD40L on Behçet disease (BD), an autoinflammatory vasculitis. We also searched for influences by platelet matrix metalloproteinases (MMP) -2 and MMP-9, implicated in several inflammatory diseases, on CD40L shedding from platelet membrane. Platelet activation were studied by flow cytometry and aggregometry, surface expression of CD40L and platelet-leukocyte aggregates by flow cytometry, sCD40L by ELISA, cellular CD40L and CD40 levels by Western blot and MMPs activity by gelatin zymography. The effect of sCD40L on MMP9 expression was studied in cultured MEG-01 cells. Plasma and platelet-released sCD40L levels were higher in BD patients. No differences in platelet activation and in platelet-leukocyte aggregates formation were observed between BD patients and controls. Plasma and platelet MMP-9 levels were increased in BD patients, whereas there was no difference in platelet MMP-2 activity. Since a correlation between plasma sCD40L and platelet MMP-9 activity was observed, we studied the influence of sCD40L on MMP-9 levels in the megakaryoblastic cell line MEG-01. Treatment of MEG-01 cells with recombinant sCD40L increased MMP-9 but did not change MMP-2 levels. In conclusion, sCD40L release from platelets was mediated by MMP-9, and MMP-9 expression was in turn upregulated by sCD40L in the MEG-01 cell line. We conclude that platelets and megakaryocytes might participate in a positive feedback loop occurring between sCD40L and MMP-9 which would contribute to the proinflammatory state observed in BD.

DOI: 10.1160/TH11-08-0556

PMID: 22116092 [Indexed for MEDLINE]

2856. Biosci Rep. 2012 Apr 1;32(2):105-12. doi: 10.1042/BSR20110089.

Tumour necrosis factor receptor trafficking dysfunction opens the TRAPS door to pro-inflammatory cytokine secretion.

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Cytokines are secreted from macrophages and other cells of the immune system in response to pathogens. Additionally, in autoinflammatory diseases cytokine secretion occurs in the absence of pathogenic stimuli. In the case of TRAPS [TNFR (tumour necrosis factor receptor)-associated periodic syndrome], inflammatory episodes result from mutations in the TNFRSF1A gene that encodes TNFR1. This work remains controversial, however, with at least three distinct separate mechanisms of receptor dysfunction having been proposed. Central to these hypotheses are the NF- $\kappa$ B (nuclear factor  $\kappa$ B) and MAPK (mitogen-activated protein kinase) families of transcriptional activators that are able to up-regulate expression of a number of genes, including pro-inflammatory cytokines. The present review examines each proposed mechanism of TNFR1 dysfunction, and addresses how these processes might ultimately impact upon cytokine secretion and disease pathophysiology.

DOI: 10.1042/BSR20110089

PMCID: PMC3204872

PMID: 22115362 [Indexed for MEDLINE]

2857. Auton Neurosci. 2012 Apr 3;167(1-2):70-4. doi: 10.1016/j.autneu.2011.11.001. Epub 2011 Nov 21.

Evaluation of various cardiac autonomic indices in patients with familial Mediterranean fever on colchicine treatment.

Canpolat U(1), Dural M, Aytemir K, Akdoğan A, Kaya EB, Sahiner L, Yalçın U, Canpolat AG, Calgüneri M, Kabakçi G, Tokgözoğlu L, Oto A.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is characterized by sporadic, acute attacks of fever and serositis. Cardiovascular involvement is one of the leading cause of morbidity and mortality among FMF patients. Herein, we aimed to evaluate cardiac autonomic functions in FMF patients without overt cardiac symptoms.

**METHODS:** We enrolled 38 patients (20 female; mean age  $34.4 \pm 10.2$  years) with FMF and 34 healthy subjects (18 female; mean age  $33.2 \pm 9.3$  years). All participants underwent 24-hour Holter recording. Heart rate recovery (HRR) indices were calculated by subtracting first, second, and third minute heart rates from maximal heart rate. All patients underwent heart rate variability (HRV), heart rate turbulence (HRT) and QT dispersion analysis. The mean FMF duration was  $9.8 \pm 4.2$  years.

**RESULTS:** Both groups were similar with regard to baseline characteristics. Mean HRR1 ( $p=0.001$ ), HRR2 ( $p=0.003$ ) and HRR3 ( $p<0.001$ ) were significantly lower in FMF group. SDNN (standard deviation of all NN intervals), SDANN (SD of the 5 min mean RR intervals), RMSSD (root square of successive differences in RR interval), and PNN50 (proportion of differences in successive NN intervals  $>50$  ms) and high-frequency (HF) components were significantly decreased, but low frequency (LF) and LF/HF were significantly higher in FMF patients. HRT onset and slope were significantly less negative in FMF patients. Also, QTd was significantly higher in FMF patients ( $p<0.001$ ).

**CONCLUSION:** Patients with FMF showed delayed recovery of heart rate and abnormal HRV and HRT parameters with respect to normal subjects. Cardiac autonomic functions might be involved in FMF patients even in patients without cardiac symptoms.

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DOI: 10.1016/j.autneu.2011.11.001

PMID: 22104493 [Indexed for MEDLINE]

2858. Am J Clin Pathol. 2011 Dec;136(6):903-12. doi: 10.1309/AJCPERI7LC4VNFYK.

Susac syndrome: an organ-specific autoimmune endotheliopathy syndrome associated with anti-endothelial cell antibodies.

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Susac syndrome (SS) is the triad of encephalopathy, branch retinal artery



occlusions (BRAOs), and hearing loss. Migraines may herald and accompany encephalopathy. Little is known about pathogenesis. Based on light microscopic findings in brain biopsy material analogous to anti-endothelial cell antibody (AECA)-mediated microvascular injury, we postulated that SS microangiopathy was attributable to AECAs. We examined serum samples from 11 patients with SS for AECAs; 9 were positive by indirect immunofluorescence and Western blot studies. A highly distinctive band on Western blots corresponding to a 50-kDa protein was observed in 8 positive SS samples; the other positive case exhibited specific reactivity with a protein band at 40 kDa. Of the 2 negative cases, 1 had been inactive since 1988; the other was an abortive variant characterized solely by BRAOs. There was enhanced surface binding of SS serum using live endothelial cell substrates compared with samples from healthy subjects. Additional serum samples from apparently healthy patients, 2 with atypical migraines, and patients with other forms of autoinflammatory disease did not show the distinctive band of immunoreactivity. SS is a distinct autoimmune endotheliopathy syndrome associated with AECAs; the antibody target seems specific in many cases and may be a disease biomarker. The exact role of AECAs in disease propagation remains unanswered.

DOI: 10.1309/AJCPER17LC4VNFYK

PMID: 22095376 [Indexed for MEDLINE]

2859. J Clin Rheumatol. 2011 Dec;17(8):432-5. doi: 10.1097/RHU.0b013e31823a55e5.

Leprosy initially misdiagnosed as sarcoidosis, adult-onset still disease, or autoinflammatory disease.

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Leprosy is a chronic granulomatous disease caused by *Mycobacterium leprae*. We describe the case of a 20-year-old man from India living in Italy since 2003, who presented with erythematous papules and nodules distributed on his arms, legs, and face in 2006. He also had episodes of high fever, polyarthrititis, and episcleritis. Sarcoidosis was suspected on the basis of elevated angiotensin-converting enzyme and bronchoalveolar lavage fluid, and the patient

was treated with corticosteroids for about a year. A flare of the disease occurred each time corticosteroid was tapered or suspended. An autoinflammatory disease was then suspected and treated with immunosuppressant. Only the third deep skin biopsy revealed the presence of *M. leprae*. The lack of clinical suspicion and the unfamiliarity with the histology of leprosy delayed diagnosis and treatment. Leprosy should be considered in the differential diagnoses of patients presenting with rheumatic and cutaneous manifestations especially when they come from countries where the disease is endemic.

DOI: 10.1097/RHU.0b013e31823a55e5

PMID: 22089994 [Indexed for MEDLINE]

2860. Curr Opin Rheumatol. 2012 Jan;24(1):103-12. doi: 10.1097/BOR.0b013e32834dd2d5.

Familial Mediterranean fever and related periodic fever syndromes/autoinflammatory diseases.

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**PURPOSE OF REVIEW:** The spectrum of periodic fever syndromes (PFS)/autoinflammation diseases is continuously expanding. This review provides an overview of the primary research and an update on the main clinical developments in these disorders published in the past 12-18 months.

**RECENT FINDINGS:** IL-1 $\beta$  is pivotal to the pathogenesis of most of the PFS. In familial Mediterranean fever (FMF) MEFV mutations lead to gain of pyrin function, resulting in inappropriate IL-1 $\beta$  release that is dependent on ASC but not the NLRP3 inflammasome. Anti-IL-1 therapy is effective in tumour necrosis factor receptor-associated periodic syndrome (TRAPS), whilst both spontaneous and pathogen-associated molecular patterns (PAMPs) induced IL-1 $\beta$  release have been demonstrated in NLRP12-associated periodic syndrome (NAPS12). Somatic NLRP3/CIAS1 mosaicism is a significant cause of cryopyrin-associated periodic syndromes (CAPS). Close connections have also been established between metabolic and inflammatory pathways. In TRAPS increased reactive oxygen species (ROS) of

mitochondrial origin leads to production of pro-inflammatory cytokines, whilst NLRP3 inflammasome activation in type 2 diabetes (T2D) is induced by oligomers of islet amyloid polypeptides (IAPP).

SUMMARY: Caspase 1 activation and IL-1 $\beta$  release is central to the pathogenesis of many autoinflammatory syndromes. This is supported by the effectiveness of anti-IL-1 biologics in treatment of these disorders.

DOI: 10.1097/BOR.0b013e32834dd2d5

PMID: 22089100 [Indexed for MEDLINE]

2861. Rheumatol Int. 2012 Nov;32(11):3559-63. doi: 10.1007/s00296-011-2251-x. Epub 2011 Nov 16.

Evaluation of the mean platelet volume in children with familial Mediterranean fever.

Arıca S(1), Ozer C, Arıca V, Karakuş A, Celik T, Güneşaçar R.

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Comment in

Rheumatol Int. 2013 Jun;33(6):1653.

Rheumatol Int. 2014 Aug;34(8):1185-6.

To evaluate the Mean Platelet Volume (MPV) levels in children diagnosed with familial Mediterranean fever (FMF), during attack and attack-free periods. The records of a total of 117 children with FMF, diagnosed using the Tel-Hashomer criteria, have been scanned. The study consisted of 53 patients during an attack (group 1), 64 patients in attack-free period (group 2), and 57 healthy controls (group 3). Erythrocyte sedimentation rate, C-reactive protein, white blood cell count, platelet count, and MPV levels were retrospectively recorded. The MPV and platelet values in FMF patients during attack (group 1) and FMF patients during attack-free periods (group 2) have been found to be significantly higher than those of the health control group (group 3). Positive correlation has been found between the MPV and platelet values in Group 1 and the disease's severity score ( $r = 0.224$ , and  $r = 0.268$ , respectively). Positive correlation ( $r = 0.528$ , and  $r$

= 0.485, respectively) has been also identified between MPV and blood platelet count in patients in Group 1 and 2. No correlation was found between the Colchicine treatment period and MPV ( $r = -0.005$ ). The MPV values in the complete group of FMF diagnosed children have been found to be much higher compared to those in healthy children. As a consequence, we consider the MPV value as a useful marker that demonstrates the risk of early stage atherosclerosis in children with FMF.

DOI: 10.1007/s00296-011-2251-x

PMID: 22086472 [Indexed for MEDLINE]

2862. Amyloid. 2011 Dec;18(4):206-10. doi: 10.3109/13506129.2011.616556.

Abnormal heart rate variability in AA amyloidosis of familial Mediterranean fever.

Nussinovitch U(1), Volovitz B, Nussinovitch M, Lidar M, Feld O, Nussinovitch N, Livneh A.

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**BACKGROUND:** A scarcity of data exists relating to the effect of amyloidosis of Familial Mediterranean fever (FMF) on the autonomic nervous system. Our aim was to further investigate the presence of dysautonomia in FMF-AA amyloidosis, using a comparative case series design.

**MATERIAL AND METHODS:** The study group consisted of 40 patients with FMF: 20 without co-morbidities or amyloidosis and 20 in various stages of renal amyloidosis. Time domain and power spectral analyses of heart rate dynamics were performed according to accepted procedures. Findings were compared with 20 healthy control subjects.

**RESULTS:** No statistically significant differences were found in any of the studied heart rate variability (HRV) parameters between patients with uncomplicated FMF and controls. In contrast, patients with progressive amyloidosis (post renal transplantation or on dialysis) had significantly lower HRV parameters compared to control subjects (i.e. mean low frequency power spectral components  $104.30 \text{ ms}^2$  vs.  $172.09 \text{ ms}^2$ ,  $p < 0.05$ , mean standard deviation of all normal RR intervals  $32.27 \text{ ms}$  vs.  $51.51 \text{ ms}$ ,  $p < 0.05$ , mean HRV triangular

index 9.08 vs. 15.82,  $p < 0.05$ ). The adjusted odds ratio was 14.5 (95%CI 1.21-165.03,  $p = 0.04$ ) for HRV triangular index lower than 12.2 in the progressive amyloidosis group, 41.24 (95%CI 1.81-938.68,  $p = 0.02$ ) for low frequency power spectral components values lower than 142.35 ms<sup>2</sup>, and 12.67 (95%CI 1.04-153.96,  $p = 0.04$ ) for standard deviation of all normal RR intervals values lower than 40.15 ms.

CONCLUSION: Amyloidosis of FMF, particularly at a progressive stage, is associated with HRV abnormalities suggestive of the presence of autonomic nervous system dysfunction.

DOI: 10.3109/13506129.2011.616556

PMID: 22080764 [Indexed for MEDLINE]

2863. Physiol Behav. 2012 Feb 1;105(3):835-40. doi: 10.1016/j.physbeh.2011.10.027. Epub 2011 Nov 3.

Social interaction with a rhythmic rat enhances the circadian pattern of the motor activity and temperature of LL-induced arrhythmic rats.

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Although light is the main factor that influences circadian rhythms, social interaction may also have a role on their regulation. Here, the influence of social interaction on rat circadian behavior was investigated, addressing the question of whether cohabitation would induce the appearance of a circadian rhythm in arrhythmic rats due to constant light. To this end, circadian rhythms of motor activity and body temperature of male and female LL-induced arrhythmic rats were studied before, during and after a 20-day period in which rats stayed in the same cage with a rat of the same sex but with stronger rhythm. Results showed that the manifestation of the circadian motor activity rhythm of LL-induced arrhythmic rats increased after cohabitation. In the case of the expression of the body temperature rhythm, there was a progressive daily increase in the power content of a daily 24 hour pattern throughout the cohabitation days, which remained when animals were again isolated. Thus, the presence of a rhythmic

rat increases the strength of the circadian behavior of rats showing a weak circadian rhythm.

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DOI: 10.1016/j.physbeh.2011.10.027

PMID: 22079195 [Indexed for MEDLINE]

2864. J Innate Immun. 2012;4(1):16-30. doi: 10.1159/000334247. Epub 2011 Nov 4.

Nucleotide-binding oligomerization domain-like receptors and inflammasomes in the pathogenesis of non-microbial inflammation and diseases.

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The nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) or nucleotide-binding domain leucine-rich repeat-containing family of genes plays an important role in the development of innate immune responses. Some family members are known to form multiprotein complexes known as inflammasomes that regulate the processing and secretion of proinflammatory mediators, such as interleukin-1 $\beta$  and interleukin-18. Activity of the inflammasome is triggered not only by microbial infection, but also by a wide range of both exogenous and endogenous noninfectious stimuli. Consequently, the dysregulation of inflammasome activity is associated with numerous proinflammatory, non-microbial human diseases. The discovery of NLRP3 gene mutations in autoinflammatory diseases such as Muckle-Wells syndrome has led to the association of NLRs in the pathogenesis of many non-microbial diseases that include arthritis, neurodegenerative disorders, metabolic disorders (obesity and diabetes), cardiovascular disease (atherosclerosis, myocardial infarction), inflammatory bowel disease, kidney disease and hypersensitivity dermatitis. A number of NLRs are also associated with human disease in the absence of inflammasome activity, suggesting additional roles for NLRs in the regulation of inflammation and disease. This review serves to provide a summary of NLR-associated diseases and, where possible, the

mechanisms behind the associations.

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DOI: 10.1159/000334247

PMID: 22067846 [Indexed for MEDLINE]

2865. *Cardiol Young*. 2012 Aug;22(4):404-9. doi: 10.1017/S1047951111001867. Epub 2011 Nov 9.

QT dispersion and cardiac involvement in children with Familial Mediterranean fever.

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Familial Mediterranean fever is a hereditary disease characterised by recurrent and self-terminated attacks of fever and polyserositis. An earlier study found that adult patients of Familial Mediterranean fever had an abnormally longer QT dispersion and corrected QT dispersion, markers for ventricular arrhythmogenicity. QT dispersion is a simple non-invasive arrhythmogenic marker that can be used to assess homogeneity of cardiac repolarisation; however, it has not been studied in children with Familial Mediterranean fever before. The aim of this study was to assess QT dispersion and corrected QT dispersion, and their relationship with systolic and diastolic function of the left ventricle in a group of children with Familial Mediterranean fever. We performed electrocardiography and Doppler echocardiography on patients and controls. Maximum QT, minimum QT, QT dispersion, corrected QT, maximum corrected QT, minimum corrected QT, and corrected QT dispersion intervals were measured from standard 12-lead electrocardiography. No statistically significant differences were found between the groups in QT dispersion, corrected QT dispersion, and systolic-diastolic function of the left ventricle parameters. During the 12 months of follow-up, no ventricular arrhythmias were documented in either group.

DOI: 10.1017/S1047951111001867

PMID: 22067271 [Indexed for MEDLINE]

2866. Clin Exp Immunol. 2011 Dec;166(3):338-45. doi: 10.1111/j.1365-2249.2011.04484.x.

Role of tumour necrosis factor (TNF)- $\alpha$  and TNFRSF1A R92Q mutation in the pathogenesis of TNF receptor-associated periodic syndrome and multiple sclerosis.

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It has long been known that tumour necrosis factor (TNF)/TNFRSF1A signalling is involved in the pathophysiology of multiple sclerosis (MS). Different genetic and clinical findings over the last few years have generated renewed interest in this relationship. This paper provides an update on these recent findings. Genome-wide association studies have identified the R92Q mutation in the TNFRSF1A gene as a genetic risk factor for MS (odds ratio 1.6). This allele, which is also common in the general population and in other inflammatory conditions, therefore only implies a modest risk for MS and provides yet another piece of the puzzle that defines the multiple genetic risk factors for this disease. TNFRSF1A mutations have been associated with an autoinflammatory disease known as TNF receptor-associated periodic syndrome (TRAPS). Clinical observations have identified a group of MS patients carrying the R92Q mutation who have additional TRAPS symptoms. Hypothetically, the co-existence of MS and TRAPS or a co-morbidity relationship between the two could be mediated by this mutation. The TNFRSF1A R92Q mutation behaves as a genetic risk factor for MS and other inflammatory diseases, including TRAPS. Nevertheless, this mutation does not appear to be a severity marker of the disease, neither modifying the clinical progression of MS nor its therapeutic response. An alteration in TNF/TNFRSF1A signalling may increase proinflammatory signals; the final clinical phenotype may possibly be determined by other genetic or environmental modifying factors that have not yet been identified.



for Immunology.

DOI: 10.1111/j.1365-2249.2011.04484.x

PMCID: PMC3232381

PMID: 22059991 [Indexed for MEDLINE]

2867. Clin Rheumatol. 2012 Mar;31(3):493-501. doi: 10.1007/s10067-011-1876-1. Epub 2011 Nov 5.

Association of clinical and genetical features in FMF with focus on MEFV strip assay sensitivity in 452 children from western Anatolia, Turkey.

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The aim of this study was to determine the relationship between clinical findings and the most common mutated alleles of MEFV gene in a childhood population and to determine the sensitivity of the 12-mutation-strip assay test in familial Mediterranean fever (FMF). Records of 452 FMF children living in western Anatolia, Turkey, ( $12.3 \pm 4.7$  years mean) were retrospectively reviewed. Of the 408 patients who met the Tel-Hashomer criteria, 364 were classified into two main groups (two-mutant/one-mutant allele) either of which had three subgroups. The two-mutant allele frequency was 51% and one-mutant allele 38%; 1% had complex-mutant alleles and 10% no mutant-alleles. The mean severity score was  $8.3 \pm 2.5$ . Most common clinical features were fever (81.9%), abdominal pain (86.3%) and myalgia (58.8%), and the least common ones: diarrhea (1.7%), protracted febrile myalgia (1.2%) and acute orchitis (1.5%). We detected 33 different genotypes of the MEFV gene: the most common mutant allele was M694V followed by symptomatic allele mutation of E148Q. Although not significantly associated with clinical findings, P369S mutation was not rare (7.5%). Phenotype-genotype correlation revealed that patients with two-allele mutations had more severe clinical presentation and high constipation rate (22.5%); 32.6% of patients with M694V/M694V had splenomegaly. Acute orchitis and protracted febrile myalgia as rare clinical findings were more common in M694V homozygotes.

Comparisons of clinical findings among patients with one-mutation allele were made for the first time, but no significant association was found. Positive predictive value of strip assay screening for 12 mutations was recorded as 89%. We suggest that whole sequence analysis for supportive diagnosis of FMF should be performed for selected patients only.

DOI: 10.1007/s10067-011-1876-1

PMID: 22057232 [Indexed for MEDLINE]

2868. Rheumatol Int. 2012 Nov;32(11):3443-7. doi: 10.1007/s00296-011-2206-2. Epub 2011 Nov 6.

The value of procalcitonin measurements in children with familial Mediterranean fever.

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It is well known that the serum procalcitonin (PCT) levels increase in severe bacterial infections. However, there is little information about the levels of PCT in diverse diseases except mainly the infectious diseases. The aim of this study was to investigate the progress of serum levels of PCT together with traditional acute phase reactants in children with familial Mediterranean fever (FMF) during the attack and attack-free periods and to test whether PCT could help to diagnose the attack in FMF patients. The study group comprised 21 FMF patients (mean age  $10 \pm 4.6$  years) and 19 healthy controls (mean age  $10.6 \pm 4.2$  years). Serum levels of PCT and traditional acute phase reactants were measured during the attack and attack-free periods. Blood samples were obtained within the first 6-24 h of the attack period, 7 days later, and at least 2 months after the attack. Traditional acute phase reactants (hs-CRP, ESR, and fibrinogen) during the attack period were significantly higher than the attack-free levels and controls. PCT levels of the FMF patients during the attack period were also significantly higher than the attack-free and control group levels (median values, 0.044 ng/ml vs. 0.028 ng/ml and 0.031 ng/ml,  $P = 0.04$ , respectively). Although this difference was statistically significant ( $P = 0.04$ ), median PCT

values of the attack, attack-free period, and healthy subjects were lower than 0.05 ng/ml. As a result, these findings suggested that PCT levels were not conspicuously affected from inflammation and could not be used as a descriptive marker for attack in FMF patients.

DOI: 10.1007/s00296-011-2206-2

PMID: 22057145 [Indexed for MEDLINE]

2869. Rheumatol Int. 2012 Nov;32(11):3421-4. doi: 10.1007/s00296-011-2181-7. Epub 2011 Nov 6.

Is there a real adrenal axis dysfunction in patients with amyloidosis associated with familial Mediterranean fever?

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Systemic amyloidosis with AA-type amyloid deposition is the major complication of FMF, leading to end stage renal disease. There is no clear data on the prevalence of adrenal involvement in patients with FMF amyloidosis. The aim of this study is to determine the adrenal axis function in patients FMF with amyloidosis. Twenty patients with FMF with amyloidosis (F/M: 10/10, mean age;  $38 \pm 11$  SD years), twenty without amyloidosis (F/M: 14/6, mean age  $32 \pm 10$  years), and healthy controls (F/M: 12/8, mean age:  $30 \pm 7.6$  SD years) were recruited. A dose of 250 mg tetracosactide (Synacthen) was then administered intravenously and further blood samples collected 30 and 60 min later. Blood samples were separated and collected at 4°C, and serum cortisol levels were measured. A normal cortisol response to Synacthen was defined as a post-stimulation peak cortisol value of  $>18$  mg/d either at 30 or 60 min. sample. The mean disease duration was  $8.8 \pm 6$  SD years, (range, 2-21) in FMF patients without amyloidosis compared to  $16 \pm 9.5$  years (range, 0-30) in FMF with amyloidosis ( $P = 0.001$ ). The cortisol concentrations increased significantly at 30 and 60 min compared to baseline after injection of synacthen in all groups. There were no statistically significant differences found among three groups, for basal, 30 and 60 min for cortisol levels ( $P = 0.154$ ). FMF patients with amyloidosis do not exhibit overt adrenal insufficiency even though their basal cortisol levels were mildly lower.

DOI: 10.1007/s00296-011-2181-7  
PMID: 22057137 [Indexed for MEDLINE]

2870. Curr Opin Pediatr. 2011 Dec;23(6):640-6. doi: 10.1097/MOP.0b013e32834cba24.

Update on the pathogenesis and treatment of systemic idiopathic arthritis.

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**PURPOSE OF REVIEW:** Systemic juvenile idiopathic arthritis (SJIA) is an inflammatory condition characterized by fever, lymphadenopathy, rash, arthritis, and serositis. Although the ultimate cause of this disorder remains elusive, recent work defining cytokine effector mechanisms has led to a new treatment paradigm for this condition. In this review, we describe the recent immunological reclassification of SJIA as an autoinflammatory disorder as well as detailing the dramatic changes in its treatment.

**RECENT FINDINGS:** SJIA is an autoinflammatory disorder in which defects of innate immune system pathways lead to significant inflammation. Recent studies of the pathophysiology, as well as successful treatment trials, have established interleukin-1 $\beta$  (IL-1 $\beta$ ) and IL-6 as key cytokines in the pathogenesis of this condition. As a result, their inhibition has become the centerpiece of the current SJIA treatment paradigm.

**SUMMARY:** There has been a major shift away from the traditional treatments of SJIA towards therapeutics that inhibit IL-1 $\beta$  and IL-6. In fact, the IL-1 blocker anakinra is now regarded as standard of care for SJIA patients with systemic symptoms, while the IL-6 inhibitor tocilizumab shows great potential. Future research holds promise for the development of more efficient cytokine inhibition as well as a more comprehensive knowledge of the innate cytokine networks in this disease.

DOI: 10.1097/MOP.0b013e32834cba24  
PMCID: PMC3315376  
PMID: 22045308 [Indexed for MEDLINE]

2871. Nihon Rinsho Meneki Gakkai Kaishi. 2011;34(5):408-19.

[Behçet's disease from the aspect of autoinflammatory disease].

[Article in Japanese]

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Behçet's disease is a systemic inflammatory disease presented with recurrent oral aphtha, cutaneous manifestations, uveitis, and genital ulcer. The etiology of Behçet's disease is still unknown, but both genetic background and environmental factors are thought to be important in the pathogenesis of Behçet's disease. Behçet's disease has long been regarded as a Th1 type autoimmune disease, because of the association with HLA-B51 and hyperreactivity against streptococcal antigen. However, it was recently found that Behçet's disease and autoinflammatory diseases share several clinical features. Furthermore, increased activity of neutrophils and elevated levels of interleukin-1 $\beta$  are observed in both Behçet's disease and autoinflammatory diseases. The relationship between Behçet's disease and autoinflammatory diseases, especially Familial Mediterranean fever, is speculated, because both diseases are prevalent in the Mediterranean basin and treated with colchicine. Genetic researches on Behçet's disease and FMF suggest that the MEFV gene mutated in Familial Mediterranean fever is a probable susceptibility gene for Behçet's disease. Although many observations suggest that Behçet's disease might be autoinflammatory, there is evidence implying autoimmune pathogenesis of Behçet's disease. For example, some symptoms of Behçet's disease is treated with T cell suppressing agents. Recent data suggest that a novel subset of T cells, Th17, plays a crucial role in pathogenesis of Behçet's disease, and genome-wide association researches verified it. IL-17, which is the secreted from of Th17 activates neutrophils. Hence, IL-17 might cause the symptoms resembling autoinflammatory diseases. Recently, Anti-IL-1 treatment proved to be effective and other susceptibility genes are being investigated. These new findings will shed light on the long-sought pathogenesis of Behçet's disease.

PMID: 22041429 [Indexed for MEDLINE]

2872. Nihon Rinsho Meneki Gakkai Kaishi. 2011;34(5):401-7.

[Periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome].

[Article in Japanese]

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Periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome is a non-hereditary autoinflammatory disease, characterized by relatively regular recurrence of febrile episodes of 3-6 days duration, accompanied by aphthous stomatitis, pharyngitis/tonsillitis, and/or cervical adenitis. It is considered to be the most common periodic fever syndrome in Japan. Although no responsible gene is identified, some genetic factors may confer the predisposition toward this disorder. Important differential diagnosis includes hereditary periodic syndromes and cyclic neutropenia. Although its etiology is still to be elucidated, a recent study suggested an environmentally triggered activation of complement and IL-1 $\beta$ /IL-18 during PFAPA syndrome flares, with induction of Th1-chemokines and subsequent retention of activated T cells in peripheral tissues. This study also demonstrated the possibility that IP-10/CXCL10 might serve as a potential biomarker to differentiate PFAPA syndrome from other periodic fever syndromes. Therapeutic strategy for PFAPA syndrome has not been well established. Recent advances in the understating of etiology and pathophysiology might lead to re-evaluation of recent therapeutic options and/or development of new treatment.

PMID: 22041428 [Indexed for MEDLINE]

2873. Nihon Rinsho Meneki Gakkai Kaishi. 2011;34(5):388-400.

[Nakajo-Nishimura syndrome].

[Article in Japanese]

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Nakajo-Nishimura syndrome (NNS) (MIM256040, ORPHA2615) is a distinct inherited inflammatory and wasting disease, which usually begins in early infancy with a pernio-like rash. The patients develop periodic high fever and nodular erythema-like eruptions, and gradually progress lipomuscular atrophy in the upper body, mainly the face and the upper extremities, to show the characteristic long clubbed fingers with joint contractures. So far about 30 cases have been reported from Kansai, especially Wakayama and Osaka, Tohoku and Kanto areas. In addition to 10 cases in Kansai area, which have been confirmed to be alive by national surveillance, an infant case has newly been discovered in Wakayama and more cases will be added. Although cause of the disease has long been undefined, a homozygous mutation of the PSMB8 gene, which encodes the  $\beta 5i$  subunit of immunoproteasome, has been identified by homozygosity mapping. By analyses of the patients-derived cells and tissues, it has been suggested that accumulation of ubiquitinated and oxidated proteins due to deficiency of proteasome activities cause hyperactivation of p38 MAPK and overproduction of IL-6. Similar diseases with PSMB8 mutations have recently been reported from Europe and the U.S.A., and therefore, it is becoming clear that proteasome deficiency syndromes are globally distributed as a new category of the autoinflammatory diseases.

PMID: 22041427 [Indexed for MEDLINE]

2874. Nihon Rinsho Meneki Gakkai Kaishi. 2011;34(5):382-7.

[Hyperimmunoglobulinemia D and periodic fever syndrome].

[Article in Japanese]

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Hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) is inherited autoinflammatory syndrome caused by deficiency of the mevalonate kinase (MK), which is involved in metabolism of cholesterol. The disease is characterized as periodic fever from early infancy accompanied by elevated serum C-reactive protein. Since clinical symptoms such as abdominal symptom, skin rash, and arthritis are common to other autoinflammatory disease, the diagnosis of HIDS during clinical work is difficult for the physicians without suspicion of HIDS for infants suffering from fever of unknown origin. Moreover, serum IgD levels are not high during infancy conflicting to the name of the disease, which is often misunderstood in the clinicians. Thus, the diagnosis of HIDS in Japan is bothering, depending on the lack of correct recognition of the disease and on the lack of commercially available examination for the disease. It is important for clinicians, especially pediatricians to update current knowledge about HIDS and to learn the appropriate way to the definitive diagnosis of HIDS, because HIDS patients exist also in Japan and the specific therapies for HIDS would be developed in the near future.

PMID: 22041426 [Indexed for MEDLINE]

2875. Nihon Rinsho Meneki Gakkai Kaishi. 2011;34(5):369-77.

[CAPS: cryopyrin-associated periodic syndrome].

[Article in Japanese]

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Cryopyrin-associated periodic syndrome (CAPS) is an autoinflammatory syndrome caused by heterozygous mutations of NLRP3 gene. CAPS consists of three



phenotypically similar but distinct syndromes: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome and CINCA syndrome. Among them, FCAS shows the mildest phenotype while CINCA is the severest. Common symptoms include sporadic or cold-induced nonpruritic urticarial rash and fever. Severe cases suffers from deafness, meningitis, articular contracture and secondary amyloidosis. Gain-of-function mutations of NLRP3 causes excessive production of a potent proinflammatory cytokine IL-1 $\beta$ , thereby evokes autoinflammatory symptoms of CAPS. Recent advances of anti-IL-1 therapy dramatically improved the prognosis of CAPS. Currently three anti-IL-1 medicines are available, and all of them significantly improved clinical symptoms of CAPS patients. Although long-term observation is still needed, the molecular-targeted therapy has opened up a new opportunity for managing CAPS.

PMID: 22041424 [Indexed for MEDLINE]

2876. Nihon Rinsho Meneki Gakkai Kaishi. 2011;34(5):361-8.

[Progress in classification and treatment for TNF receptor-associated periodic syndrome].

[Article in Japanese]

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TNF receptor-associated periodic syndrome (TRAPS) is an autosomal dominant autoinflammatory disorder characterized by recurrent febrile attacks. TRAPS is associated with mutation in the gene encoding TNF Receptor I (TNFRI) and seven mutations have been reported in Japan. Molecular modeling experiments indicate that the mutant TNFRI accumulates intracellularly in the endoplasmic reticulum due to misfolding and activates MAP kinase (MAPK) through induction of mitochondrial reactive oxygen species production. MAPK activation is further enhanced by the stimulation through toll-like receptor, resulting in the enhanced proinflammatory cytokine production. Febrile attacks last 21 days on average and

occur every one to several months. Myalgia, erythematous macular rash, abdominal pain, conjunctivitis, periorbital edema, chest pain and arthralgia are commonly seen during the attacks. Glucocorticoid is effective in decreasing the severity and duration of the febrile attacks. Soluble TNF receptor etanercept, IL-1 receptor antagonist Anakinra(TM) and IL-6 receptor antagonist tocilizumab are effective in some patients. Japanese study group of TRAPS conducted national survey to make new diagnostic criteria in 2010.

PMID: 22041423 [Indexed for MEDLINE]

2877. Nihon Rinsho Meneki Gakkai Kaishi. 2011;34(5):355-60.

[Clinical aspects of Familial Mediterranean fever].

[Article in Japanese]

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Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease characterized by recurrent and short duration (1-3 days) of fever, and serositis. Based on the nationwide survey of FMF in Japan, the estimated number of Japanese FMF patients is about three hundred. High grade fever was observed in 95.5%, chest pain in 35.8% abdominal pain in 62.7% and arthritis in 31.3% among Japanese FMF patients. AA amyloidosis was confirmed in 5 patients (3.7%). Colchicine was effective in 91.8% of Japanese FMF patients. A significant number of FMF patients exist in Japan, and early diagnosis and treatments should be required to prevent AA amyloidosis.

PMID: 22041422 [Indexed for MEDLINE]

2878. Nihon Rinsho Meneki Gakkai Kaishi. 2011;34(5):346-54.

["The inflammasomes"].

[Article in Japanese]

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Inflammation is a host adaptational response to cell injury caused by various exogenous and endogenous stimuli. IL-1 $\beta$ , which is an important proinflammatory cytokine secreted at the site of cellular injury, plays an important role in inflammation. Inflammasome is an intracellular multi-protein complex that mediates caspase-1-dependent processing of IL-1 $\beta$ . In this review, inflammasome function and its dysregulation are discussed in relation to autoinflammatory diseases.

PMID: 22041421 [Indexed for MEDLINE]

2879. Nihon Rinsho Meneki Gakkai Kaishi. 2011;34(5):329-45.

[Pattern recognition receptors].

[Article in Japanese]

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Immunity is based on self/nonself discrimination. In vertebrates, two major systems, innate and adaptive immune systems, constitute host defense against invading microbes. Adaptive immunity is characterized by specific immune responses through B- or T-cell antigen receptors that are generated by somatic recombination, whereas nonspecific responses to microbes had been accentuated in

innate immunity. However, the discovery of pattern recognition receptors (PRRs) that are encoded in the germ-line, including Toll-like receptors, RIG-I-like receptors, NOD-like receptors and AIM2-like receptors, advanced our understanding of a mechanism for innate immune recognition. These types of PRR recognize pathogen- or damage-associated molecular patterns (PAMPs or DAMPs) during infection or tissue damage, and commonly evoke the downstream gene induction programme, such as expression of type I interferons, inflammatory cytokines and chemokines. Dysregulation of PRR-triggered signal activation leads to pathologic inflammatory responses. In this regard, it has been shown that many of "autoinflammatory diseases", recently defined clinical entity, have putatively causative mutations in the genes that encode PRRs or their signaling mediators. In this review article, we describe recent overview of PRRs as innate sensors and update knowledge of "autoinflammatory diseases" particularly by focusing on their association with innate signaling.

PMID: 22041420 [Indexed for MEDLINE]

2880. Clin Exp Rheumatol. 2011 Jul-Aug;29(4 Suppl 67):S77-86. Epub 2011 Sep 27.

Therapeutic approach to familial Mediterranean fever: a review update.

Ozturk MA(1), Kanbay M, Kasapoglu B, Onat AM, Guz G, Furst DE, Ben-Chetrit E.

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Erratum in

Clin Exp Rheumatol. 2012 Jan-Feb;30(1):146.

Familial Mediterranean fever (FMF) is a hereditary disorder characterised by recurrent attacks of fever with peritonitis or pleuritis, arthritis, myalgia or erysipelas-like skin lesions. The continuous inflammation in FMF is associated with increased serum amyloid A (SAA) protein which may lead to secondary amyloidosis and deposition of this insoluble protein in the kidney, gut, spleen, liver, heart etc. Therefore, treatment of patients with FMF is beneficial not only for the prevention of the acute attacks but also for improving their

prognosis. In the present review we summarise the medical literature concerning FMF treatment, including new therapeutic agents and management of colchicine-resistant patients. Three electronic databases (MEDLINE, EMBASE, and the Cochrane Library) were searched from 1 January 1960 to 28 February 2010 for any therapeutic approach to FMF, with MeSH headings and text words (Familial Mediterranean Fever, FMF treatment, colchicine, infliximab, anakinra, SSRI). In conclusion, colchicine remains the mainstay therapeutic option in FMF. It is effective in various manifestations of the disease such as fever, peritonitis and pleuritis. It prevents the development of amyloidosis. It is safe in humans regarding fertility, and can be used during pregnancy and nursing. Dose adjustment should be made in patients with renal or hepatic failure. It is less effective in arthritis or myalgia, requiring additional treatment with NSAIDs and steroids. In the few cases where FMF is resistant to colchicine other measures, including corticosteroids, non-biological and biological DMARDs, interferon alpha and SSRIs should be employed.

PMID: 21968242 [Indexed for MEDLINE]

2881. Clin Exp Rheumatol. 2011 Jul-Aug;29(4 Suppl 67):S44-6. Epub 2011 Sep 27.

The frequency of familial Mediterranean fever in an emergency unit.

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Approximately 90% of patients with familial Mediterranean fever (FMF) complain of recurrent attacks of fever and abdominal pain of various severities. Prior to the diagnosis of FMF, the majority of patients are admitted to emergency units with a suspicion of acute abdomen pain and at least half of them undergo unnecessary abdominal interventions. The purpose of this study is to determine the frequency of FMF among the patients who are admitted to emergency units for acute abdominal pain. One hundred consecutive patients who were admitted to an emergency unit in Istanbul, Turkey, with acute abdominal pain were screened for FMF. When the definite cases were considered, a frequency of 2% was encountered which was

significantly high compared to the frequency of FMF in Turkey. Physicians working in emergency units should include FMF in their differential diagnosis list when evaluating a patient with acute abdominal pain, especially in countries where the disease is prevalent.

PMID: 21968235 [Indexed for MEDLINE]

2882. Clin Exp Rheumatol. 2011 Jul-Aug;29(4 Suppl 67):S87-90. Epub 2011 Sep 27.

Familial Mediterranean fever in small children in Turkey.

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**OBJECTIVES:** Familial Mediterranean fever (FMF) is an autosomal recessive disease, characterised by recurrent, self limited attacks of fever with serositis. The aim of our study was to describe the demographic, clinical and genetic features of FMF patients who had early disease onset and to compare them with late onset patients. Our second aim was to investigate the factors associated with delay in diagnosis.

**METHODS:** The study group consisted of recently diagnosed FMF patients who came to routine follow-up visits between January and July 2009. Patients were divided into two groups according to age of disease onset (Group I:  $\leq 3$  years of age; Group II:  $>3$  years of age). In the second part, patients were analysed according to the duration of delay in diagnosis.

**RESULTS:** There were 83 patients in group I and 73 patients in Group II. Median delay in diagnosis was 4 years in Group I and 2 years in Group II ( $p<0.001$ ). The presence of M694V mutation was more frequent in Group I (81%) as compared to Group II (65%), ( $p=0.034$ ). Mean attack Hb was lower ( $p<0.01$ ) and mean attack leukocyte count was higher ( $p=0.017$ ) in Group I. Final colchicine dosages were higher in Group I as compared to Group II. There was a statistically significant negative correlation between the age at disease onset and period of delay in diagnosis ( $p<0.001$ ).

**CONCLUSIONS:** This study suggests that FMF patients with early disease onset have

more severe disease. Moreover, the smaller the age of disease onset, the more likely their diagnoses are delayed.

PMID: 21813071 [Indexed for MEDLINE]

2883. Clin Exp Rheumatol. 2011 Jul-Aug;29(4 Suppl 67):S24-7. Epub 2011 Sep 27.

MEFV, TNFRSF1A and CARD15 mutation analysis in Behçet's disease.

Baruch Y(1), Dagan E, Rosner I, Fiorilli M, Gershoni-Baruch R, Rozenbaum M.

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**OBJECTIVES:** Given the pathological similarities between Behçet's disease (BD), Familial Mediterranean fever (FMF), TNF receptor-associated periodic syndrome (TRAPS) and Crohn's disease (CD) we evaluated the frequency of mutations and polymorphisms in MEFV, TNFRSF1A and CARD15 in Israeli BD patients of either Jewish or Arab descent.

**METHODS:** Fifty-four BD patients (11 Jews and 43 Arabs), evaluated with respect to the entire spectrum of BD disease manifestations, were granted a systemic severity score for BD. An association between BD manifestations and MEFV, TNFRSF1A and CARD15 variants was analysed.

**RESULTS:** Twelve patients (20.7%) displayed a single MEFV mutation and four patients (7.4%) had two mutated FMF alleles. Two patients (3.8%) carried a CARD15 variation and none carried a TNFRSF1A polymorphism. The frequency and distribution of mutated alleles between patients and controls was comparable ( $p=0.27$ ). No statistically significant differences between carriers and non-carriers with respect to disease manifestations and severity score were calculated. Arab patients were diagnosed earlier than Jewish patients ( $25.8\pm 11.6$  and  $37.2\pm 10.7$ , respectively,  $p=0.06$ ).

**CONCLUSIONS:** The overall MEFV high carrier frequency in our cohort of BD patients seems to be attributed to their Mediterranean extraction rather than related to BD. The propensity of Arab patients (79.6%) in a cohort of BD patients from northern Israel is highlighted in face of their proportion (20%) in the general population lending further support to arguments that favour a genetic component

for BD.

PMID: 21385537 [Indexed for MEDLINE]

2884. Rheumatology (Oxford). 2012 Jan;51(1):196-9. doi: 10.1093/rheumatology/ker341. Epub 2011 Oct 27.

Inflammatory cytokine expression in the skin lesions of tumour necrosis factor receptor-associated periodic syndrome.

Ohmori S, Hino R, Kobayashi M, Nakamura M, Tokura Y.

DOI: 10.1093/rheumatology/ker341

PMID: 22039228 [Indexed for MEDLINE]

2885. Rheumatol Int. 2012 Oct;32(10):3253-60. Epub 2011 Oct 30.

Incidence and clinical features of hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) and spectrum of mevalonate kinase (MVK) mutations in German children.

Lainka E(1), Neudorf U, Lohse P, Timmann C, Bielak M, Stojanov S, Huss K, von Kries R, Niehues T.

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Autoinflammatory diseases (AIDs) are characterized by recurrent, self-limiting systemic inflammation. Disorders include hereditary recurrent fever (HRF) syndromes such as hyperimmunoglobulinemia D and periodic fever syndrome (HIDS). To determine the incidence of HIDS and report clinical and genetic characteristics together with the underlying MVK genotypes in German children, a prospective active surveillance was conducted in Germany during a period of 3 years. Monthly inquiries were sent to 370 children's hospitals by the German Paediatric Surveillance Unit (Clinic-ESPED, n1) and to two laboratories



(Laboratory-ESPED, n2) performing genetic analyses. Inclusion criteria were a MVK mutation-positive patient  $\leq 16$  years of age with more than three self-limiting episodes of fever  $>38.5^{\circ}\text{C}$  associated with increased inflammation markers. Clinical, epidemiological, and genetic data were assessed via questionnaires. Eight out of 16 patients were identified in Clinic-ESPED (n1) and 15 of 16 in Laboratory-ESPED (n2). Clinical and laboratory surveys overlapped in 7 of 16 cases. Incidence of HIDS was estimated to be 0.39 (95% CI: 0.22, 0.64) per 10(6) person-years. HIDS symptoms generally started in infancy with recurrent fever episodes lasting 3-12 (median, 4.5) days and recurring every 1-12 weeks. Fever was accompanied by abdominal pain, vomiting, diarrhea, cervical lymphadenopathy, and sometimes by headache, skin and joint symptoms. The patients carried 11 different MVK mutations mostly in compound heterozygosity (75%, 12 out of 16). The most frequent mutation was p.Val377Ile (81%, 13 out of 16). In Germany, the incidence of HIDS is very low with 0.39 per 10(6) person-years.

DOI: 10.1007/s00296-011-2180-8

PMID: 22038276 [Indexed for MEDLINE]

2886. Gene. 2012 Jan 15;492(1):285-9. doi: 10.1016/j.gene.2011.10.012. Epub 2011 Oct 13.

Homozygous M694V as a risk factor for amyloidosis in Turkish FMF patients.

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Secondary amyloidosis is the most severe complication of familial Mediterranean fever (FMF). Since the M694V mutation was associated with clinical severity, it was expected to be associated with amyloidosis as well. However, a number of contradicting reports have been published, especially pertinent to Turkish patients nearly 10 years ago. The aim of this study was to analyze recent data regarding the association between M694V mutation and amyloidosis among FMF patients in Turkey. We conducted a comprehensive review of the literature regarding the role of M694V mutation in the development of amyloidosis secondary to FMF. Twenty-seven papers from 20 centers including 3505 Turkish subjects were

reviewed. Four-hundred patients had amyloidosis and homozygous M694V was detected in 189 (47%) of the 400 amyloidotic patients which was significantly higher than that in the FMF patients not developing amyloidosis ( $p < 0.0001$ ). In the presented analysis we were able to reach a patient number of 400 which is much higher than all those published hitherto. Our findings confirmed that homozygous M694V is associated with amyloidosis in the Turkish population as well similar to Armenia, Israel, and Arabian countries. The necessity to treat asymptomatic or mildly symptomatic FMF patients with this genotype, even in countries where amyloidosis is rare, should be considered carefully.

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DOI: 10.1016/j.gene.2011.10.012

PMID: 22037353 [Indexed for MEDLINE]

2887. Med Clin (Barc). 2012 Feb 4;138(2):64-8. doi: 10.1016/j.medcli.2011.07.018. Epub 2011 Oct 28.

[PFAPA syndrome: study of 10 cases].

[Article in Spanish]

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**BACKGROUND AND OBJECTIVES:** «PFAPA syndrome» is an autoinflammatory entity consisting of periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis. Its etiology is unknown although a dysregulation in the control of the autoinflammatory response seems to play a role. Although a genetic origin is suspected, no specific mutation has been determined yet. Corticosteroids are the mainstay of the treatment during the acute attacks. However, in long-term follow-up the role of tonsillectomy is controversial.

**PATIENTS AND METHODS:** A retrospective study of the pediatric cases diagnosed with the PFAPA syndrome was performed in our center during the last 4 years.

**RESULTS:** Ten patients were diagnosed with the syndrome who received corticosteroids as the only treatment with improvement and favourable prognosis.

**CONCLUSION:** PFAPA syndrome is the most common periodic fever disorder described in childhood whose genetic background has not been yet clarified. Our contribution with 10 patients further supports the common existence of this entity and the need to keep it in mind when having recurrent fevers.

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DOI: 10.1016/j.medcli.2011.07.018

PMID: 22036463 [Indexed for MEDLINE]

2888. Clin Exp Rheumatol. 2011 Nov-Dec;29(6):1040-3. Epub 2011 Dec 22.

Mutation screening of the IL-1 receptor antagonist gene in chronic non-bacterial osteomyelitis of childhood and adolescence.

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**OBJECTIVES:** Chronic non-bacterial osteomyelitis CNO is an inflammatory disorder of the musculoskeletal system with unknown etiology. In addition to bone inflammation, patients may present with inflammatory involvement of other tissues including, e.g., skin. Recently, a novel syndrome due to deficiency of interleukin-1 receptor antagonist (IL1RN), DIRA has been identified. Clinically the syndrome is characterized by neonatal onset of pustular dermatosis, periostitis and chronic sterile multifocal osteomyelitis, strongly resembling CNO. Homozygous mutations of IL1RN have been identified and resulted in a truncated protein that is not secreted, hence leaving the action of interleukin-1 unopposed.

**METHODS:** Because of similar clinical, radiological and histological features of CNO and DIRA, we hypothesized that both disorders might share a common autoinflammatory process. Thus, we searched for the presence of mutations in the interleukin-1 receptor antagonist gene in 60 patients diagnosed with CNO.

**RESULTS:** In one patient with chronic multifocal osteomyelitis a heterozygous missense variant: c.281G>T (p.Cys94Phe) was detected. In the other patients only

frequent polymorphisms were found.

CONCLUSIONS: Our findings were not able to confirm mutations in IL1RN being an important contributing factor to the pathogenesis of CNO.

PMID: 22032624 [Indexed for MEDLINE]

2889. J Pediatr Hematol Oncol. 2012 Mar;34(2):162. doi: 10.1097/MPH.0b013e31822031b1.

Leucopenia resolved with colchicine in familial mediterranean Fever.

Sakallioglu O.

DOI: 10.1097/MPH.0b013e31822031b1

PMID: 22031120 [Indexed for MEDLINE]

2890. Genet Couns. 2011;22(3):309-12.

A case with multiple sclerosis and familial Mediterranean fever.

Sayin R, Alpayci M, Soyoral YU.

PMID: 22029173 [Indexed for MEDLINE]

2891. Autoimmun Rev. 2012 Mar;11(5):348-56. doi: 10.1016/j.autrev.2011.10.008. Epub 2011 Oct 17.

The fresco of autoinflammatory diseases from the pediatric perspective.

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Autoinflammatory diseases are genetic or acquired clinical entities globally caused by the aberrant release of the proinflammatory cytokine interleukin-1 and mostly characterized by recurrent spontaneous inflammatory events which do not produce antigen-specific T cells or autoantibodies. Within the past decade, the list of autoinflammatory diseases has included cryopyrin-associated periodic syndromes, familial Mediterranean fever, mevalonate kinase deficiency, tumor necrosis factor receptor-associated periodic syndrome, hereditary pyogenic disorders, pediatric granulomatous autoinflammatory diseases, idiopathic febrile syndromes, complement dysregulation syndromes and Behçet's disease. Most of these conditions interact with the inflammasomes, intracellular molecular complexes coordinating the phylogenetically ancient response of the innate immune system. The pathogenetic mechanisms of these diseases have shown the evidence of disrupted interleukin-1 signaling for most of them and allowed to locate interleukin-1 as an attractive therapeutic target. The whole fresco of autoinflammatory diseases in pediatrics will be discussed in this review with the aim of establishing both diagnostic clues and treatments for each condition.

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DOI: 10.1016/j.autrev.2011.10.008

PMID: 22024500 [Indexed for MEDLINE]

2892. Rheumatol Int. 2012 Nov;32(11):3705-6. doi: 10.1007/s00296-011-2167-5. Epub 2011 Oct 22.

Myalgia as a symptom of familial Mediterranean fever in children.

Kavukçu S, Turkmen MA, Soylu A, Bayram MT, Ulgenalp A.

Comment on

Rheumatol Int. 2011 Jun;31(6):779-84.

DOI: 10.1007/s00296-011-2167-5

PMID: 22020390 [Indexed for MEDLINE]

2893. Rheumatology (Oxford). 2011 Dec;50(12):2306-10. doi: 10.1093/rheumatology/ker328. Epub 2011 Oct 22.

# Spectrum of mutations and carrier frequency of familial Mediterranean fever gene in the Algerian population.

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**OBJECTIVES:** FMF is characterized by recurrent self-limiting episodes of fever and painful polyserositis. We aimed to study the spectrum and distribution of MEFV mutations in an Algerian patient cohort using a comprehensive mutation detection method. Using the same methodology, we also studied the carrier rate in an unaffected ethnically matched control cohort.

**METHODS:** We recruited 71 unrelated subjects clinically diagnosed with FMF from various clinics in the central region of Algeria. Two hundred and thirty control subjects were recruited as well. Mutation detection in MEFV was performed by re-sequencing the promoter region, the entire coding sequence and all exon-intron boundaries.

**RESULTS:** We detected eight different mutations located in exons 10 (p.M694I, p.M694V, p.A744S, p.M680I, p.I692Del), 9 (p.I591T), 3 (p.P369S/p.R408Q) and 2 (p.E148Q). Out of the 71 patients, 31 carried at least one mutation. While the 71 patients are expected to have 142 mutant chromosomes, only 50 were identified. p.M694I (17.6%) is the most common mutation, followed by p.M694V (5%), p.E148Q (4.2%), p.A744S (3.5%) and p.M680I (3%). One novel variant was identified in the promoter region in the heterozygous state in three patients and in two controls. The carrier rate of the identifiable mutations is estimated to be 1 : 5.

**CONCLUSION:** This study describes the MEFV mutational spectrum and distribution in the Algerian population. It shows that p.M694I is the most common MEFV mutation in Algerians. It also shows that, similar to other Arabic populations, <50% of mutant chromosomes are identified, even when employing comprehensive strategies.

DOI: 10.1093/rheumatology/ker328

PMID: 22019805 [Indexed for MEDLINE]

The relative contribution of environmental and genetic factors to phenotypic variation in familial Mediterranean fever (FMF).

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**INTRODUCTION:** Familial Mediterranean fever (FMF) is an autosomal recessive disease, caused by mutations in the FMF gene MEFV (MEditerranean FeVer). It has a large phenotypic diversity even in patients with similar genotypes. Despite evidence that environmental factors (EFs) and genetic factors, including MEFV mutations (such as M694V, E148Q) and background modifier genes (MGs), affect the clinical manifestations of FMF, the relative contribution of each remains unknown.

**METHODS:** To investigate the relative contribution of environmental and genetic factors to the phenotype of FMF, we compared the intra-pair clinical concordance of 10 mono and 7 dizygotic twins with FMF. The part played by EFs was determined by the phenotypic discordance of the monozygous twins, and the MGs effect was determined by deducing the environmental effect, computed for MZ twins, from the phenotypic discordance of the dizygous twins.

**RESULTS:** The mean $\pm$ SD of intra-pair concordance was higher in the MZ than in DZ twin group (88.1 $\pm$ 13.2 vs. 70.7 $\pm$ 14.1 respectively, P value<0.05). Based on the concordance in clinical manifestations in MZ and DZ twins, the environmental effect on the phenotype of FMF is estimated as 11.9% $\pm$ 6.6% and the MGs effect as 17.4% $\pm$ 15.5% in average.

**CONCLUSIONS:** In FMF the phenotype is affected by MEFV mutations, MGs and EFs in an estimated ratio of about 6:1.5:1 respectively.

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DOI: 10.1016/j.gene.2011.10.005

PMID: 22019429 [Indexed for MEDLINE]

2895. Endocr Res. 2012;37(1):35-45. doi: 10.3109/07435800.2011.620579. Epub 2011 Oct 20.

Neutrophil proteinase 3 induces diabetes in a mouse model of glucose tolerance.

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Type 1 diabetes is considered to be an autoimmune disease in which T cells attack pancreatic islet cells. Impaired glucose tolerance with type 2 diabetes has been classified as an obesity-associated metabolic syndrome. However, recent studies have revealed that type 2 diabetes is an autoinflammatory disease due to an imbalance of inflammatory cytokine production and related molecular components that cause inflammation. Insulin-like growth factor (IGF) and the insulin-like growth factor-binding protein-3 (IGFBP3) system are known to be involved in the development of experimental diabetic nephropathy, and urinary IGFBP3 protease activity has been observed in patients with type 2 diabetes. A serine protease was found to be responsible for the proteolytic activity in diabetic urine; however, the identity of the precise enzyme remains unknown. We investigated neutrophil proteinase 3 (PR3) to see whether it has specific enzymatic activity associated with insulin-like growth factor-1 and IGFBP3. In our study, both molecules were sufficiently degraded, which leads us to believe that PR3 may induce insulin resistance in the mouse model utilized. In addition, we found that PR3 in the urine of diabetic patients similarly affects insulin resistance. Moreover, PR3-immunized mice had an increase in glucose clearance due to inhibition of PR3 activity. As such, PR3 can be considered as an inflammatory enzyme directly linking inflammation to type 2 diabetes through downregulation of insulin-like growth factor-1/IGFBP3.

DOI: 10.3109/07435800.2011.620579

PMID: 22014109 [Indexed for MEDLINE]

2896. Arthritis Rheum. 2012 Mar;64(3):908-13. doi: 10.1002/art.33416.

Efficacy of etanercept in the tumor necrosis factor receptor-associated periodic syndrome: a prospective, open-label, dose-escalation study.



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**OBJECTIVE:** To investigate the efficacy of etanercept in improving the symptoms and underlying inflammation in patients with tumor necrosis factor receptor-associated periodic syndrome (TRAPS).

**METHODS:** Fifteen patients with TRAPS were enrolled in a prospective, open-label, dose-escalation study. Patients recorded attacks, symptom severity, and use of ancillary medications in a daily diary. Blood samples were collected during each period and measured for levels of acute-phase reactants. Between 7 years and 9 years after the conclusion of the initial study, patients completed a followup survey and were evaluated to determine the long-term outcome of etanercept treatment.

**RESULTS:** Etanercept treatment significantly attenuated the total symptom score and reduced the frequency of symptoms. Etanercept also reduced levels of acute-phase reactants, particularly during asymptomatic periods. During a 10-year followup period, patients continued to receive etanercept for a median of 3.3 years, with a number of patients switching to anti-interleukin-1 $\beta$  receptor therapy or not receiving biologic agents, most frequently citing injection site reactions and lack of efficacy as reasons for discontinuation. However, patients continuing to receive etanercept had reduced symptoms at followup.

**CONCLUSION:** Etanercept reduces symptoms and serum levels of inflammatory markers of TRAPS in a dose-dependent manner, but does not completely normalize symptoms or acute-phase reactant levels. Although long-term adherence to etanercept is poor, continuing to receive etanercept may provide continued symptomatic benefit.

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DOI: 10.1002/art.33416

PMCID: PMC3882089

PMID: 22006113 [Indexed for MEDLINE]

The anti-inflammatory drug colchicine lacks efficacy in hidradenitis suppurativa.

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**BACKGROUND:** Hidradenitis suppurativa (HS) is a chronic, inflammatory skin disease. Since current treatments are unsatisfactory for many patients, there is a high need for effective drugs for this debilitating disease. Recent pathogenic insights suggest inflammasome activation and IL-1 $\beta$  production are important in HS. Colchicine is efficacious in the IL-1 $\beta$ - and inflammasome-mediated diseases gout, familial Mediterranean fever and Behçet's disease, and therefore a potentially effective drug in HS.

**OBJECTIVE:** To investigate the efficacy of colchicine in HS.

**METHODS:** In an open prospective pilot study, 8 HS patients were treated with the accepted gout maintenance regimen of 0.5 mg colchicine b.i.d. orally up to 4 months. Efficacy was assessed by a physician global assessment.

**RESULTS:** Colchicine treatment did not result in a clinically relevant improvement of disease severity. Three patients experienced nausea and diarrhea as known side effects.

**CONCLUSION:** Colchicine in the used dose regimen does not ameliorate HS severity.

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DOI: 10.1159/000332846

PMID: 21997700 [Indexed for MEDLINE]

2898. Clin Genet. 2012 Sep;82(3):288-91. doi: 10.1111/j.1399-0004.2011.01785.x. Epub 2011 Oct 14.

'Silent' carriage of two familial Mediterranean fever gene mutations in large families with only a single identified patient.

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The presence of two mutations in the familial Mediterranean fever gene, without overt familial Mediterranean fever (FMF), designated as phenotype III, predisposes to developing 'silent' AA amyloidosis, recognized as phenotype II, due to the absence of medical supervision and colchicine prophylaxis. We sought to determine the prevalence of phenotype III in large families with only one subject affected with FMF, in order to assess the population at risk for transformation to phenotype II. A total of seven large families were recruited for the study. Siblings were screened for MEFV mutations and underwent a clinical interview to assess for unrecognized FMF manifestations. Phenotype III, most commonly associated with a V726A/E148Q genotype, was detected in 10% of siblings of index cases from informative families, corresponding to a 10-fold increase in comparison to the expected rate in the general population ( $p < 0.01$ ). Unnoticed 'FMF-like' manifestations were detected among two siblings in the five families in which the index case was heterozygous, but in none of the siblings of the homozygous index cases. The enrichment for phenotype III and detection of occult FMF in large families, in which only a single member is afflicted with FMF, mandates routine clinical evaluation and genetic screening of siblings.

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DOI: 10.1111/j.1399-0004.2011.01785.x

PMID: 21995303 [Indexed for MEDLINE]

2899. Int J Immunopathol Pharmacol. 2011 Jul-Sep;24(3):695-702.

Validation of a diagnostic score for the diagnosis of autoinflammatory diseases in adults.

Cantarini L(1), Iacoponi F, Lucherini OM, Obici L, Brizi MG, Cimaz R, Rigante D, Benucci M, Sebastiani GD, Brucato A, Sabadini L, Simonini G, Giani T, Laghi Pasini F, Baldari CT, Bellisai F, Valentini G, Bombardieri S, Paolazzi G, Galeazzi M.

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Most autoinflammatory disorders typically come out in the pediatric population, although a limited number of patients may experience disease onset during adulthood. To date, a late disease onset has been described only in familial Mediterranean fever, caused by mutations in the MEFV gene, and in tumor necrosis factor receptor-associated periodic syndrome, caused by mutations in the TNFRSF1A gene. The relative rarity and lack of information on adult-onset autoinflammatory diseases make it likely that mutations will be found in an even smaller percentage of cases. With the aim of improving the genetic diagnosis in adults with suspected autoinflammatory disorders, we recently identified a set of variables related to the probability of detecting gene mutations in MEFV and TNFRSF1A and, in addition, we have also proposed a diagnostic score for identifying those patients at high risk of carrying mutations in these genes. In the present study we evaluated the preliminary score sensitivity and specificity on a wider number of patients in order to validate the goodness of fit of the model. Two hundred and nineteen consecutive patients with a clinical history of periodic fever attacks were screened for mutations in MEFV and TNFRSF1A genes; detailed information about family/personal history and clinical manifestations were also collected. For the validation of the score we considered data both from the 110 patients used to build the preliminary diagnostic score and from the additional 219 patients enrolled in the present study, for a total number of 329 patients. Early age at disease onset, positive family history for recurrent fever episodes, thoracic pain, abdominal pain and skin rash, which are the variables that had previously been shown to be significantly associated with a positive genetic test result (12), were used for validation. On univariate analysis the associations with a positive genetic test were: age at onset (odds ratio [OR] 0.43,  $p=0.003$ ), positive family history for recurrent fever episodes (OR 5.81,  $p<0.001$ ), thoracic pain (OR 3.17,  $p<0.001$ ), abdominal pain (OR 3.80,  $p<0.001$ ) and skin rash (OR 1.58,  $p=0.103$ ). The diagnostic score was calculated using the linear combination of the estimated coefficients of the logistic multivariate model (cut-off equals to 0.24) revealing good sensitivity (0.778) and good specificity (0.718). In conclusion, our score may serve in the diagnostic evaluation of adult patients presenting with recurrent fever episodes suspected of having an autoinflammatory disorder, helping identify the few subjects among them who may be carriers of mutations in MEFV and TNFRSF1A genes.

DOI: 10.1177/039463201102400315  
PMID: 21978701 [Indexed for MEDLINE]

2900. Ann Med. 2012 Nov;44(7):664-73. doi: 10.3109/07853890.2011.598546. Epub 2011 Oct 5.

Clinical and biochemical landmarks in systemic autoinflammatory diseases.

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Systemic autoinflammatory diseases are a group of inherited disorders of the innate immune system characterized by seemingly unprovoked inflammation recurring at variable intervals and involving skin, serosal membranes, joints, and gastrointestinal apparatus, with reactive amyloidosis as a possible severe long-term complication. Recent advances in genetics and molecular biology have improved our understanding of the pathogenesis of these diseases, including familial Mediterranean fever, mevalonate kinase deficiency syndrome, tumor necrosis factor receptor-associated periodic syndrome, cryopyrin-associated periodic syndromes, and hereditary pyogenic and granulomatous disorders: the vast majority of these conditions are related to the activation of the interleukin-1 pathway, which results in (or from?) a common unifying pathogenetic mechanism. Their diagnostic identification derives from the combination of clinical data, evaluation of acute phase reactants, clinical efficacy in response to specific drugs, and recognition of specific mutations in the relevant genes, although genetic tests may be unconstructive in some cases. This review will discuss clinical and laboratory clues useful for a diagnostic approach to systemic autoinflammatory diseases.

DOI: 10.3109/07853890.2011.598546  
PMID: 21972825 [Indexed for MEDLINE]

2901. BMC Immunol. 2011 Sep 28;12:54. doi: 10.1186/1471-2172-12-54.

Regulation of IL-2 gene expression by Siva and FOXP3 in human T cells.

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**BACKGROUND:** Severe autoinflammatory diseases are associated with mutations in the Foxp3 locus in both mice and humans. Foxp3 is required for the development, function, and maintenance of regulatory T cells (Tregs), a subset of CD4 cells that suppress T cell activation and inflammatory processes. Siva is a pro-apoptotic gene that is expressed across a range of tissues, including CD4 T cells. Siva interacts with three tumor necrosis factor receptor (TNFR) family members that are constitutively expressed on Treg cells: CD27, GITR, and OX40.

**RESULTS:** Here we report a biophysical interaction between FOXP3 and Siva. We mapped the interaction domains to Siva's C-terminus and to a central region of FOXP3. We showed that Siva repressed IL-2 induction by suppressing IL-2 promoter activity during T cell activation. Siva-1's repressive effect on IL-2 gene expression appears to be mediated by inhibition of NFkappaB, whereas FOXP3 repressed both NFkappaB and NFAT activity.

**CONCLUSIONS:** In summary, our data suggest that both FOXP3 and Siva function as negative regulators of IL-2 gene expression in Treg cells, via suppression of NFAT by FOXP3 and of NFkappaB by both FOXP3 and Siva. Our work contributes evidence for Siva's role as a T cell signalling mediator in addition to its known pro-apoptotic function. Though further investigations are needed, evidence for the biophysical interaction between FOXP3 and Siva invites the possibility that Siva may be important for proper Treg cell function.

DOI: 10.1186/1471-2172-12-54

PMCID: PMC3208582

PMID: 21955384 [Indexed for MEDLINE]

2902. NDT Plus. 2011 Oct;4(5):346-51. doi: 10.1093/ndtplus/sfr080. Epub 2011 Jul 6.

Periodic fever syndrome with relapsing glomerulonephritis: a case report and

teaching points.

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We report a case of relapsing mesangial and endocapillary proliferative glomerulonephritis (GN) associated with a periodic fever syndrome. The patient presented 11 times in >4 years with acute febrile episode followed in 1-3 days by hematuria, thrombocytopenia and other symptoms of acute GN with variable severity of acute kidney injury. In three episodes, the patient required renal replacement therapy for 7, 10 and 2 treatments, respectively. Shortly after the acute symptoms of the febrile episode had resolved each time, the kidney function would recover and the serum creatinine would return to baseline. Two kidney biopsies obtained during separate episodes showed acute tubular injury along with morphological changes resembling post-infectious GN but with no clinical evidence to support an infectious etiology. Multiple treatment regimens were unable to control the disease. Symptoms were alleviated by rituximab but did not completely remit. Stable remission of the periodic fever and GN was finally achieved after anakinra therapy was initiated 18 months ago. Since then, the patient had several episodes of documented infection without high fever and nephritic kidney manifestations. His kidney function remained stable with normal serum creatinine.

DOI: 10.1093/ndtplus/sfr080

PMCID: PMC4421743

PMID: 25984185

2903. Caspian J Intern Med. 2011 Fall;2(4):344-6.

Familial mediterranean fever in an Iranian patient with behcet disease.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is the most prevalent disorder among the hereditary autoinflammatory syndromes. This disorder is characterized by fever and some painful attacks such as abdominal, chest or joint pain and potentially development of AA amyloidosis. Several vasculitis are more common in FMF than general population. There are some reports about association of FMF with Behcet Disease (BD).

**CASE PRESENTATION:** In this study, we describe a 27 year old patient with BD who suffered from attacks of fever, arthralgia, abdominal pain and genetic study confirmed the diagnosis of FMF.

**CONCLUSION:** FMF should be considered in a patient with Behcet disease who is suffering from attacks of fever, arthralgia and abdominal pain.

PMCID: PMC3895835

PMID: 24551444

2904. Arthritis Rheum. 2012 Mar;64(3):895-907. doi: 10.1002/art.33368.

Mutations in proteasome subunit  $\beta$  type 8 cause chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature with evidence of genetic and phenotypic heterogeneity.

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**OBJECTIVE:** Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE syndrome) is an autoinflammatory syndrome recently described in children. We undertook this study to investigate the clinical



phenotype, genetic cause, and immune dysregulation in 9 CANDLE syndrome patients.

**METHODS:** Genomic DNA from all patients was screened for mutations in PSMB8 (proteasome subunit  $\beta$  type 8). Cytokine levels were measured in sera from 3 patients. Skin biopsy samples were evaluated by immunohistochemistry, and blood microarray profile and STAT-1 phosphorylation were assessed in 4 patients and 3 patients, respectively.

**RESULTS:** One patient was homozygous for a novel nonsense mutation in PSMB8 (c.405C>A), suggesting a protein truncation; 4 patients were homozygous and 2 were heterozygous for a previously reported missense mutation (c.224C>T); and 1 patient showed no mutation. None of these sequence changes was observed in chromosomes from 750 healthy controls. Of the 4 patients with the same mutation, only 2 shared the same haplotype, indicating a mutational hot spot. PSMB8 mutation-positive and -negative patients expressed high levels of interferon- $\gamma$  (IFN $\gamma$ )-inducible protein 10. Levels of monocyte chemotactic protein 1, interleukin-6 (IL-6), and IL-1 receptor antagonist were moderately elevated. Microarray profiles and monocyte STAT-1 activation suggested a unique IFN signaling signature, unlike in other autoinflammatory disorders.

**CONCLUSION:** CANDLE syndrome is caused by mutations in PSMB8, a gene recently reported to cause "JMP" syndrome (joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced childhood-onset lipodystrophy) in adults. We extend the clinical and pathogenic description of this novel autoinflammatory syndrome, thereby expanding the clinical and genetic disease spectrum of PSMB8-associated disorders. IFN may be a key mediator of the inflammatory response and may present a therapeutic target.

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DOI: 10.1002/art.33368

PMCID: PMC3278554

PMID: 21953331 [Indexed for MEDLINE]

2905. Mod Rheumatol. 2012 Jun;22(3):431-7. doi: 10.1007/s10165-011-0517-5. Epub 2011 Sep 23.

Acute phase response and oxidative stress status in familial Mediterranean fever (FMF).

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We aimed to determine acute phase response (APR) and oxidative stress in patients with familial Mediterranean fever (FMF) and compare these characteristics with those in healthy controls; 20 patients with FMF and 15 healthy controls were enrolled in the study. The erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), fibrinogen, and leukocyte levels were determined as markers of APR. Thiobarbituric acid reactive substances (TBARS), conjugated diene, and lipid hydroperoxide levels were measured as markers of lipid peroxidation. Carbonyl group and thiol (T-SH) levels were analyzed to determine the oxidative damage to proteins, and 8-hydroxy-2-deoxyguanosine (8-OHdG) was measured to reflect DNA oxidation. The erythrocyte glutathione (GSH) level, and glutathione peroxidase (GSH-Px), CuZn superoxide dismutase (CuZn SOD), and catalase activities were measured as markers of antioxidant status. Conjugated diene ( $p < 0.001$ ) and carbonyl group ( $p < 0.05$ ) levels were significantly higher and GSH-Px activity ( $p < 0.01$ ) was significantly lower in FMF patients compared with controls. FMF patients in the attack period ( $n = 8$ ) had significantly higher CRP, ESR, fibrinogen, and leukocyte levels ( $p < 0.001$ ) than patients in the attack-free period ( $n = 12$ ). The T-SH level ( $p < 0.05$ ) was significantly higher and CuZn SOD activity was significantly lower ( $p < 0.05$ ) in FMF patients in the attack period. The findings revealed upregulated APR during the attack period in FMF patients and enhanced oxidative stress in the FMF patients as compared to controls.

DOI: 10.1007/s10165-011-0517-5

PMID: 21947799 [Indexed for MEDLINE]

2906. J Clin Rheumatol. 2011 Oct;17(7):373-6. doi: 10.1097/RHU.0b013e3182320680.

Clarithromycin in adult-onset still's disease: a potentially useful therapeutic.

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Comment in

J Clin Rheumatol. 2013 Oct;19(7):420.

Adult-onset Still's disease (AOSD), an autoinflammatory syndrome of unknown etiology, typically manifests with spiking fevers, polyarthritis, and characteristic evanescent rash. We describe a young woman with AOSD complicated by calf fasciitis that serendipitously responded to clarithromycin administered for another indication. Remarkable improvement followed rechallenges with clarithromycin for subsequent AOSD flares. In addition to their antibacterial actions, macrolides demonstrate immunomodulatory effects, including suppression of proinflammatory cytokine production and neutrophil action. Previous clinical trials provide promising preliminary evidence of a therapeutic effect of macrolides in chronic inflammatory diseases. Although AOSD pathogenesis remains unclear, a role for dysregulation of innate immunity is supported by recent literature. Based on this possible innate immune mechanism, we suspect that macrolides may have induced a therapeutic response in this patient with AOSD. A clinical trial is warranted to establish or refute their therapeutic efficacy.

DOI: 10.1097/RHU.0b013e3182320680

PMID: 21946464 [Indexed for MEDLINE]

2907. J Clin Rheumatol. 2011 Oct;17(7):358-62. doi: 10.1097/RHU.0b013e31823682f5.

Effects of anti-tumor necrosis factor agents for familial mediterranean fever patients with chronic arthritis and/or sacroiliitis who were resistant to colchicine treatment.

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BACKGROUND: Effectiveness of anti-tumor necrosis factor (anti-TNF) agents in colchicine-resistant familial Mediterranean fever (FMF) patients has attracted attention in recent years.

**OBJECTIVE:** We analyzed the effect of anti-TNF agents on clinical findings of colchicine-resistant FMF patients with chronic arthritis and/or sacroiliitis.

**METHODS:** Data from 10 FMF patients (5 male and 5 female patients: mean age, 30.1 [SD, 8.5] years) with chronic arthritis and/or sacroiliitis who were on anti-TNF agents are reviewed. Frequency of FMF attacks before and after treatment with anti-TNF agents was recorded from hospital files. The effects of the anti-TNF treatment were determined by using the number of tender and/or swollen joints, serum acute phase reactant levels, and Bath Ankylosing Spondylitis Disease Activity Index scores. Change in urine protein loss was also evaluated in patients with amyloidosis. In 6 patients, FMF attacks had been considered to be unresponsive to colchicine, and 4 patients were partial responders before treatment with anti-TNF agents.

**RESULTS:** Mean attack frequency of the patients in the 3 months' period before anti-TNF agent treatment was 3.8 (SD, 3.1). After anti-TNF treatment, in 3 patients, FMF attack frequency decreased, and in the remaining 7 patients, no attack occurred. Serum acute phase reactant levels were decreased significantly at 3 and 6 months after anti-TNF treatment ( $P < 0.05$  for all). After anti-TNF treatment Bath Ankylosing Spondylitis Disease Activity Index scores were also decreased significantly (6.2 [SD], 1.7 vs. 2.1 [SD], 1.7;  $P = 0.012$ ). In all 3 patients with amyloidosis, urine protein loss decreased without any increase in serum creatinine levels.

**CONCLUSION:** Anti-TNF treatment can have beneficial effects for controlling FMF attacks in FMF patients with chronic arthritis and/or sacroiliitis.

DOI: 10.1097/RHU.0b013e31823682f5

PMID: 21946459 [Indexed for MEDLINE]

2908. Semin Arthritis Rheum. 2012 Feb;41(4):611-7. doi: 10.1016/j.semarthrit.2011.07.008. Epub 2011 Sep 25.

Tumor necrosis factor receptor associated periodic fever syndrome with photographic evidence of various skin disease and unusual phenotypes: case report and literature review.

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**OBJECTIVES:** To report a case of tumor necrosis factor receptor associated periodic fever syndrome (TRAPS) with unusual clinical phenotypes and a systematic review.

**METHODS:** The relevant English literature of TRAPS was searched using the keywords TRAPS, autoinflammatory disease, and gene mutation. Original and review articles were reviewed and the clinical scenarios were exemplified with a case report.

**RESULTS:** A 58-year-old Jewish woman with Eastern European Ashkenazic background presented with photographic evidence of various skin disease, including previously unreported vesicles and alopecia, as well as other systemic manifestations. The complaints of urinary foreign bodies prompted a discovery of ureteral strictures with atypia perhaps from autoinflammation. A R92Q gene mutation of TNFRSFA1 was detected. The clinical manifestations of this disease are protean and its pathogenesis is complex, involving the interaction of wild-type and mutated gene products, innate immune system, and proinflammatory cytokines. Glucocorticoid and anticytokine therapy is generally efficacious but some cases remain refractory to the current treatment.

**CONCLUSIONS:** TRAPS is a systemic autoinflammatory disease with variable clinical phenotypes associated with gene mutations. Recognition of the unusual phenotypes may enhance early accurate diagnosis.

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DOI: 10.1016/j.semarthrit.2011.07.008

PMID: 21943788 [Indexed for MEDLINE]

2909. Ugeskr Laeger. 2011 Sep 19;173(38):2340-3.

[Danger signals and inflammasomes in autoinflammatory and autoimmune diseases].

[Article in Danish]

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Cytoplasmic inflammasomes are formed through activation of pattern recognition receptors (PRR) of the innate immune system. Endogenous and exogenous danger signals, e.g. DNA- and RNA-fragments, urate- and cholesterol crystals, silica and asbestos,  $\beta$ -amyloid, UV-light and skin irritants, may induce NOD-like receptor protein (NLRP)3 inflammasomes. These inflammasomes govern the induction of proinflammatory cytokines such as IL-1 $\beta$ , IL-18 and IL-33. PRR and inflammasome dysfunctions may underly immunoinflammatory diseases such as gout and other arthritides, type 1 diabetes and arteriosclerosis.

PMID: 21936977 [Indexed for MEDLINE]

2910. Ugeskr Laeger. 2011 Sep 19;173(38):2337-40.

[Innate immunity, autoimmunity and autoinflammation].

[Article in Danish]

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T and B lymphocytes of the acquired immune system are functionally superimposed on the evolutionary old innate immune system. The latter recognizes conserved microbial structures through pattern recognition receptors (PRR) which are coactivated by "danger" signals through cytoplasmic PRR termed NOD-like receptors (NLR). These signals include nuclear fragments released by stressed or dying cells. NLR-signalling activates the enzyme caspase-1, which is required for release of pro-inflammatory cytokines such as interleukin (IL)-1 $\beta$ , IL-18 and IL-33. Dysfunction of innate immunity is central to autoinflammation and may contribute to autoimmunity.

PMID: 21936976 [Indexed for MEDLINE]

2911. Nephrol Dial Transplant. 2012 May;27(5):1898-901. doi: 10.1093/ndt/gfr528. Epub 2011 Sep 19.

Dramatic beneficial effect of interleukin-1 inhibitor treatment in patients with familial Mediterranean fever complicated with amyloidosis and renal failure.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disorder, for which systemic AA amyloidosis is the major complication revealed most of the time by renal abnormalities. Current treatment is daily colchicine that prevents both recurrent inflammatory attacks and amyloidosis deposition in most patients. However, some patients still develop amyloidosis and renal failure. Functional studies suggest that interleukin (IL)-1 is implicated in the inflammatory reaction in FMF and therefore, IL-1 inhibitors could be a new approach to treat FMF. The aim of this series study was to evaluate anakinra in patients with FMF complicated with amyloidosis and renal failure.

**METHODS:** We studied a series of adult patients with FMF complicated with amyloidosis and treated with anakinra in one reference centre were reviewed. A search for published patients with FMF associated amyloidosis treated with anakinra was performed by screening PubMed.

**RESULTS:** We report four cases of patients with FMF-associated amyloidosis treated with anakinra and discuss the clinical pertinence of its use in these particular clinical settings.

**CONCLUSIONS:** Anakinra has a strong effect on both inflammatory attacks and general status in patients with FMF-associated amyloidosis. It may contribute to changing the prognosis of these patients. Long-term studies are needed to appreciate the effect of anakinra or other IL-1 inhibitors on the natural history of amyloidosis in these patients.

DOI: 10.1093/ndt/gfr528

PMID: 21931121 [Indexed for MEDLINE]

2912. Nihon Rinsho. 2011 Sep;69(9):1679-89.

[Fever of unknown cause and autoinflammatory disease].

[Article in Japanese]

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Autoinflammatory diseases are often associated with various kinds of febrile episodes such as fever of unknown origin, periodic fever and recurrent fever. Therefore, in the differential diagnosis of fever of unknown cause, autoinflammatory diseases should be considered after exclusion of infections, malignancy and autoimmune diseases. As autoinflammatory diseases now include TRAPS (TNF receptor-associated periodic syndrome), CAPS (cryopyrin -associated periodic syndromes), FMF(familial Mediterranean fever), MAPS (mevalonate kinase-associated periodic fever syndrome, hyper-IgD syndrome) and many others, and show symptoms and signs of wide variations, we need to make an accurate diagnosis of them to prevent possible complications such as amyloidosis.

PMID: 21922774 [Indexed for MEDLINE]

2913. Arthritis Res Ther. 2011;13(5):R148. doi: 10.1186/ar3462. Epub 2011 Sep 14.

A new category of autoinflammatory disease associated with NOD2 gene mutations.

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**INTRODUCTION:** Autoinflammatory diseases are characterized by seemingly unprovoked episodes of inflammation, without high titers of autoantibodies or antigen-specific T cells, and derive from genetic variants of the innate immune system. This study characterized a cohort of patients with similar phenotypes and nucleotide oligomerization domain 2 (NOD2) gene mutations.

**METHODS:** Diagnostically challenging patients with the following clinical and genetic characteristics were prospectively studied between January 2009 and April 2011: periodic fever, dermatitis, polyarthritis, serositis, negative serum autoantibodies and additional positive NOD2 IVS8+158 gene mutation. Genetic testing for gene mutations of NOD2, tumor necrosis factor receptor-associated periodic fever syndrome (TRAPS) and familial Mediterranean fever (FMF) was performed.

**RESULTS:** All seven patients with the disease were Caucasians, with four being male. The mean age at disease onset was 40.7 years and disease duration was 3.2 years. These patients characteristically presented with periodic fever, dermatitis and inflammatory polyarthritis. There were gastrointestinal symptoms in three patients, granulomas of the skin and gut in two, and recurrent chest pain in two, with one having pleuritis and pericarditis. Three patients had sicca-like symptoms. Five patients had increased acute phase reactants. All seven patients had negative tests for autoantibodies but carried the NOD2 gene mutation IVS8+158 with four having concurrent R702W mutation.

**CONCLUSIONS:** Our cohort may represent a new disease category of autoinflammatory disease with characteristic clinical phenotypes and genotypes. It may somewhat resemble pediatric Blau's syndrome.

DOI: 10.1186/ar3462

PMCID: PMC3308076

PMID: 21914217 [Indexed for MEDLINE]

2914. Proc Natl Acad Sci U S A. 2011 Oct 11;108(41):E823-32. doi: 10.1073/pnas.1107913108. Epub 2011 Sep 12.

B cell-derived IL-10 suppresses inflammatory disease in Lyn-deficient mice.

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Lyn kinase deficient mice represent a well established genetic model of autoimmune/autoinflammatory disease that resembles systemic lupus erythematosus. We report that IL-10 plays a crucial immunosuppressive role in this model, modulating the inflammatory component of the disease caused by myeloid and T-cell activation. Double-mutant lyn(-/-)IL-10(-/-) mice manifested severe splenomegaly and lymphadenopathy, dramatically increased proinflammatory cytokine production, and severe tissue inflammation. Single-mutant lyn(-/-)mice showed expansion of IL-10-producing B cells. Interestingly, WT B cells adoptively transferred into lyn(-/-) mice showed increased differentiation into IL-10-producing B cells that assumed a similar phenotype to endogenous lyn(-/-) IL-10-producing B cells, suggesting that the inflammatory environment present in lyn(-/-) mice induces IL-10-producing B-cell differentiation. B cells, but not T or myeloid cells, were the critical source of IL-10 able to reduce inflammation and autoimmunity in double mutant lyn(-/-)IL-10(-/-) mice. IL-10 secretion by B cells was also crucial to sustain transcription factor Forkhead Box P3 (Foxp3) expression in regulatory T cells during disease development. These data reveal a dominant immunosuppressive function of B-cell-derived IL-10 in the Lyn-deficient model of autoimmunity, extending our current understanding of the role of IL-10 and IL-10-producing B cells in systemic lupus erythematosus.

DOI: 10.1073/pnas.1107913108

PMCID: PMC3193193

PMID: 21911371 [Indexed for MEDLINE]

2915. Ann Rheum Dis. 2011 Dec;70(12):2075-2081. doi: 10.1136/ard.2011.152496. Epub 2011 Sep 8.

MRP8 and MRP14, phagocyte-specific danger signals, are sensitive biomarkers of disease activity in cryopyrin-associated periodic syndromes.

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- (#)Contributed equally

**OBJECTIVES:** To assess the sensitivity of the phagocyte-specific molecules myeloid-related protein (MRP) 8 and MRP14 (calprotectin) for monitoring disease activity during anti-interleukin (IL)-1 therapies in patients with cryopyrin-associated periodic syndromes (CAPS), including familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and chronic infantile neurological, cutaneous and articular (CINCA) syndrome.

**METHODS:** A total of 39 patients with CAPS, including 5 FCAS, 16 MWS and 18 CINCA syndrome, received anti-IL-1 therapy. All patients with CINCA and 12 with MWS were treated with IL-1Ra (anakinra), 14 patients with MWS with a monoclonal anti-IL-1 $\beta$  antibody (canakinumab) and patients with FCAS received IL-1 Trap (rilonacept). During serial clinical visits serum amyloid A, C-reactive protein, erythrocyte sedimentation rate and MRP8/14 serum levels were analysed.

**RESULTS:** Untreated patients with CAPS had significantly elevated MRP8/14 values. In response to treatment there was a significant reduction of MRP8/14 levels in CINCA (2,830 (range 690 - 8,480) ng/ml to 670 ng/ml,  $p < 0.001$ ) and MWS patients (anakinra-treated: 4,390 (1790 - 9780) ng/ml to 1,315 ng/ml ( $p = 0.003$ ); canakinumab-treated: 3,000 (500 - 13060) ng/ml to 630 ng/ml ( $p=0.001$ )). However, in many patients with CAPS, MRP8/14 levels were still elevated compared with healthy individuals, reflecting residual disease activity. However, canakinumab-treated patients with CAPS showed normalised MRP8/14 levels, suggesting control of phagocyte activation.

**CONCLUSIONS:** Monitoring of cellular systems involved in inflammatory cascades of the innate immunity was successfully applied to the IL-1-driven CAPS diseases.

This is the first study illustrating different states of subclinical disease activity in all types of CAPS depending on the type of anti-IL-1 therapy. MRP8/14 is a sensitive biomarker for monitoring disease activity, status of inflammation and response to IL-1 blockade in patients with CAPS.

DOI: 10.1136/ard.2011.152496

PMCID: PMC4174360

PMID: 21908452 [Indexed for MEDLINE]

2916. Klin Onkol. 2011;24(4):271-7.

[Schnitzler syndrome: diagnostics and treatment].

[Article in Czech]

Szturz P(1), Adam Z, Sedivá A, Fojtík Z, Corbová D, Neubauer J, Prásek J, Hájek R, Mayer J.

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**BACKGROUNDS:** The most important diagnostic criteria for Schnitzler syndrome include chronic urticaria, the presence of monoclonal IgM immunoglobulin, marked inflammation (leukocytosis, elevated CRP and erythrocyte sedimentation rate), subfebrile temperatures or fevers and bone and joint pains. It is a rare idiopathic disease that may lead to potentially life-threatening complications such as development of secondary amyloidosis or transformation into malignant lymphoproliferation. Schnitzler syndrome should be included in differential diagnostics of chronic urticaria and fevers of unknown origin. The diagnostic algorithm is based on clinical presentation and serum and urine electrophoreses to detect monoclonal components. Blockade of interleukin-1 (IL-1), key cytokine in the pathogenesis of the disease, dominates current therapeutic protocols. Anakinra (Kineret), recombinant human IL-1 receptor antagonist, is the most widely used treatment option. According to literature, disease remission was obtained in all treated patients. Therefore, anakinra represents a significant diagnostic possibility to differentiate Schnitzler syndrome from e.g. monoclonal gammopathy of unknown significance (MGUS) associated with urticaria of different aetiology. Biological therapy with rilonacept (Arcalyst) and canakinumab (Ilaris)

represents a new treatment alternative for patients, allowing prolonged dosing intervals of 1 and 8 weeks, respectively (compared to 24 hours with anakinra). The review article also presents findings of various imaging methods (conventional radiography, computed tomography, traditional bone scintigraphy) and photographs of patients with Schnitzler syndrome before and after anakinra therapy.

**DESIGN:** The aim of the review is to draw attention to the existence of this rare autoinflammatory and potentially premalignant condition, present a simple diagnostic algorithm and provide an overview of therapeutic options for the patients.

**CONCLUSIONS:** Malign potential of Schnitzler syndrome, possible development into systemic amyloidosis and the fact that patients are frequently referred to oncology clinics for differential diagnostics of monoclonal gammopathy, are the main reasons why clinical oncologists should be aware of Schnitzler syndrome.

PMID: 21905617 [Indexed for MEDLINE]

2917. J Oral Pathol Med. 2012 Feb;41(2):158-64. doi: 10.1111/j.1600-0714.2011.01064.x. Epub 2011 Sep 7.

Recurrent aphthous ulcers--a Toll-like receptor-mediated disease?

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**BACKGROUND:** Recurrent aphthous ulcer (RAU) is characterized by acute and painful inflammatory ulcerations, which heal spontaneously but tend to recur. Many pathogens have been proposed as causative agents, but none has been consistently proven. According to our hypothesis, RAU is an autoinflammatory disorder triggered by pathogen-associated molecular patterns (PAMPs) shared by different pathogenic and commensal microbes.

**METHODS:** PAMP-reactive Toll-like receptors (TLRs) were mapped in oral epithelium in healthy controls compared to RAU.

RESULTS: In controls, the superficial epithelium formed a TLR(-), a PAMP non-reactive physical barrier zone, but all TLRs were found deeper in the epithelium, usually restricted to suprabasal and basal cell layers. In RAU, the epithelial TLR polarity was lost: TLRs 1, 2, 5, 7, and 8 were found throughout the epithelium, but also TLRs 4, 6, and 10 extended higher up than normally, whereas TLR-3 was almost lost in RAU. In RAU lesions, connective tissue stroma was heavily infiltrated by TLR(+) inflammatory cells.

CONCLUSIONS: Normal TLR architecture prevents inflammatory responses against normal microbes but still contains a deep TLR(+) , PAMP-reactive dormant defense zone. In RAU, the TLR(+), PAMP-reactive zone extends to surface or subsurface exposed to microbial PAMPs. TLR reactivity is further enhanced by recruitment of inflammatory leukocytes forming a new deep line of defense. The organization of the TLR system in healthy mucosa and its changes in RAU are compatible with active pathogenic involvement of TLRs, which together with the typical clinical picture and course suggest that RAU is a TLR-mediated disease.

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DOI: 10.1111/j.1600-0714.2011.01064.x

PMID: 21899597 [Indexed for MEDLINE]

2918. Rheumatol Int. 2012 Oct;32(10):3321-2. Epub 2011 Sep 7.

Isolated myositis as a sole presentation of familial Mediterranean fever.

Akl K, Rawashdeh MO.

DOI: 10.1007/s00296-011-2108-3

PMID: 21898063 [Indexed for MEDLINE]

2919. Autoimmun Rev. 2011 Dec;11(2):112-22. doi: 10.1016/j.autrev.2011.08.010. Epub 2011 Aug 28.

Vaccination in paediatric patients with auto-immune rheumatic diseases: a systemic literature review for the European League against Rheumatism evidence-based recommendations.

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**OBJECTIVES:** To analyze available evidence on vaccinations in paediatric patients with rheumatic and autoinflammatory diseases. This evidence formed the basis of the recently constructed European League against Rheumatism (EULAR) recommendations for vaccination of these patients.

**METHODS:** A systematic literature review in the MEDLINE and EMBASE databases was conducted using various terms for vaccinations, paediatric rheumatic and autoinflammatory diseases and immunosuppressive drugs. Only papers on paediatric patients (<18 years of age) were selected. A panel of 13 experts in the field graded methodological quality and extracted data using predefined criteria.

**RESULTS:** 27 papers were available. No studies were found on autoinflammatory diseases. 14 studies considered live-attenuated vaccines. Evidence so far supports the safety and immunogenicity of non-live composite vaccines, although studies were underpowered to accurately assess safety. Live-attenuated vaccines did not cause disease flares or severe adverse events, not even in patients on methotrexate and low dose glucocorticosteroids. Seven patients on anti-TNFalpha therapy were described receiving the live-attenuated measles, mumps, rubella (n=5) or varicella (n=2) booster without severe adverse events.

**CONCLUSIONS:** Data on safety and efficacy of vaccinations in paediatric patients with rheumatic diseases is reassuring, but too limited to draw definite conclusions. More research is needed on the safety and efficacy of especially live-attenuated vaccines in patients with rheumatic and autoinflammatory diseases using high dose immunosuppressive drugs.

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DOI: 10.1016/j.autrev.2011.08.010

PMID: 21896342 [Indexed for MEDLINE]

2920. J Clin Rheumatol. 2011 Sep;17(6):338-42. doi: 10.1097/RHU.0b013e318227e84c.

Basic science for the clinician 51: the inflammasome.

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The innate immune system is packaged in a number of discrete, but intercommunicating, systems. The inflammasome is a multimolecular complex that detects intracellular foreign molecules of a variety of sorts and promptly promotes the secretion of IL-1 $\beta$  and IL-18. When all goes well, defense of the organism in the early period of infection is enhanced by this system; when certain elements of the inflammasomal systems go awry, inflammatory diseases of a variety of sorts result. A family of multimolecular detection systems are activated at times of infection and tissue damage; it is the dysfunction of this innate immune defense system that intrigues rheumatologists, as this is the cause of a series of newly described autoinflammatory diseases.

DOI: 10.1097/RHU.0b013e318227e84c

PMID: 21885926 [Indexed for MEDLINE]

2921. Immunol Rev. 2011 Sep;243(1):163-73. doi: 10.1111/j.1600-065X.2011.01042.x.

Deregulated inflammasome signaling in disease.

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Inflammasomes are multi-protein complexes that sense microbial molecules and endogenous danger signals in intracellular compartments. Inflammasome assembly results in caspase-1 activation, which in turn drives maturation and secretion of the pro-inflammatory cytokines interleukin 1 $\beta$  (IL-1 $\beta$ ) and IL-18, and induces pyroptosis to eliminate the infectious agent. The importance of inflammasomes in regulating immune responses was recognized with the discovery of polymorphisms in genes encoding inflammasome components and their linkage to aberrant production



of IL-1 $\beta$  and IL-18 in autoimmune and hereditary periodic fevers syndromes. We review the current knowledge on the role of inflammasomes in regulating innate and adaptive immune responses with an emphasis on the role of these immune complexes in autoinflammatory disorders and autoimmune diseases such as colitis, type I diabetes, multiple sclerosis and vitiligo.

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DOI: 10.1111/j.1600-065X.2011.01042.x

PMCID: PMC3170132

PMID: 21884175 [Indexed for MEDLINE]

2922. Immunol Rev. 2011 Sep;243(1):136-51. doi: 10.1111/j.1600-065X.2011.01046.x.

The inflammasome: an integrated view.

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An inflammasome is a multiprotein complex that serves as a platform for caspase-1 activation and caspase-1-dependent proteolytic maturation and secretion of interleukin-1 $\beta$  (IL-1 $\beta$ ). Though a number of inflammasomes have been described, the NLRP3 inflammasome is the most extensively studied but also the most elusive. It is unique in that it responds to numerous physically and chemically diverse stimuli. The potent proinflammatory and pyrogenic activities of IL-1 $\beta$  necessitate that inflammasome activity is tightly controlled. To this end, a priming step is first required to induce the expression of both NLRP3 and proIL-1 $\beta$ . This event renders the cell competent for NLRP3 inflammasome activation and IL-1 $\beta$  secretion, and it is highly regulated by negative feedback loops. Despite the wide array of NLRP3 activators, the actual triggering of NLRP3 is controlled by integration a comparatively small number of signals that are common to nearly all activators. Minimally, these include potassium efflux, elevated levels of reactive oxygen species (ROS), and, for certain activators, lysosomal destabilization. Further investigation of how these and potentially other as yet uncharacterized signals are integrated by the NLRP3 inflammasome and the relevance of these biochemical events in vivo should provide new insight into the mechanisms of host defense and

autoinflammatory conditions.

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DOI: 10.1111/j.1600-065X.2011.01046.x

PMID: 21884173 [Indexed for MEDLINE]

2923. Immunol Rev. 2011 Sep;243(1):61-73. doi: 10.1111/j.1600-065X.2011.01048.x.

Recognition of nucleic acids by pattern-recognition receptors and its relevance in autoimmunity.

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Host cells trigger signals for innate immune responses upon recognition of conserved structures in microbial pathogens. Nucleic acids, which are critical components for inheriting genetic information in all species including pathogens, are key structures sensed by the innate immune system. The corresponding receptors for foreign nucleic acids include members of Toll-like receptors, RIG-I-like receptors, and intracellular DNA sensors. While nucleic acid recognition by these receptors is required for host defense against the pathogen, there is a potential risk to the host of self-nucleic acids recognition, thus precipitating autoimmune and autoinflammatory diseases. In this review, we discuss the roles of nucleic acid-sensing receptors in guarding against pathogen invasion, discriminating between self and non-self, and contributing to autoimmunity and autoinflammatory diseases.

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DOI: 10.1111/j.1600-065X.2011.01048.x

PMID: 21884167 [Indexed for MEDLINE]

2924. J Clin Invest. 2011 Oct;121(10):4150-60. doi: 10.1172/JCI58414. Epub 2011 Sep 1.

A mutation in the immunoproteasome subunit PSMB8 causes autoinflammation and lipodystrophy in humans.

Kitamura A(1), Maekawa Y, Uehara H, Izumi K, Kawachi I, Nishizawa M, Toyoshima Y, Takahashi H, Standley DM, Tanaka K, Hamazaki J, Murata S, Obara K, Toyoshima I, Yasutomo K.

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Proteasomes are multisubunit proteases that play a critical role in maintaining cellular function through the selective degradation of ubiquitinated proteins. When 3 additional  $\beta$  subunits, expression of which is induced by IFN- $\gamma$ , are substituted for their constitutively expressed counterparts, the structure is converted to an immunoproteasome. However, the underlying roles of immunoproteasomes in human diseases are poorly understood. Using exome analysis, we found a homozygous missense mutation (G197V) in immunoproteasome subunit,  $\beta$  type 8 (PSMB8), which encodes one of the  $\beta$  subunits induced by IFN- $\gamma$  in patients from 2 consanguineous families. Patients bearing this mutation suffered from autoinflammatory responses that included recurrent fever and nodular erythema together with lipodystrophy. This mutation increased assembly intermediates of immunoproteasomes, resulting in decreased proteasome function and ubiquitin-coupled protein accumulation in the patient's tissues. In the patient's skin and B cells, IL-6 was highly expressed, and there was reduced expression of PSMB8. Downregulation of PSMB8 inhibited the differentiation of murine and human adipocytes in vitro, and injection of siRNA against Psmb8 in mouse skin reduced adipocyte tissue volume. These findings identify PSMB8 as an essential component and regulator not only of inflammation, but also of adipocyte differentiation, and indicate that immunoproteasomes have pleiotropic functions in maintaining the homeostasis of a variety of cell types.

DOI: 10.1172/JCI58414

PMCID: PMC3195477

PMID: 21881205 [Indexed for MEDLINE]

2925. Rheumatol Int. 2012 Sep;32(9):2819-22. doi: 10.1007/s00296-011-2094-5. Epub 2011 Aug 30.

Down-regulation of adiponectin in patients with familial Mediterranean fever during attack-free period.

Gerdan V(1), Sari I, Kozacı D, Önen F, Yüksel F, Soysal O, Solmaz D, Günay N, Akkoc N, Akar S.

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To evaluate the circulating levels of adipokines (leptin and adiponectin) and ghrelin in patients with familial Mediterranean fever (FMF) and also to assess the relationships between these molecules and disease-related parameters. Forty-eight FMF patients in attack-free period (31 men, [M], 17 women, [F], mean age  $35.8 \pm 8.6$  years, and a mean body mass index [BMI] of  $24.7 \pm 3.1$ ) and 40 age-, sex-, and BMI-matched healthy controls (24 M, 16 F, mean age  $35.5 \pm 8.5$  years, and a mean BMI of  $24.5 \pm 2.8$ ) were included in the study. Patients and controls with a history of any other chronic diseases and obese or underweight subjects were excluded. High-sensitive C-reactive protein (hs-CRP), leptin, adiponectin, and total ghrelin concentrations were studied. Age, sex, BMI, waist circumference, and smoking status were similar between FMF patients and controls ( $P > 0.05$ ). Adipose tissue-derived molecules including leptin, and adiponectin were lower than healthy controls but only adiponectin levels reached the statistical significance ( $16.7 \pm 8.9$  ng/ml vs.  $27.7 \pm 15.9$  ng/ml,  $P < 0.001$ ) and leptin concentrations just missed significance ( $25.2 \pm 16.2$  ng/ml vs.  $34.9 \pm 27.2$  ng/ml,  $P = 0.051$ ). Ghrelin concentrations were not different between the groups. Adiponectin levels were significantly and negatively correlated with hs-CRP ( $P < 0.05$ ,  $r = -0.24$ ). The results of this study suggest that low-grade chronic inflammation during attack-free period in FMF patients may suppress adiponectin production or low levels of adiponectin might contribute to subclinical inflammation in these patients.

DOI: 10.1007/s00296-011-2094-5

PMID: 21877244 [Indexed for MEDLINE]

2926. J Clin Rheumatol. 2011 Sep;17(6):325-8. doi: 10.1097/RHU.0b013e31822e092c.

Tumor necrosis factor receptor-associated periodic fever syndrome in a 58-year-old man: caution not to discount TRAPS as a diagnosis in older patients.

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Tumor necrosis factor receptor-associated periodic fever syndrome (TRAPS) is a rare systemic autoinflammatory disorder characterized by recurrent episodes of fever and localized inflammation of different organs. The disease is dominantly inherited, with an onset usually in early childhood. We describe a case of a 58-year-old patient with TRAPS caused by the low-penetrance R92Q mutation in TNFRSF1A gene. The patient responded well to anti-tumor necrosis factor  $\alpha$  therapy. Although periodic fever syndromes, including TRAPS, mainly begin in early childhood, it is important to consider periodic fever syndrome also in patient presenting at an age older than the average reported case for TRAPS.

DOI: 10.1097/RHU.0b013e31822e092c

PMID: 21869706 [Indexed for MEDLINE]

2927. Nat Rev Immunol. 2011 Aug 25;11(9):617-25. doi: 10.1038/nri3043.

Antiviral TRIMs: friend or foe in autoimmune and autoinflammatory disease?

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The concept that viral sensing systems, via their ability to drive pro-inflammatory cytokine and interferon production, contribute to the development of autoimmune and autoinflammatory disease is supported by a wide range of clinical and experimental observations. Recently, the tripartite

motif-containing proteins (TRIMs) have emerged as having key roles in antiviral immunity - either as viral restriction factors or as regulators of pathways downstream of viral RNA and DNA sensors, and the inflammasome. Given their involvement in these pathways, we propose that TRIM proteins contribute to the development and pathology of autoimmune and autoinflammatory conditions, thus making them potential novel targets for therapeutic manipulation.

DOI: 10.1038/nri3043

PMID: 21866173 [Indexed for MEDLINE]

2928. J Clin Endocrinol Metab. 2011 Nov;96(11):3313-25. doi: 10.1210/jc.2011-1159. Epub 2011 Aug 24.

Clinical review#: Lipodystrophies: genetic and acquired body fat disorders.

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**CONTEXT:** Lipodystrophies are heterogeneous, genetic or acquired disorders characterized by selective loss of body fat and predisposition to insulin resistance. The extent of fat loss determines the severity of associated metabolic complications such as diabetes mellitus, hypertriglyceridemia, and hepatic steatosis.

**EVIDENCE ACQUISITION AND SYNTHESIS:** Both original and review articles were found via PubMed search reporting on clinical features and management of various types of lipodystrophies and were integrated with the author's knowledge of the field.

**CONCLUSION:** The autosomal recessive congenital generalized lipodystrophy and autosomal dominant familial partial lipodystrophy (FPL) are the two most common types of genetic lipodystrophies. Mutations in AGPAT2, BSCL2, CAV1, and PTRF have been reported in congenital generalized lipodystrophy and in LMNA, PPARG, AKT2, and PLIN1 in FPL. CIDEA is the disease gene for autosomal recessive, FPL and LMNA and ZMPSTE24 for autosomal recessive, mandibuloacral dysplasia-associated lipodystrophy. Recently, an autosomal recessive autoinflammatory lipodystrophy syndrome was reported to be due to PSMB8 mutation. Molecular genetic bases of

many rare forms of genetic lipodystrophies remain to be elucidated. The most prevalent subtype of acquired lipodystrophy currently occurs with prolonged duration of protease inhibitor-containing, highly-active antiretroviral therapy in HIV-infected patients. The acquired generalized and partial lipodystrophies are mainly autoimmune in origin and display complement abnormalities. Localized lipodystrophies occur due to drug or vaccine injections, pressure, panniculitis, and other unknown reasons. The current management includes cosmetic surgery and early identification and treatment of metabolic and other complications with diet, exercise, hypoglycemic drugs, and lipid-lowering agents.

DOI: 10.1210/jc.2011-1159

PMID: 21865368 [Indexed for MEDLINE]

2929. Autoimmun Rev. 2011 Dec;11(2):154-6. doi: 10.1016/j.autrev.2011.08.004. Epub 2011 Aug 16.

B cells are resistant to immunomodulation by 'IVIg-educated' dendritic cells.

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Intravenous immunoglobulin (IVIg) can exert beneficial effects in autoimmune and inflammatory diseases via several mutually non-exclusive mechanisms. While, IVIg can directly modulate the functions of both innate and adaptive immune cells such as dendritic cells (DC), macrophages, B and T cells, several reports have also highlighted that the regulation of immune responses by IVIg can be indirect. In view of these results, we aimed at exploring whether indirect regulation of immune cells by 'IVIg-educated' innate cells is a universal phenomenon. We addressed this question by deciphering the modulation of B cell functions by 'IVIg-educated' DC. Our results indicate that human B cells are resistant to immunomodulation by 'IVIg-educated' DC. However, IVIg at therapeutic concentrations can directly inhibit B cell activation and proliferation. These results thus suggest that, indirect modulation of immune cells by IVIg is not a universal phenomenon.

DOI: 10.1016/j.autrev.2011.08.004

PMID: 21864723 [Indexed for MEDLINE]

2930. Strategies Trauma Limb Reconstr. 2011 Nov;6(3):173-6. doi: 10.1007/s11751-011-0119-y. Epub 2011 Aug 24.

Staged correction of an equinovarus deformity due to pyoderma gangrenosum using a Taylor spatial frame and tibiotalar calcaneal fusion with an intramedullary device.

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Pyoderma gangrenosum is a rare autoinflammatory syndrome manifested by skin lesions eventually creating ulcers. Surgical management can lead to scarring and contracture at the site of the lesion due to the pathergy phenomenon. A 43-year-old woman presented with a 5-year history of severe equinovarus deformity due to chronic pyoderma gangrenosum on her posteromedial ankle. She underwent a staged fusion. A gradual "closed" correction was performed in a Taylor spatial frame for 8 weeks in order to obviate the need for a surgical release in the area of the ulcer. She was ambulatory and full weight-bearing within 4 weeks of her frame removal. She maintained her correction with an accommodative foot orthosis until she had an uneventful tibiotalar calcaneal fusion with an intramedullary device. This case represents the success of using a Taylor spatial frame for staged fusion involving soft-tissue correction of severe, rigid equinovarus deformity due to pyoderma gangrenosum.

DOI: 10.1007/s11751-011-0119-y

PMCID: PMC3225573

PMID: 21863298



2931. Endocrinology. 2011 Nov;152(11):4039-45. doi: 10.1210/en.2011-1326. Epub 2011 Aug 23.

Elimination of the NLRP3-ASC inflammasome protects against chronic obesity-induced pancreatic damage.

Youm YH(1), Adijiang A, Vandanmagsar B, Burk D, Ravussin A, Dixit VD.

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Comment in

Endocrinology. 2011 Nov;152(11):4005-6.

Clinical evidence that the blockade of IL-1 $\beta$  in type-2 diabetic patients improves glycemia is indicative of an autoinflammatory mechanism that may trigger adiposity-driven pancreatic damage. IL-1 $\beta$  is a key contributor to the obesity-induced inflammation and subsequent insulin resistance, pancreatic  $\beta$ -cell dysfunction, and the onset of type 2 diabetes. Our previous studies demonstrated that the ceramides activate the Nod-like receptor family, pyrin domain containing 3 (Nlrp3) inflammasome to cause the generation of mature IL-1 $\beta$  and ablation of the Nlrp3 inflammasome in diet-induced obesity improves insulin signaling. However, it remains unclear whether the posttranslational processing of active IL-1 $\beta$  in pancreas is regulated by the NLRP3 inflammasome or whether the alternate mechanisms play a dominant role in chronic obesity-induced pancreatic  $\beta$ -cell exhaustion. Here we show that loss of ASC, a critical adaptor required for the assembly of the NLRP3 and absent in melanoma 2 inflammasome substantially improves the insulin action. Surprisingly, despite lower insulin resistance in the chronically obese NLRP3 and ASC knockout mice, the insulin levels were substantially higher when the inflammasome pathway was eliminated. The obesity-induced increase in maturation of pancreatic IL-1 $\beta$  and pancreatic islet fibrosis was dependent on the NLRP3 inflammasome activation. Furthermore, elimination of NLRP3 inflammasome protected the pancreatic  $\beta$ -cells from cell death caused by long-term high-fat feeding during obesity with significant increase in the size of the islets of Langerhans. Collectively, this study provides direct in vivo evidence that activation of the NLRP3 inflammasome in diet-induced obesity is a critical trigger in causing pancreatic damage and is an

important mechanism of progression toward type 2 diabetes.

DOI: 10.1210/en.2011-1326

PMCID: PMC3199005

PMID: 21862613 [Indexed for MEDLINE]

2932. Ann Rheum Dis. 2011 Dec;70(12):2155-8. doi: 10.1136/ard.2011.149922. Epub 2011 Aug 21.

On-demand anakinra treatment is effective in mevalonate kinase deficiency.

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**BACKGROUND:** Mevalonate kinase deficiency (MKD) is a hereditary autoinflammatory syndrome marked by recurrent attacks of fever and inflammation. Severe enzyme deficiency results in mevalonic aciduria (MA) and milder deficiency in hyperimmunoglobulin D syndrome (HIDS). Treatment remains a challenge.

**OBJECTIVE:** To observe the effect of the recombinant interleukin-1 receptor antagonist anakinra in patients with MKD.

**METHODS:** A prospective observational study was undertaken. Two patients with MA started continuous treatment with anakinra (1-2 mg/kg/day) and nine patients with HIDS chose between continuous treatment and on-demand treatment (starting at first symptoms of attack, 100 mg/day or 1 mg/kg/day for 5-7 days).

**RESULTS:** Anakinra induced partial remission in one patient with MA but there was no response in the other patient with MA. In one patient with HIDS continuous treatment induced complete remission for 7 months but was stopped because of side effects. Eight patients with HIDS preferred on-demand treatment from the start. This induced a clinical response ( $\geq 50\%$  reduction in duration) in 8 of 12 treated attacks without a change in attack frequency. Anakinra prevented fever attacks due to vaccination without inhibiting antibody induction. No major side effects were seen.

**CONCLUSIONS:** On-demand treatment with anakinra in HIDS decreases the duration and severity of fever attacks. Because of the burden of daily injections and relatively long asymptomatic intervals of HIDS, all patients with HIDS preferred

on-demand treatment.

DOI: 10.1136/ard.2011.149922

PMID: 21859689 [Indexed for MEDLINE]

2933. Clin Med (Lond). 2011 Aug;11(4):396-401.

Does this patient have periodic fever syndrome?

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PMID: 21853843 [Indexed for MEDLINE]

2934. Proc Natl Acad Sci U S A. 2011 Sep 6;108(36):14914-9. doi:  
10.1073/pnas.1106015108. Epub 2011 Aug 18.

Proteasome assembly defect due to a proteasome subunit beta type 8 (PSMB8)  
mutation causes the autoinflammatory disorder, Nakajo-Nishimura syndrome.

Arima K(1), Kinoshita A, Mishima H, Kanazawa N, Kaneko T, Mizushima T, Ichinose  
K, Nakamura H, Tsujino A, Kawakami A, Matsunaka M, Kasagi S, Kawano S, Kumagai S,  
Ohmura K, Mimori T, Hirano M, Ueno S, Tanaka K, Tanaka M, Toyoshima I, Sugino H,  
Yamakawa A, Tanaka K, Niikawa N, Furukawa F, Murata S, Eguchi K, Ida H, Yoshiura  
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Nakajo-Nishimura syndrome (NNS) is a disorder that segregates in an autosomal  
recessive fashion. Symptoms include periodic fever, skin rash, partial

lipomuscular atrophy, and joint contracture. Here, we report a mutation in the human proteasome subunit beta type 8 gene (PSMB8) that encodes the immunoproteasome subunit  $\beta 5i$  in patients with NNS. This G201V mutation disrupts the  $\beta$ -sheet structure, protrudes from the loop that interfaces with the  $\beta 4$  subunit, and is in close proximity to the catalytic threonine residue. The  $\beta 5i$  mutant is not efficiently incorporated during immunoproteasome biogenesis, resulting in reduced proteasome activity and accumulation of ubiquitinated and oxidized proteins within cells expressing immunoproteasomes. As a result, the level of interleukin (IL)-6 and IFN- $\gamma$  inducible protein (IP)-10 in patient sera is markedly increased. Nuclear phosphorylated p38 and the secretion of IL-6 are increased in patient cells both in vitro and in vivo, which may account for the inflammatory response and periodic fever observed in these patients. These results show that a mutation within a proteasome subunit is the direct cause of a human disease and suggest that decreased proteasome activity can cause inflammation.

DOI: 10.1073/pnas.1106015108

PMCID: PMC3169106

PMID: 21852578 [Indexed for MEDLINE]

2935. *Cardiol Young*. 2012 Apr;22(2):188-93. doi: 10.1017/S1047951111001168. Epub 2011 Aug 19.

Assessment of cardiac functions using tissue Doppler imaging in children with familial Mediterranean fever.

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**OBJECTIVE:** Familial Mediterranean fever may carry a potential for cardiovascular disorders because of sustained inflammation during its course; however, there has been a limited number of studies investigating the cardiac functions in children. The aim of this study was to assess both ventricular diastolic functions using conventional echocardiography and tissue Doppler imaging in children with familial Mediterranean fever.

**PATIENTS AND METHODS:** The study population included 25 patients with familial Mediterranean fever - mean age was 11.8 plus or minus 5.30 years - and 23 healthy patients as controls - mean age was 9.88 plus or minus 3.69 years. Both ventricular functions were measured using echocardiography comprising standard M-mode and conventional Doppler and tissue Doppler imaging during an attack-free period.

**RESULTS:** The conventional echocardiographic parameters with myocardial performance index were in normal ranges and similar in patients with familial Mediterranean fever and controls, with a p-value more than 0.05. However, right ventricular diastolic dysfunction was observed in patients with familial Mediterranean fever documented by tissue Doppler imaging, with a p-value less than 0.05 for E't and A't wave ratio.

**CONCLUSION:** Using tissue Doppler imaging, we have demonstrated that although left ventricular functions were comparable in the patients and healthy children, right ventricular diastolic function indices were impaired in patients with familial Mediterranean fever during childhood. Impaired right ventricular diastolic function may be an early manifestation of cardiac involvement in children with familial Mediterranean fever.

DOI: 10.1017/S1047951111001168

PMID: 21851761 [Indexed for MEDLINE]

2936. J Med Case Rep. 2011 Aug 18;5:390. doi: 10.1186/1752-1947-5-390.

Renal and suprarenal insufficiency secondary to familial Mediterranean fever associated with amyloidosis: a case report.

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**INTRODUCTION:** Familial Mediterranean fever is an autosomal recessive disease that predominantly affects people of the Mediterranean coast. One of the most frequent complications of the disease is amyloidosis. This clinical entity is known as secondary (also called AA) amyloidosis.

**CASE PRESENTATION:** In this report, we describe the case of a 33-year-old Turkish

man with familial Mediterranean fever and chronic renal insufficiency. He was admitted to our clinic with symptoms of suprarenal insufficiency. The patient died three months later as a result of cardiac arrest.

**CONCLUSION:** Our aim is to make a contribution to the literature by reporting a case of combined insufficiency due to the accumulation of renal and adrenal amyloid in a patient with familial Mediterranean fever, which has very rarely been described in the literature. We hope that adrenal insufficiency, which becomes fatal if not diagnosed and treated rapidly, will come to mind as easily as chronic renal failure in clinical practice.

DOI: 10.1186/1752-1947-5-390

PMCID: PMC3177917

PMID: 21851607

2937. Ren Fail. 2011;33(9):899-903. doi: 10.3109/0886022X.2011.605980. Epub 2011 Aug 18.

Association between ABCB1 (MDR1) gene 3435 C>T polymorphism and colchicine unresponsiveness of FMF patients.

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The multidrug resistance gene-1 (MDR1, adenosine triphosphate-binding cassette transporter: ABCB1, P-glycoprotein) encodes membrane proteins that play a crucial role in protecting cells from xenobiotics, chemicals, and drugs. The TT genotype of 3435 codon in exon 26 of MDR1 gene causes overexpression of gene activity and effluxes many chemically diverse compounds across the plasma membrane. We studied the association between C3435T polymorphisms (single nucleotide polymorphism) of MDR1 gene and colchicine-resistant familial Mediterranean fever (FMF) patients. Total genomic DNA samples from 52 FMF patients of colchicine unresponsiveness were used for FMF (MEFV) and MDR1 genes profile analyses. Target genes were genotyped by multiplex PCR-based reverse-hybridization Strip Assay method. The preliminary current results showed increased T allele frequency (0.596) in colchicine unresponsiveness of FMF patients. The distributions of the CC, CT, and

TT genotypes in colchicine nonresponder FMF patients were 17%, 46%, and 37%, respectively. Our results indicate that C3435T polymorphism in exon 26 of MDR1 gene is associated with colchicine resistance in nonresponder FMF patients during the common therapy protocol.

DOI: 10.3109/0886022X.2011.605980

PMID: 21851199 [Indexed for MEDLINE]

2938. Rheumatol Int. 2012 Sep;32(9):2629-36. doi: 10.1007/s00296-011-2019-3. Epub 2011 Jul 22.

"Mutation negative" familial cold autoinflammatory syndrome (FCAS) in an 8-year-old boy: clinical course and functional studies.

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Cryopyrinopathies are a subgroup of autoinflammatory syndromes. Most cases have mutations in the CIAS1/NLRP3 gene, encoding the cryopyrin/NLRP3 protein. Cryopyrin, together with other proteins, is involved in the assembly of the cryopyrin/NLRP3 inflammasome. Mutations in CIAS1/NLRP3 result in increased IL-1 $\beta$  cleavage from biologically inactive pro-IL-1 $\beta$ . This results in systemic inflammation and three associated disorders of different severity, forming a clinical continuum with overlapping features. The mildest form, familial cold autoinflammatory syndrome (FCAS), is characterized by remitting fevers, urticaria-like rash, polyarthralgia/arthritis, and usually caused by cold exposure. More severe forms are Muckle-Wells syndrome (MWS) and CINCA/NOMID. We report an 8-year-old boy with FCAS, who presented with overlapping features with MWS. He showed good response to seasonal anakinra treatment. Mutation analysis in CIAS1/NLRP3, PYCARD, and CASP1 was performed. Serum cytokine profiles, and cytokine expression from resting monocytes, and in response to mild hypothermia, and LPS stimulation were determined. Mutations in CIAS1/NLRP3, PYCARD, and CASP1 were not found. In response to mild hypothermia, an enhanced IL-1 $\beta$  expression by

patient monocytes resulted in increased IL-6 and TNF- $\alpha$  secretion, as compared to control cells. The addition of the IL-1 $\beta$  receptor antagonist (anakinra) reversed these effects. In response to LPS stimulation, patient monocytes produced high level of IL-1 $\beta$ , IL-6 and TNF- $\alpha$ . This was markedly less pronounced in control monocytes. FCAS results in cold-induced cytokine dysregulation and systemic inflammation. Symptoms can be treated, using IL-1 $\beta$  antagonists. Further research is warranted, particularly in order to investigate pathophysiological mechanisms in "mutation negative" individuals.

DOI: 10.1007/s00296-011-2019-3

PMID: 21833523 [Indexed for MEDLINE]

2939. J Cardiol Cases. 2011 Aug 12;4(2):e93-e97. doi: 10.1016/j.jccase.2011.07.003. eCollection 2011 Oct.

A case series and systematic literature review of anakinra and immunosuppression in idiopathic recurrent pericarditis.

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Idiopathic recurrent pericarditis (IRP) impairs quality of life. Although its precise etiology is not certain, it is believed to be immunologically mediated. Its optimal treatments are unknown. Initial therapy is with non-steroidal anti-inflammatory drugs and colchicine. Steroids, which are often used, however may promote recurrences. European guidelines advocate azathioprine or cyclophosphamide in refractory cases despite limited evidence. We report two adults with IRP successfully treated with the interleukin-1 antagonist, anakinra. We combine this experience with the first systematic literature review of immunosuppression in IRP. A total of 8 papers were included in the review, which alongside our patients described 18 cases. The best treatments comprised anakinra and intravenous immunoglobulin, with respective remission rates of 100% and 67%. Cyclophosphamide and azathioprine were less efficacious. The unprovoked



inflammatory episodes in our patients alongside their prompt response to anakinra indicate that in some instances IRP may represent an autoinflammatory condition. We suggest that in IRP refractory to initial treatment, anakinra should be considered as a potential therapy. Clinical trials are required to confirm its benefits in IRP.

DOI: 10.1016/j.jccase.2011.07.003

PMCID: PMC6265095

PMID: 30534275

2940. BMC Med Genet. 2011 Aug 7;12:105. doi: 10.1186/1471-2350-12-105.

Analysis of MEFV exon methylation and expression patterns in familial Mediterranean fever.

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**BACKGROUND:** MEFV mutations and decreased expression level of the gene are related to FMF pathology. DNA methylation at CpG islands is a well-known mechanism for transcriptional silencing. MEFV has a CpG island, spanning a part of the first intron and the whole of the second exon of the gene covering 998 bp region. Here, we tested the hypothesis that the MEFV transcript level in FMF patients correlates with its methylation level, and methylation, by allowing transcription silencing, has a role in FMF ethiopathogenesis.

**METHODS:** The study group was composed of pediatric FMF patients (N = 51) and age-gender matched healthy controls (N = 21). The relative expression level of MEFV was assessed via quantitative real-time PCR (qRT-PCR) and bisulfite sequencing (BS) was performed to analyse the methylation level quantitatively.

**RESULTS:** MEFV expression in FMF patients were decreased compared to healthy controls (P = 0.031). Methylation level of exon 2 of MEFV was found to be slightly higher in FMF patients compared to healthy controls (76% versus 74%) (P = 0.049). The expression level of the MEFV was negatively correlated with the methylation level of the CpG island in both FMF and healthy controls groups (cor

= -0.29, P = 0.041) but more so in the FMF only group (cor = -0.36, P = 0.035).

CONCLUSIONS: In this study, the relation between reduced MEFV expression level and FMF was confirmed. Observed slight increase in methylation in FMF patients, and correlation of methylation with expression might be indicative of its role in FMF, however a larger dataset is needed to confirm our preliminary findings.

DOI: 10.1186/1471-2350-12-105

PMCID: PMC3175150

PMID: 21819621 [Indexed for MEDLINE]

2941. J Dtsch Dermatol Ges. 2012 Mar;10(3):174-8. doi: 10.1111/j.1610-0387.2011.07760.x. Epub 2011 Aug 3.

Biologics in atopic dermatitis.

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Atopic dermatitis (AD) accounts for a significant share of chronic inflammatory skin disorders. There is a niche for the development of biologics to treat recalcitrant autoinflammatory stage AD seen mostly in adults. The heterogeneity of patient response to various existing biotherapies points to involvement of various immune responses and suggests that therapies must preferably target early development of allergen-specific B- and T-cell clones. In addition to immune targets, tissue factors that help restore the normal epidermal environment constitute interesting therapeutic tools. Several approaches are needed to find the appropriate targets in a field where so many have been investigated without definitive proof of concept for human systemic therapy. The keys to success are probably (1) to influence the inflammatory skin pattern towards less pruritogenic effects, requiring us to better understand pruritogenic inflammation and (2) to limit the amplification loop of disease by attacking abnormal regulatory mechanisms which perpetuate skin autoinflammation.

DOI: 10.1111/j.1610-0387.2011.07760.x

PMID: 21812930 [Indexed for MEDLINE]

2942. Oral Dis. 2011 Nov;17(8):755-70. doi: 10.1111/j.1601-0825.2011.01840.x. Epub 2011 Aug 4.

Urban legends: recurrent aphthous stomatitis.

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Comment in

Oral Dis. 2012 Jul;18(5):521; author reply 520.

Recurrent aphthous stomatitis (RAS) is the most common idiopathic intraoral ulcerative disease in the USA. Aphthae typically occur in apparently healthy individuals, although an association with certain systemic diseases has been reported. Despite the unclear etiopathogenesis, new drug trials are continuously conducted in an attempt to reduce pain and dysfunction. We investigated four controversial topics: (1) Is complex aphthosis a mild form of Behçet's disease (BD)? (2) Is periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome a distinct medical entity? (3) Is RAS associated with other systemic diseases [e.g., celiac disease (CD) and B12 deficiency]? (4) Are there any new RAS treatments? Results from extensive literature searches, including a systematic review of RAS trials, suggested the following: (1) Complex aphthosis is not a mild form of BD in North America or Western Europe; (2) Diagnostic criteria for PFAPA have low specificity and the characteristics of the oral ulcers warrant further studies; (3) Oral ulcers may be associated with CD; however, these ulcers may not be RAS; RAS is rarely associated with B12 deficiency; nevertheless, B12 treatment may be beneficial, via mechanisms that warrant further study; (4) Thirty-three controlled trials published in the past 6 years reported some effectiveness, although potential for bias was high.

DOI: 10.1111/j.1601-0825.2011.01840.x

PMCID: PMC3192917

PMID: 21812866 [Indexed for MEDLINE]

2943. Clin Dev Immunol. 2012;2012:252460. doi: 10.1155/2012/252460. Epub 2011 Jul 25.

Current concepts of hyperinflammation in chronic granulomatous disease.

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Chronic granulomatous disease (CGD) is the most common inherited disorder of phagocytic functions, caused by genetic defects in the leukocyte nicotinamide dinucleotide phosphate (NADPH) oxidase. Consequently, CGD phagocytes are impaired in destroying phagocytosed microorganisms, rendering the patients susceptible to bacterial and fungal infections. Besides this immunodeficiency, CGD patients suffer from various autoinflammatory symptoms, such as granuloma formation in the skin or urinary tract and Crohn-like colitis. Owing to improved antimicrobial treatment strategies, the majority of CGD patients reaches adulthood, yet the autoinflammatory manifestations become more prominent by lack of causative treatment options. The underlying pathomechanisms driving hyperinflammatory reactions in CGD are poorly understood, but recent studies implicate reduced neutrophil apoptosis and efferocytosis, dysbalanced innate immune receptors, altered T-cell surface redox levels, induction of Th17 cells, the enzyme indolamine-2,3-dioxygenase (IDO), impaired Nrf2 activity, and inflammasome activation. Here we discuss immunological mechanisms of hyperinflammation and their potential therapeutic implications in CGD.

DOI: 10.1155/2012/252460

PMCID: PMC3144705

PMID: 21808651 [Indexed for MEDLINE]

2944. Turk J Gastroenterol. 2011 Jun;22(3):260-9.

The diagnosis and outcomes of persistent diarrhea in infants aged 0-24 months--a Turkish cohort study.

Eğritaş O(1), Sari S, Dalgıç B, Poyraz A, Ensarı A.

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**BACKGROUND/AIMS:** Infantile persistent diarrhea series are not well documented in the literature. Evaluating the literature, the aim of this study was to document persistent diarrhea cases followed in our center and to constitute a practical diagnostic algorithm for the pediatrician by means of surveying methods.

**METHODS:** Diarrheas lasting more than 14 days were accepted as persistent diarrhea. Forty-one persistent diarrhea cases aged 0-24 months were investigated in this study. The cases were evaluated for the presence of mucus and/or leukocytes in stool and were thus divided into two major groups as colitis or enteropathies. For the differential diagnosis of the persistent colitis group, stool cultures, dietary restrictions, complete blood count, acute phase reactants, pathergy test, gene analysis for familial Mediterranean fever and Behçet's disease, colonoscopy, and biopsies were performed. In the persistent enteropathy group, differential diagnosis was made with the following tests: serum and stool electrolytes, arterial blood gases, serum albumin, total protein, lipid profile, stool alpha-1 antitrypsin level, stool pH, presence of stool fat and reducing substance, endoscopy, and biopsies.

**RESULTS:** The 27 persistent enteropathy cases included 7 celiac disease, 5 intestinal lymphangiectasia, 2 microvillus inclusion disease, 2 abetalipoproteinemia, and 11 cow's milk allergy. The 13 cases of the infantile colitis group included 1 Behçet's disease, 1 colitis ulcerosa and 11 cow's milk allergy. Two cases presenting as pancreatic insufficiency were diagnosed as cystic fibrosis. One case was diagnosed as cystic fibrosis plus cow's milk allergy.

**CONCLUSIONS:** Reviewing the literature, these cases represent the largest non-infectious infantile group of persistent diarrheas. A practical diagnostic algorithm for persistent diarrheas has been constituted.

2945. Curr Opin Pharmacol. 2011 Aug;11(4):423-8. doi: 10.1016/j.coph.2011.07.002. Epub 2011 Jul 29.

NLRs in immune privileged sites.

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Innate immune receptors such as the nucleotide-binding domain, leucine-rich repeat-containing (NBD-LRR) receptors, referred to as NLRs, are known to serve as a critical component of host defense. However, their participation in inflammatory responses within immune privileged sites such as the brain and eye is less understood. The potential importance of NLRs in regulation of inflammation within these particular sites is further underscored by their association with autoinflammatory disorders, wherein localized inflammation can occur within the brain or eye as neuroinflammation or uveitis, respectively. Many NLRs are expressed within the brain and eye and in this review, we discuss their roles in the inflammation of the central nervous system (CNS) and uveitis.

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DOI: 10.1016/j.coph.2011.07.002

PMCID: PMC3157845

PMID: 21803656 [Indexed for MEDLINE]

2946. Eurasian J Med. 2011 Aug;43(2):79-82. doi: 10.5152/eajm.2011.18.

Trace element levels in patients with familial mediterranean Fever.

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**OBJECTIVE:** Although the genetic etiology of familial Mediterranean fever (FMF) is known, limited information is available regarding the regulation of inflammation during attack-free periods. The aim of this study was to determine the alterations in serum copper (Cu), zinc (Zn) and selenium (Se) levels that may be associated with inflammation during attack-free periods in FMF patients.

**MATERIALS AND METHODS:** This study included 33 patients with FMF and 30 healthy volunteers. Erythrocyte sedimentation rate (ESR), the serum C-reactive protein (CRP) level and serum levels of Cu, Zn and Se in FMF patients and healthy volunteers were assessed by the atomic absorption spectrophotometry method.

**RESULTS:** ESR and serum CRP levels and serum Cu and Zn levels were similar between patients with FMF during an attack-free period and healthy controls ( $p>0.05$ ). Serum Se levels in the patient group were significantly higher than in the control group ( $p<0.05$ ).

**CONCLUSION:** Our study shows that levels of trace elements in serum are variable in patients with FMF during attack-free periods. Serum Se concentrations may at least in part contribute to the subclinical inflammation in FMF patients during attack-free periods. However, further studies are necessary to confirm this result.

**Publisher:** Ailesel Akdeniz ateşi (FMF) hastalığının genetik etiyolojisi bilinmesine rağmen, ataksız dönemdeki inflamasyonun düzenlenişi hakkındaki bilgiler sınırlıdır. Bu çalışmanın amacı, FMF hastalığının ataksız döneminde inflamasyonla ilişkili olabilecek serum bakır (Cu), çinko (Zn) ve selenyum (Se) seviyelerindeki değişimleri değerlendirmektir. Bu çalışma 33 FMF hastası ve 30 sağlıklı gönüllüyle düzenlendi. FMF hastalarındaki eritrosit sedimentasyon hızı (ESH), serum C reaktif protein (CRP), Cu, Zn ve Se düzeyleri atomik absorbsiyon spektrofotometri metoduyla değerlendirildi. ESH, serum CRP, Cu ve Zn seviyeleri ataksız periyottaki FMF hastaları ve sağlıklı kontroller arasında benzer düzeydeydi ( $p>0.05$ ). Hasta grubunda serum Se düzeyleri kontrol grubundan anlamlı derecede daha yüksekti ( $p<0.05$ ). Bizim çalışmamız ataksız dönemdeki FMF hastalarında serumdaki eser element seviyelerinin değişken olabildiğini göstermektedir. Serum Se konsantrasyonları FMF hastalarında en azından ataksız dönemdeki subklinik inflamasyona katkıda bulunabilir. Bu sonuçları değerlendirmek

için yeni çalışmalara ihtiyaç bulunmaktadır.

DOI: 10.5152/eajm.2011.18

PMCID: PMC4261345

PMID: 25610168

2947. Reumatol Clin. 2011 Jan-Feb;7(1):45-50. doi: 10.1016/j.reuma.2010.01.010. Epub 2010 May 13.

[Hereditary systemic autoinflammatory diseases].

[Article in Spanish]

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Systemic autoinflammatory diseases encompass different rare clinical entities characterized by recurrent acute inflammatory episodes secondary to a dysregulated inflammatory process. Since their first clinical descriptions, the Mendelian hereditary nature of some of them became evident, with their genetic and molecular basis being recently elucidated. There are disease-causing mutations in genes encoding for different proteins involved in the innate immune response and inflammation. Herein, we will introduce the reader to an updated review of the main clinical, physiopathological and therapeutic features of the different hereditary systemic autoinflammatory diseases.

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DOI: 10.1016/j.reuma.2010.01.010

PMID: 21794778 [Indexed for MEDLINE]

2948. Discov Med. 2011 Jul;12(62):65-74.

Inflammasome activation in obesity-related inflammatory diseases and autoimmunity.



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The inflammasome is a highly regulated protein complex that triggers caspase-1 activation and subsequent secretion of IL-1 $\beta$  and IL-18. Recognition of microbial components and danger signals by NOD-like receptor (NLR) family members in the cytosol promotes inflammasome activation and downstream inflammatory cytokine production. Pathogen recognition by NLRs and downstream release of inflammasome-derived cytokines are important in host defense against numerous infections. Recent studies have also identified a unique role for inflammasome regulation in the induction and pathogenesis of multiple autoimmune and inflammatory disorders. We now know that obesity-related factors and endogenous markers of cellular stress can lead to unchecked activation of the inflammasome and provoke inflammation and subsequent destruction of vital organs. This review will highlight recent findings that link inflammasome signaling to the progression of autoinflammatory and autoimmune diseases. We will focus on the contribution of inflammasome activation to the pathogenesis of autoinflammatory and autoimmune diseases that are of major significance to human health including type 2 diabetes, atherosclerosis, multiple sclerosis, and type 1 diabetes.

PMCID: PMC4266394

PMID: 21794210 [Indexed for MEDLINE]

2949. Arthritis Rheum. 2011 Dec;63(12):4018-22. doi: 10.1002/art.30565.

The first reported case of compound heterozygous IL1RN mutations causing deficiency of the interleukin-1 receptor antagonist.

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Interleukin-1 receptor antagonist (IL-1Ra) deficiency is a rare autoinflammatory disease involving neonatal onset of pustulosis, periostitis, and sterile osteomyelitis. We report the case of a 2-week-old male who presented with a swollen, erythematous left index finger and elevated serum markers of inflammation. He later developed cyclical fevers, diffuse pustular skin lesions, and thrombus formation. After not responding to broad-spectrum antimicrobial therapy and achieving only moderate success with systemic steroid therapy, he was ultimately treated with recombinant IL-1Ra, anakinra, and experienced significant clinical improvement. Sequencing of his IL1RN gene revealed that the patient was compound heterozygous for a known mutation (E77X) associated with IL-1Ra deficiency and a novel mutation in exon 2 of the gene (c.140delC; p.T47TfsX4). His case highlights IL-1Ra deficiency as an autoinflammatory disease that is distinct from neonatal-onset multisystem inflammatory disease but that also responds well to anakinra. Our patient is the first reported compound heterozygote for E77X and the novel mutation in exon 2 of the gene, the latter of which adds to what will surely be a growing database of pathologic mutations in IL1RN.

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DOI: 10.1002/art.30565

PMID: 21792839 [Indexed for MEDLINE]

2950. Clin Exp Dermatol. 2011 Dec;36(8):889-95. doi: 10.1111/j.1365-2230.2011.04137.x. Epub 2011 Jul 25.

Mutations in the PSTPIP1 gene and aberrant splicing variants in patients with pyoderma gangrenosum.

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**BACKGROUND:** Pyoderma gangrenosum (PG) is a rare, noninfectious form of skin ulceration, typically accompanied by neutrophilic infiltration. Several familial cases have been reported, suggesting the involvement of genetic factors in the

aetiology of PG. Two mutations (A230T and E250Q) in the PSTPIP1 gene, encoding proline-serine-threonine phosphatase-interacting protein (PSTPIP)1 have been identified in patients with PAPA (pyogenic sterile arthritis with PG and acne) syndrome, a rare autoinflammatory disorder with autosomal dominant inheritance. AIM: The aim of this study was to sequence PSTPIP1 complementary cDNA and genomic DNA for mutations, and to identify genetic polymorphisms in the promoter region of PSTPIP1 in patients with PG.

METHODS: The genomic region and cDNA of the PSTPIP1 gene were sequenced from peripheral blood leucocytes of 14 patients with PG and 20 healthy controls.

RESULTS: One patient (PG1) had aberrant splicing variants of the PSTPIP1 transcript with deletions of exons 9, 11 and 12 and of exons 9-12 together, and all other patients with PG carried deletions of exon 11 and of 11-12. We also identified a novel mutation (G258A) in patient PG3, and novel polymorphisms [(CCTG)(6) and (CCTG)(8) tandem repeats] in the promoter region of the PSTPIP1 gene.

CONCLUSION: All combinations of aberrant splicing variants had frame shifts and premature stop codons leading to truncated proteins and loss of function of PSTPIP1. The (CCTG)(n) tandem repeats in the promoter region of PSTPIP1 had no association with PG. The mutations G258A and R52Q are predicted by the improved prediction algorithm to have a possibly damaging effect on PSTPIP1 function.

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DOI: 10.1111/j.1365-2230.2011.04137.x

PMID: 21790734 [Indexed for MEDLINE]

2951. Z Rheumatol. 2011 Aug;70(6):511-6. doi: 10.1007/s00393-011-0751-4.

[MEFV gene mutation spectrum in familial Mediterranean fever (FMF) : a single center study in the Aegean region of Turkey].

[Article in German]

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**OBJECTIVES:** Familial Mediterranean fever (FMF), an autosomal recessive autoinflammatory disorder, is characterized by recurrent, self-limiting fever and serositis which is frequently seen in Mediterranean populations. In this study, we retrospectively evaluated the MEFV gene mutation distribution of 883 citizens of the Aegean region with preliminary diagnosis of FMF who were referred to the Tepecik Research and Education Hospital's Tissue Typing and Molecular Diagnostic Laboratory (Izmir, Turkey) between 2006 and 2009.

**METHODS:** The FMF Strip Assay® (ViennaLab Diagnostics, Vienna, Austria) was used to determine the 12 most common MEFV gene mutations in patients prediagnosed with FMF.

**FINDINGS:** Allelic frequencies of the major mutations in the mutation positive groups, including M694V, E148Q, M680I(G>C), and V726A, accounted for 48.4, 16.5, 13.5, and 9.7%, respectively.

**CONCLUSION:** The M694V mutation was found to be the most common mutation among FMF patients in the Aegean region, which is in accordance with mutation studies reported from other regions of the country and different ethnic populations. An English full-text version of this article is available at SpringerLink as supplemental.

DOI: 10.1007/s00393-011-0751-4

PMID: 21789721 [Indexed for MEDLINE]

2952. *Pediatr Radiol.* 2012 Apr;42(4):495-8. doi: 10.1007/s00247-011-2208-y. Epub 2011 Jul 26.

Deficiency of interleukin-1-receptor antagonist syndrome: a rare auto-inflammatory condition that mimics multiple classic radiographic findings.

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Deficiency of interleukin-1-receptor antagonist (DIRA) syndrome is a newly identified inflammatory disease of the skeleton and appendicular soft tissues presenting in early infancy that has yet to be reported in the radiology

literature. The radiological manifestations of DIRA syndrome include multifocal osteitis of the ribs and long bones, heterotopic ossification and periarticular soft-tissue swelling. Thus, the pediatric radiologist should be made aware of this novel disease because its radiographic findings can mimic multiple other disease entities. With knowledge of the unique clinical presentation of DIRA syndrome and its multiple radiographic manifestations, the pediatric radiologist may be the first to suggest the correct diagnosis.

DOI: 10.1007/s00247-011-2208-y

PMID: 21789664 [Indexed for MEDLINE]

2953. Clin Med Insights Arthritis Musculoskelet Disord. 2011;4:33-41. doi: 10.4137/CMAMD.S6763. Epub 2011 May 9.

Prevalence of connective tissue diseases in egyptian patients presenting with Fever of unknown origin.

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**OBJECTIVE:** To estimate the prevalence of connective tissue diseases in patients presenting with fever of unknown origin (FUO).

**PATIENTS AND METHODS:** In this study thirty patients diagnosed as FUO (Group 1), in 2008, were included in an observational study and diagnostic workup.

Additionally, retrospective analysis of seventy patients' files (Group 2), for patients who presented with prolonged unexplained pyrexia to the same hospital in the previous two years, was performed. Patients were subjected to: full clinical assessment including full history taking, thorough clinical examination, laboratory investigations including the basic investigations for patients with prolonged fever, complete blood count, erythrocytes sedimentation rate, urine analysis and culture, blood culture, sputum culture and plain chest X ray. Further diagnostic work up and/or procedures were requested according to the potential diagnostic clues (PDC) present in every patient.

**RESULTS:** Out of 100 FUO patients, 50% were found to have infectious diseases, 24% were found to have connective tissue diseases, 8% miscellaneous causes and 7% neoplastic diseases ( $P < 0.05$ ). In 11 patients no definite cause for FUO could be

identified. Connective tissue patients were: eight systemic lupus patients (33.3%), five patients with familial mediterranean fever (20.8%), four patients with rheumatoid arthritis (16.6%), three patients (12.5%) with Still's disease and Rheumatic fever and one patient with Behçet syndrome/Crohn's disease (4.3%), ( $P < 0.05$ ).

**CONCLUSIONS:** Despite the advanced technology, FUO remains a challenging medical problem. Infections were the most common cause of FUO in Egypt, confirming the trends found in other parts of the world. There was an increased prevalence of connective tissue patients presented with prolonged unexplained fever. A keen clinical eye, meticulous history taking and repeated physical examination remained the most important diagnostic tools in FUO patients.

DOI: 10.4137/CMAMD.S6763

PMCID: PMC3115637

PMID: 21789030

2954. Curr Opin Rheumatol. 2011 Sep;23(5):424-31. doi: 10.1097/BOR.0b013e328349c363.

Clinical care of children with sterile bone inflammation.

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**PURPOSE OF REVIEW:** To review the current literature of sterile bone inflammation in childhood and to evaluate the evidence for clinical care including diagnostic methods and treatment.

**RECENT FINDINGS:** Chronic noninfectious osteomyelitis includes several different entities marked by sterile bone inflammation associated with histologic evidence of a predominant neutrophil infiltration in the absence of autoantibodies and autoreactive T cells, some of which are associated with a genetic mutation. Whole body MRI is helpful in detecting asymptomatic lesions. Initial treatment with NSAIDs is usually sufficient to control symptoms as the bone heals. However, if the lesions persist and do not respond to first-line treatment, or involve the spine or hip, treatment with bisphosphonate will usually lead to a resolution of symptoms. Rarely, treatment with anti-TNF agents is required.

**SUMMARY:** This review summarizes recent information on diagnosis, treatment and prognosis of disorders involving sterile bone inflammation in childhood. It also addresses the evolving differential diagnosis for autoinflammatory disorders that include sterile bone inflammation and presents a treatment algorithm for management.

DOI: 10.1097/BOR.0b013e328349c363

PMID: 21788901 [Indexed for MEDLINE]

2955. J Immunol. 2011 Sep 1;187(5):2666-76. doi: 10.4049/jimmunol.1003819. Epub 2011 Jul 25.

Inhibition of SOCS1-/- lethal autoinflammatory disease correlated to enhanced peripheral Foxp3+ regulatory T cell homeostasis.

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Suppressor of cytokine signaling 1-deficient (SOCS1(-/-)) mice, which are lymphopenic, die <3 wk after birth of a T cell-mediated autoimmune inflammatory disease characterized by leukocyte infiltration and destruction of vital organs. Notably, Foxp3(+) regulatory T cells (Tregs) have been shown to be particularly potent in inhibiting inflammation-associated autoimmune diseases. We observed that SOCS1(-/-) mice were deficient in peripheral Tregs despite enhanced thymic development. The adoptive transfer of SOCS1-sufficient Tregs, CD4(+) T lymphocytes, or administration of SOCS1 kinase inhibitory region (KIR), a peptide that partially restores SOCS1 function, mediated a statistically significant but short-term survival of SOCS1(-/-) mice. However, the adoptive transfer of SOCS1-sufficient CD4(+) T lymphocytes, combined with the administration of SOCS1-KIR, resulted in a significant increase in the survival of SOCS1(-/-) mice both short and long term, where 100% death occurred by day 18 in the absence of treatment. Moreover, the CD4(+)/SOCS1-KIR combined therapy resulted in decreased leukocytic organ infiltration, reduction of serum IFN- $\gamma$ , and enhanced peripheral accumulation of Foxp3(+) Tregs in treated mice. These data show that

CD4(+)/SOCS1-KIR combined treatment can synergistically promote the long-term survival of perinatal lethal SOCS1(-/-) mice. In addition, these results strongly suggest that SOCS1 contributes to the stability of the Foxp3(+) Treg peripheral population under conditions of strong proinflammatory environments.

DOI: 10.4049/jimmunol.1003819

PMCID: PMC3159835

PMID: 21788442 [Indexed for MEDLINE]

2956. Reumatismo. 2011;63(2):101-10.

[The laboratory approach in the diagnosis of systemic autoinflammatory diseases].

[Article in Italian]

Cantarini L(1), Rigante D, Brizi MG, Sebastiani GD, Lucherini OM, Galeazzi M, Frediani B.

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Systemic autoinflammatory diseases are a group of inherited disorders of the innate immunity characterized by the recurrence of febrile attacks lasting from few hours to few weeks and multi-district inflammation of different severity involving skin, serosal membranes, joints, gastrointestinal tube and central nervous system. The vast majority of these conditions is caused by mutations in genes involved in the control of inflammation and apoptosis mechanisms. The group includes familial Mediterranean fever, mevalonate kinase deficiency syndrome, tumor necrosis factor receptor-associated periodic syndrome, cryopyrin-associated periodic syndromes, hereditary pyogenic and granulomatous disorders. Their diagnostic identification derives from the combination of clinical and biohumoral data, though can be sometimes confirmed by genotype analysis.

PMID: 21776447 [Indexed for MEDLINE]



2957. Self Nonself. 2011 Jan;2(1):35-42. Epub 2011 Jan 1.

A role of IL-1R1 signaling in the differentiation of Th17 cells and the development of autoimmune diseases.

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IL-1 cytokine family plays a key role in the innate immune response against pathogen- and danger-associated molecular patterns. More recently, IL-1 receptor type 1 (IL-1R1) signaling has been identified as a critical step in the differentiation and commitment of Th17 cells, which mediate the development of autoimmune diseases. Given its significance in the induction of the adoptive immune response, this complex signaling pathway is tightly regulated. Upon binding of IL-1 to IL-1R1, IL-1R accessory protein (AcP) is recruited to form a high affinity IL-1R1-IL-1RAcP heterodimeric receptor, which initiates the downstream signaling cascade. Multiple negative regulators of this pathway, including inhibitory membrane-bound IL-1RII, secreted soluble (s)IL-1RI, sIL-1RII and sIL-1RAcP, the regulatory IL-1R1 antagonist (IL-1R1a) and the IL-1R1-signaling-induced single Ig-IL-1R-related (SIGIRR), provide a negative feedback control of this pathway, and suppress excessive IL-1 signaling and Th17 cell differentiation. IL-1R1 signaling induces human Th17 cell differentiation, leading to the expression of IL-1R-associated protein kinase (IRAK)4 and retinoic acid-related orphan nuclear hormone receptor (ROR), Th17 cell lineage transcription factors, which together with signal transducer and activator of the transcription (STAT)3, activate this cell lineage's specific cytokine expression profile, including IL-17A, IL-17F, IL-21 and IL-22. Given the role of IL-1 signaling and Th17 cells in the development of the autoinflammatory and autoimmune diseases, therapeutic strategies inhibiting IL-1R1 signaling are discussed as a novel approach for the treatment of autoimmune diseases and particularly multiple sclerosis (MS).

DOI: 10.4161/self.2.1.15639

PMCID: PMC3136902

PMID: 21776333

2958. Genes Immun. 2011 Oct;12(7):497-503. doi: 10.1038/gene.2011.53. Epub 2011 Jul 21.

The regulation of MEFV expression and its role in health and familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is a hereditary recurrent fever associated with mutations in the gene MEFV encoding pyrin. It is expressed mainly in neutrophils and macrophages, and modulates the production of the potent pro-inflammatory cytokine interleukin-1 $\beta$  through regulation of nuclear factor- $\kappa$ B and caspase-1. The MEFV gene expression depends on multiple levels of regulation. Sequence variants located in the promoter and at the 3'-untranslated region of the gene modulate this expression. Two studies demonstrated decreased mRNA levels in FMF patients compared with healthy subjects, whereas two others found no significant differences. The diverse experimental settings may have resulted in variable quantification of the 15 splice variants that have been identified recently. Some of these isoforms are regulated by nonsense-mediated decay in both cell- and transcript-specific manner, and may be differentially translated in THP1 cells. In addition, pyrin may be cleaved by caspase 1. The full-length pyrin was less abundant than the cleaved fragment in mononuclear cells from FMF patients than in controls, whereas the opposite was observed in granulocytes. Altogether, the regulation of MEFV expression is more complex than anticipated in both physiological and pathological conditions. Its deregulation is likely to alter the inflammasome function and subsequently result in uncontrolled inflammation as seen in FMF.

DOI: 10.1038/gene.2011.53

PMID: 21776013 [Indexed for MEDLINE]

2959. Rheumatol Int. 2012 Jun;32(6):1827-9. doi: 10.1007/s00296-011-2020-x. Epub 2011 Jul 19.

Adult-onset Still's disease and chronic recurrent multifocal osteomyelitis: a hitherto undescribed manifestation of autoinflammation.

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Still's disease and chronic recurrent multifocal osteomyelitis (CRMO) are febrile rheumatic diseases of unknown etiology, which predominantly affect children but can also have their initial manifestation in adults. Both can present as intermittent, relapsing episodes and are considered potential candidates within the expanding spectrum of autoinflammatory disorders, although no genetic abnormalities have been described for either of them. Here, we describe a man with an initial manifestation of abacterial multifocal osteitis at the age of 41. During a relapsing-remitting course of his illness, he increasingly developed symptoms of adult-onset Still's disease (AOSD), and the diagnosis was established according to the Yamaguchi criteria. When treated with anakinra, not only the acute symptoms disappeared promptly, but also the osteitis went into complete remission. This is to our knowledge the first description of a simultaneous occurrence of these two manifestations of autoinflammation in adulthood.

DOI: 10.1007/s00296-011-2020-x

PMID: 21769488 [Indexed for MEDLINE]

2960. Clin Exp Immunol. 2011 Oct;166(1):1-15. doi: 10.1111/j.1365-2249.2011.04440.x. Epub 2011 Jul 15.

The NLRP3 inflammasome in health and disease: the good, the bad and the ugly.

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While interleukin (IL)-1 $\beta$  plays an important role in combating the invading pathogen as part of the innate immune response, its dysregulation is responsible for a number of autoinflammatory disorders. Large IL-1 $\beta$  activating platforms, known as inflammasomes, can assemble in response to the detection of endogenous host and pathogen-associated danger molecules. Formation of these protein complexes results in the autocatalysis and activation of caspase-1, which processes precursor IL-1 $\beta$  into its secreted biologically active form. Inflammasome and IL-1 $\beta$  activity is required to efficiently control viral, bacterial and fungal pathogen infections. Conversely, excess IL-1 $\beta$  activity contributes to human disease, and its inhibition has proved therapeutically beneficial in the treatment of a spectrum of serious, yet relatively rare, heritable inflammasomopathies. Recently, inflammasome function has been implicated in more common human conditions, such as gout, type II diabetes and cancer. This raises the possibility that anti-IL-1 therapeutics may have broader applications than anticipated previously, and may be utilized across diverse disease states that are linked insidiously through unwanted or heightened inflammasome activity.

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DOI: 10.1111/j.1365-2249.2011.04440.x

PMCID: PMC3193914

PMID: 21762124 [Indexed for MEDLINE]

2961. Curr Opin Rheumatol. 2011 Sep;23(5):419-23. doi: 10.1097/BOR.0b013e328349c3b1.

Hyper-IgD syndrome or mevalonate kinase deficiency.

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PURPOSE OF REVIEW: The hyper-IgD and periodic fever syndrome (HIDS) is one of the classical monogenetic hereditary autoinflammatory disorders, and together with the more severe mevalonic aciduria it is also known as 'mevalonate kinase

deficiency' (MKD). In this study, we will give an overview of the primary research on mevalonate kinase deficiency published in the past 2 years.

RECENT FINDINGS: Besides an inventory of a number of recent case reports, literature review shows there are several interesting developments in the basic field of research. First, a group of articles was recently published on chemically instead of genetically induced MKD mouse and cell models, investigating the effects of several isoprenoid pathway intermediates. Second, another study confirms a role for small GTPases and their isoprenylation in the inflammatory response in mevalonate kinase deficiency. Lastly, there are now, finally, modest new indications about the role of IgD.

SUMMARY: Both pathophysiological studies and clinical observations in the last 2 years have supported the central role of IL-1 in HIDS. There are some intriguing results and hypotheses about the link between isoprenoid metabolism and the IL-1 pathway through geranylgeranylation that deserve to be further examined.

DOI: 10.1097/BOR.0b013e328349c3b1

PMID: 21760510 [Indexed for MEDLINE]

2962. Curr Opin Pediatr. 2010 Dec;22(6):836-9.

Bibliography. Allergy, immunology and related disorders. Current world literature.

[No authors listed]

PMID: 21751471 [Indexed for MEDLINE]

2963. Eur J Neurol. 2011 Aug;18(8):e96; author reply e97. doi: 10.1111/j.1468-1331.2011.03408.x.

Is there any association between multiple sclerosis and familial Mediterranean fever?

Zahednasab H, Esmaeili A, Bahreini SA.

Comment on

Eur J Neurol. 2011 Sep;18(9):1146-50.

DOI: 10.1111/j.1468-1331.2011.03408.x

PMID: 21749568 [Indexed for MEDLINE]

2964. Exp Clin Cardiol. 2011 Summer;16(2):54-6.

Large pericardial effusion in a family with recurrent pericarditis: A report of probable x-linked transmission.

Maggiolini S(1), Tiberti G, Cantarini L, Carbone C, Mariani S, Achilli F, Maestroni S, Brucato A.

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Three cases of recurrent pleuropericarditis were observed within the same family - in two sisters and their niece, who were 18, 35 and 18 years of age, respectively. One patient was treated with pericardiectomy, and the other two were treated with colchicine. Mutations associated with autoinflammatory diseases (tumour necrosis factor receptor-associated periodic syndrome and familial Mediterranean fever) were absent; the condition was found to be sex linked.

PMCID: PMC3126685

PMID: 21747666

2965. J Am Acad Dermatol. 2012 Mar;66(3):409-15. doi: 10.1016/j.jaad.2010.12.025. Epub 2011 Jul 13.

Pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH)--a new autoinflammatory syndrome distinct from PAPA syndrome.

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**BACKGROUND:** PAPA syndrome is a recently identified hereditary autoinflammatory syndrome clinically characterized by pyogenic arthritis, severe acne, and pyoderma gangrenosum. It is caused by mutations in the PSTPIP1 gene and may be closely linked to the aseptic abscesses syndrome, which has been shown to be associated with CCTG repeat amplification in the promoter region of PSTPIP1.

**OBJECTIVE:** We describe two unrelated patients with a clinical presentation quite similar to, yet distinct from, PAPA syndrome.

**RESULTS:** Both patients had pyoderma gangrenosum and acute or remittent acne conglobata, but, in contrast to PAPA syndrome, lacked any episodes of pyogenic arthritis. Instead, they had suppurative hidradenitis. Mutations in PSTPIP1 exons 1 to 15 were excluded. In the promoter region, an increased repetition of the CCTG microsatellite motif was present on one allele in both patients. Alterations of the most commonly affected exons of the MEFV, NLRP3, and TNFRSF1A genes also were not detectable. One patient was treated with the interleukin (IL)-1 receptor antagonist anakinra and responded well, although without complete remission. This implies that IL-1 $\beta$  may be of pathogenetic importance.

**LIMITATIONS:** Small number of patients, no gene mutation identified, and unclear efficacy of therapy are limitations.

**CONCLUSIONS:** The clinical triad of pyoderma gangrenosum, acne, and suppurative hidradenitis represents a new disease entity within the spectrum of autoinflammatory syndromes, similar to PAPA and aseptic abscesses syndrome. For this disease, we propose the acronym "PASH" syndrome. PASH syndrome may respond to IL-1 $\beta$  blockade.

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DOI: 10.1016/j.jaad.2010.12.025

PMID: 21745697 [Indexed for MEDLINE]

2966. BMC Evol Biol. 2011 Jul 11;11:202. doi: 10.1186/1471-2148-11-202.

Genetic adaptation of the antibacterial human innate immunity network.

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**BACKGROUND:** Pathogens have represented an important selective force during the adaptation of modern human populations to changing social and other environmental conditions. The evolution of the immune system has therefore been influenced by these pressures. Genomic scans have revealed that immune system is one of the functions enriched with genes under adaptive selection.

**RESULTS:** Here, we describe how the innate immune system has responded to these challenges, through the analysis of resequencing data for 132 innate immunity genes in two human populations. Results are interpreted in the context of the functional and interaction networks defined by these genes. Nucleotide diversity is lower in the adaptors and modulators functional classes, and is negatively correlated with the centrality of the proteins within the interaction network. We also produced a list of candidate genes under positive or balancing selection in each population detected by neutrality tests and showed that some functional classes are preferential targets for selection.

**CONCLUSIONS:** We found evidence that the role of each gene in the network conditions the capacity to evolve or their evolvability: genes at the core of the network are more constrained, while adaptation mostly occurred at particular positions at the network edges. Interestingly, the functional classes containing most of the genes with signatures of balancing selection are involved in autoinflammatory and autoimmune diseases, suggesting a counterbalance between the beneficial and deleterious effects of the immune response.

DOI: 10.1186/1471-2148-11-202

PMCID: PMC3155920

PMID: 21745391 [Indexed for MEDLINE]

2967. Diabetologia. 2011 Sep;54(9):2451-62. doi: 10.1007/s00125-011-2223-4. Epub 2011 Jul 10.

Hypercholesterolaemia, signs of islet microangiopathy and altered angiogenesis precede onset of type 2 diabetes in the Goto-Kakizaki (GK) rat.



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**AIMS/HYPOTHESIS:** The adult non-obese Goto-Kakizaki (GK) rat model of type 2 diabetes, particularly females, carries in addition to hyperglycaemia a genetic predisposition towards dyslipidaemia, including hypercholesterolaemia. As cholesterol-induced atherosclerosis may be programmed in utero, we looked for signs of perinatal lipid alterations and islet microangiopathy. We hypothesise that such alterations contribute towards defective pancreas/islet vascularisation that might, in turn, lead to decreased beta cell mass. Accordingly, we also evaluated islet inflammation and endothelial activation in both prediabetic and diabetic animals.

**METHODS:** Blood, liver and pancreas were collected from embryonic day (E)21 fetuses, 7-day-old prediabetic neonates and 2.5-month-old diabetic GK rats and Wistar controls for analysis/quantification of: (1) systemic variables, particularly lipids; (2) cholesterol-linked hepatic enzyme mRNA expression and/or activity; (3) pancreas (fetuses) or collagenase-isolated islet (neonates/adults) gene expression using Oligo GEArray microarrays targeted at rat endothelium, cardiovascular disease biomarkers and angiogenesis, and/or RT-PCR; and (4) pancreas endothelial immunochemistry: nestin (fetuses) or von Willebrand factor (neonates).

**RESULTS:** Systemic and hepatic cholesterol anomalies already exist in GK fetuses and neonates. Hyperglycaemic GK fetuses exhibit a similar percentage decrease in total pancreas and islet vascularisation and beta cell mass. Normoglycaemic GK neonates show systemic inflammation, signs of islet pre-microangiopathy, disturbed angiogenesis, collapsed vascularisation and altered pancreas development. Concomitantly, GK neonates exhibit elevated defence mechanisms.

**CONCLUSIONS/INTERPRETATION:** These data suggest an autoinflammatory disease, triggered by in utero programming of cholesterol-induced islet microangiopathy interacting with chronic hyperglycaemia in GK rats. During the perinatal period, GK rats show also a marked deficient islet vascularisation in conjunction with decreased beta cell mass.

DOI: 10.1007/s00125-011-2223-4  
PMID: 21744291 [Indexed for MEDLINE]

2968. Rheumatol Int. 2012 Aug;32(8):2453-7. doi: 10.1007/s00296-011-1980-1. Epub 2011 Jul 8.

Bone mineral density in familial Mediterranean fever.

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The aim of this study was to evaluate the bone mineral density (BMD) in familial Mediterranean fever (FMF) and to search the effects of genetic factors, family history of FMF and types of clinical attacks on BMD. Forty-four attack-free patients with FMF and 36 healthy voluntary subjects were included in the study. BMD measurements of lumbar spine and left proximal femur were performed by dual energy X-ray absorptiometry (DEXA). There was no statistically significant difference between patient and control groups regarding median values of lumbar BMD ( $P = 0.06$ ), lumbar T ( $P = 0.08$ ) and Z ( $P = 0.12$ ) scores, femoral neck BMD ( $P = 0.13$ ), femoral T ( $P = 0.22$ ) and Z ( $P = 0.16$ ) scores and total femur BMD ( $P = 0.14$ ), T ( $P = 0.19$ ) and Z ( $P = 0.27$ ) scores. Patients with negative FMF family history had significantly lower femoral neck BMD ( $P = 0.018$ ), femoral neck T ( $P = 0.009$ ) and Z ( $P = 0.01$ ) scores and total femur BMD ( $P = 0.033$ ) than patients with positive FMF family history. There was no significant difference among the groups regarding mutation characteristic and types of attacks in lumbar BMD, T and Z scores, femoral neck BMD, T and Z scores and total femur BMD, T and Z scores ( $P > 0.05$ ). We found that the bone loss of patients with FMF is not different from that of the controls. The increased bone loss in the patients with negative family history for FMF should be further investigated with larger patient groups taking into consideration of the risk factors related to family history for osteoporosis.

DOI: 10.1007/s00296-011-1980-1  
PMID: 21739129 [Indexed for MEDLINE]

2969. Clin Exp Immunol. 2011 Sep;165(3):301-9. doi: 10.1111/j.1365-2249.2011.04438.x. Epub 2011 Jul 7.

Clinical immunology review series: An approach to the patient with a periodic fever syndrome.

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The periodic fever syndromes are disorders of innate immunity. They may be inherited or acquired and present as recurrent attacks of apparently spontaneous self-limiting inflammation without evidence of autoantibodies or infection. Over the past decade-and-a-half there has been significant progress in their understanding and treatment.

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DOI: 10.1111/j.1365-2249.2011.04438.x

PMCID: PMC3170979

PMID: 21736563 [Indexed for MEDLINE]

2970. Clin Rheumatol. 2012 Feb;31(2):225-9. doi: 10.1007/s10067-011-1806-2. Epub 2011 Jul 7.

Resistin and visfatin: are they valuable enough to be the differential diagnosis in familial Mediterranean fever with acute appendicitis?

Kisacik B(1), Erol MF, Yilmaz G, Yilmaz FM, Maras Y, Kalyoncu U, Karadag O, Kiraz S, Ertenli I, Calguneri M.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease which predominantly affects certain ethnic groups mainly Sephardic Jews, Turks, Arabs, and Armenians. Differential diagnosis of an attack of FMF with appendicitis could be difficult in patients presenting with acute abdomen. Circulating levels of resistin and visfatin have been shown to increase in several inflammatory conditions. In this study we aimed to investigate the role of resistin and visfatin in diseases activity by monitoring these adipokines' levels in patients with FMF (attacks and attack-free period) and acute appendicitis. The study involves four groups: group 1-31 FMF patients at attack (M/F, 14/17), group 2-27 FMF patients at attack-free period (M/F, 9/18), group 3-29 acute appendicitis patients (M/F, 16/13), and group 4-20 healthy controls (M/F, 10/10). Erythrocyte sedimentation rate, C-reactive protein, white blood cell count, fibrinogen, resistin, visfatin, interleukin-1 $\beta$ , interleukin-6, interleukin-10, TNF- $\alpha$ , and IFN- $\gamma$  were evaluated concurrently. Resistin level could be a useful test in diagnosis of FMF patients in attacks period but not in acute appendicitis as differential diagnosis. Measuring visfatin levels would not give additional information neither for attacks and attack-free period nor FMF attack and appendicitis.

DOI: 10.1007/s10067-011-1806-2

PMID: 21735058 [Indexed for MEDLINE]

2971. Curr Allergy Asthma Rep. 2011 Oct;11(5):361-8. doi: 10.1007/s11882-011-0207-6.

The emerging role of interleukin-1 $\beta$  in autoinflammatory diseases.

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The autoinflammatory syndromes are a group of multisystem disorders characterized by recurrent episodes of fever and systemic inflammation affecting the eyes, joints, skin, and serosal surfaces in the absence of an immune reaction. Recent

advances have revealed the importance of interleukin-1 $\beta$ , not only in the pathogenesis of many of these rare inherited diseases, but also in acquired diseases. The development and availability of anti-interleukin-1 $\beta$  therapeutics have introduced the possibility of proof-of-concept studies, which are likely to further widen this field.

DOI: 10.1007/s11882-011-0207-6

PMID: 21728024 [Indexed for MEDLINE]

2972. Nat Rev Rheumatol. 2011 Jul 5;7(8):469-78. doi: 10.1038/nrrheum.2011.94.

Genetics of monogenic autoinflammatory diseases: past successes, future challenges.

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The term autoinflammation was initially coined to distinguish disorders characterized by recurrent episodes of inflammation in the absence of high-titer autoantibodies and antigen-specific T cells from the more common autoimmune diseases. Although this concept originally applied to monogenic hereditary recurrent fevers, it has expanded over time to include polygenic (complex) autoinflammatory diseases. Understanding of the pathogenesis of autoinflammatory diseases has grown rapidly in the past decade owing to advances in genome research and technology. Genome-wide linkage analysis, positional cloning, homozygosity mapping and candidate gene screening have led to the identification of mutations in 12 genes that are associated with monogenic diseases. Genome-wide association studies have begun to elucidate the molecular basis of complex autoinflammatory diseases. The discovery of disease-causing genetic variants has defined autoinflammation as disorder within the innate immune system, implicating IL-1 as a master cytokine, and has led to a breakthrough in therapy, with IL-1 inhibitors producing rapid and sustained amelioration of symptoms. Despite major advances, however, a substantial number of patients have no mutations in the known autoinflammatory genes. The challenge now is to find the undiscovered

genes, considering that most cases are sporadic or occur within small families. New approaches and tools such as next-generation sequencing are discussed.

DOI: 10.1038/nrrheum.2011.94

PMID: 21727933 [Indexed for MEDLINE]

2973. Pediatrics. 2011 Aug;128(2):e464-70. doi: 10.1542/peds.2010-2998. Epub 2011 Jul 4.

Novel protagonists in autoinflammatory arthritis of familial Mediterranean fever.

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To clarify mechanisms responsible for the self-limiting and nonerosive features of autoinflammatory joint disease in familial Mediterranean fever (FMF), we performed a study on synovial tissue obtained surgically from an acutely inflamed hip joint from a boy feared to have septic arthritis but later found to be homozygous for mutation M694I in pyrin/marenostrin. We defined by immunohistology the infiltrating cells and examined the in situ expression of plausible protagonists in synovitis of FMF: myeloperoxidase, lysozyme, galectin 1, galectin 3, p65 (RelA)/nuclear factor  $\kappa$ B, inducible nitric-oxide synthase, cyclooxygenase 2, and cleaved caspase 3. Neutrophils deficient in myeloperoxidase and lysozyme, macrophages, and mast cells outnumbered T and B lymphocytes as well as plasma cells. Among cells of adaptive immunity, B lymphocytes were predominant. Galectin 1 was detected in numerous cells of the innate immune system throughout the synovial tissue, whereas expression of galectin 3 was less abundant and scattered. p65 (RelA)/nuclear factor  $\kappa$ B and inducible nitric-oxide synthase were both upregulated in most of the infiltrating cells. Cyclooxygenase 2 expression was low, and cleaved caspase 3 was undetectable. We conclude that the exquisitely inflammatory yet nondestructive character of FMF arthritis could correlate with the presence of nonpathogenic neutrophils lacking effector molecules and the widespread expression of anti-inflammatory galectin 1 in regulatory cells of the innate immune system. Intrinsic apoptosis seemed irrelevant for confining synovial autoinflammation, but regulation through pyroptosis or the adaptive

immune system remains possible.

DOI: 10.1542/peds.2010-2998

PMID: 21727109 [Indexed for MEDLINE]

2974. Trends Mol Med. 2011 Sep;17(9):494-505. doi: 10.1016/j.molmed.2011.05.006. Epub 2011 Jul 2.

Disease causing mutations in the TNF and TNFR superfamilies: Focus on molecular mechanisms driving disease.

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The tumor necrosis factor (TNF) and TNF receptor (TNFR) superfamilies comprise multidomain proteins with diverse roles in cell activation, proliferation and cell death. These proteins play pivotal roles in the initiation, maintenance and termination of immune responses and have vital roles outside the immune system. The discovery and analysis of diseases associated with mutations in these families has revealed crucial mechanistic details of their normal functions. This review focuses on mutations causing four different diseases, which represent distinct pathological mechanisms that can exist within these superfamilies: autoimmune lymphoproliferative syndrome (ALPS; FAS mutations), common variable immunodeficiency (CVID; TACI mutations), tumor necrosis factor receptor associated periodic syndrome (TRAPS; TNFR1 mutations) and hypohidrotic ectodermal dysplasia (HED; EDA1/EDAR mutations). In particular, we highlight how mutations have revealed information about normal receptor-ligand function and how such studies might direct new therapeutic approaches.

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DOI: 10.1016/j.molmed.2011.05.006

PMID: 21724465 [Indexed for MEDLINE]

2975. J Visc Surg. 2011 Jun;148(3):e217-9. doi: 10.1016/j.jviscsurg.2011.05.007. Epub 2011 Jul 1.

Pitfalls in familial mediterranean fever: acute intestinal strangulation/obstruction due to primary adhesions.

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Familial Mediterranean Fever (FMF) presents in 90% of patients with painful attacks of peritoneal inflammation, which may mimic an acute surgical abdomen. These episodes characteristically resolve spontaneously within 72 hours. However, recurrent episodes of primary peritonitis may lead to the development of primary intraperitoneal adhesions, even in the absence of previous abdominal surgery. When an atypical bout of pain fails to resolve spontaneously and rapidly, the surgeon must consider the diagnosis of intestinal obstruction due to an adhesive band with the associated risk of strangulation with bowel necrosis. In this case report, we describe this rare but classical presentation of FMF for which any delay in diagnosis or treatment may result in severe morbidity.

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DOI: 10.1016/j.jviscsurg.2011.05.007

PMID: 21723803 [Indexed for MEDLINE]

2976. Mediterr J Hematol Infect Dis. 2011;3(1):e2011017. doi: 10.4084/MJHID.2011.017. Epub 2011 May 16.

Familial mediterranean Fever and hypercoagulability.

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Familial Mediterranean fever (FMF) is an autosomal recessive hereditary disease which is characterized by recurrent attacks of fever and peritonitis, pleuritis, arthritis, or erysipelas-like skin disease. As such, FMF is a prototype of autoinflammatory diseases where genetic changes lead to acute inflammatory episodes. Systemic inflammation - in general - may increase procoagulant factors, and decrease natural anticoagulants and fibrinolytic activity. Therefore, it is anticipated to see more thrombotic events among FMF patients compared with healthy subjects. However, reviewing the current available literature and based upon our personal experience, thrombotic events related purely to FMF are very rare. Possible explanation for this discrepancy is that along with the procoagulant activity during FMF acute attacks, anticoagulant and fibrinolytic changes are also taking place. Colchicine which is the treatment of choice in FMF may also play a role in reducing inflammation thereby decreasing hypercoagulability.

DOI: 10.4084/MJHID.2011.017

PMCID: PMC3113278

PMID: 21713077

2977. Curr Opin Rheumatol. 2011 Sep;23(5):437-43. doi: 10.1097/BOR.0b013e328348b278.

Psoriatic juvenile idiopathic arthritis: a tale of two subgroups.

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**PURPOSE OF REVIEW:** The International League of Associations for Rheumatology criteria parse out juvenile idiopathic arthritis (JIA) into seven groups, with the aim of creating homogeneous subgroups suitable for clinical and research evaluation. However, prior studies have shown that psoriatic JIA (psJIA) may be a heterogeneous entity.

**RECENT FINDINGS:** PsJIA is composed of two subgroups, differentiated by age at onset. Older children with psJIA have features of spondyloarthritis, including

relative male preponderance, increased risk of axial involvement, and enthesitis. Extrapolating from studies on adults with psoriatic arthritis, the mechanism of older-onset PsJIA appears to involve autoinflammatory dysregulation centered at the synovial-entheseal complex; there may also be a role for gut inflammation in a subset of patients. In contrast, patients with early-onset PsJIA bear similarities to early-onset oligoarticular and polyarticular JIA patients, including female preponderance, antinuclear antibody (ANA) positivity, and certain human leukocyte antigen types, suggesting a possible role for traditional autoimmune mechanisms. Both groups, however, share a high frequency of dactylitis.

**SUMMARY:** This review demonstrates that PsJIA is a heterogeneous entity, with different clinical, genetic, and possibly pathophysiological features. Future studies are needed to explore the mechanisms of arthritis in both subgroups, particularly in the early-onset children.

DOI: 10.1097/BOR.0b013e328348b278

PMID: 21709556 [Indexed for MEDLINE]

2978. *Pediatrics*. 2011 Jul;128(1):e152-9. doi: 10.1542/peds.2010-3639. Epub 2011 Jun 27.

Mevalonate kinase deficiency: a survey of 50 patients.

Bader-Meunier B(1), Florkin B, Sibilia J, Acquaviva C, Hachulla E, Grateau G, Richer O, Farber CM, Fischbach M, Hentgen V, Jegou P, Laroche C, Neven B, Lequerré T, Mathian A, Pellier I, Touitou I, Rabier D, Prieur AM, Cuisset L, Quartier P; SOFREMIP (Société Francophone pour la Rhumatologie et les Maladies Inflammatoires en Pédiatrie); CRI (Club Rhumatismes et Inflammations).

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**OBJECTIVE:** The goal of this study was to describe the spectrum of clinical signs of mevalonate kinase deficiency (MKD).

**METHODS:** This was a retrospective French and Belgian study of patients identified on the basis of MKD gene mutations.

**RESULTS:** Fifty patients from 38 different families were identified, including 1

asymptomatic patient. Symptoms began during the first 6 months of life in 30 patients (60%) and before the age of 5 years in 46 patients (92%). Symptoms consisted of febrile diarrhea and/or rash in 23 of 35 patients (66%). Febrile attacks were mostly associated with lymphadenopathy (71%), diarrhea (69%), joint pain (67%), skin lesions (67%), abdominal pain (63%), and splenomegaly (63%). In addition to febrile attacks, 27 patients presented with inflammatory bowel disease, erosive polyarthritis, Sjögren syndrome, and other chronic neurologic, renal, pulmonary, endocrine, cutaneous, hematologic, or ocular symptoms. Recurrent and/or severe infections were observed in 13 patients, hypogammaglobulinemia in 3 patients, and renal angiomyolipoma in 3 patients. Twenty-nine genomic mutations were identified; the p.Val377Ile mutation was the most frequently found (29 of 38 families). Three patients died of causes related to MKD. The disease remained highly active in 17 of the 31 surviving symptomatic patients followed up for >5 years, whereas disease activity decreased over time in the other 14 patients. Interleukin 1 antagonists were the most effective biological agents tested, leading to complete or partial remission in 9 of 11 patients.

CONCLUSION: MKD is not only an autoinflammatory syndrome but also a multisystemic inflammatory disorder, a possible immunodeficiency disorder, and a condition that predisposes patients to the development of renal angiomyolipoma.

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DOI: 10.1542/peds.2010-3639

PMID: 21708801 [Indexed for MEDLINE]

2979. J Allergy Clin Immunol. 2011 Dec;128(6):1352-4. doi: 10.1016/j.jaci.2011.05.023. Epub 2011 Jun 25.

Successful canakinumab treatment identifies IL-1 $\beta$  as a pivotal mediator in Schnitzler syndrome.

de Koning HD, Schalkwijk J, van der Meer JW, Simon A.

Comment on

J Allergy Clin Immunol. 2008 Jan;121(1):260-2.

J Allergy Clin Immunol. 2009 Dec;124(6):1129-38; quiz 1139-40.

DOI: 10.1016/j.jaci.2011.05.023

PMID: 21704363 [Indexed for MEDLINE]

2980. Arthritis Rheum. 2011 Nov;63(11):3625-32. doi: 10.1002/art.30512.

High incidence of NLRP3 somatic mosaicism in patients with chronic infantile neurologic, cutaneous, articular syndrome: results of an International Multicenter Collaborative Study.

Tanaka N(1), Izawa K, Saito MK, Sakuma M, Oshima K, Ohara O, Nishikomori R, Morimoto T, Kambe N, Goldbach-Mansky R, Aksentijevich I, de Saint Basile G, Neven B, van Gijn M, Frenkel J, Aróstegui JI, Yagüe J, Merino R, Ibañez M, Pontillo A, Takada H, Imagawa T, Kawai T, Yasumi T, Nakahata T, Heike T.

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**OBJECTIVE:** Chronic infantile neurologic, cutaneous, articular (CINCA) syndrome, also known as neonatal-onset multisystem inflammatory disease (NOMID), is a dominantly inherited systemic autoinflammatory disease. Although heterozygous germline gain-of-function NLRP3 mutations are a known cause of this disease, conventional genetic analyses fail to detect disease-causing mutations in ~40% of patients. Since somatic NLRP3 mosaicism has been detected in several mutation-negative NOMID/CINCA syndrome patients, we undertook this study to determine the precise contribution of somatic NLRP3 mosaicism to the etiology of NOMID/CINCA syndrome.

**METHODS:** An international case-control study was performed to detect somatic NLRP3 mosaicism in NOMID/CINCA syndrome patients who had shown no mutation during conventional sequencing. Subcloning and sequencing of NLRP3 was performed in these mutation-negative NOMID/CINCA syndrome patients and their healthy relatives. Clinical features were analyzed to identify potential genotype-phenotype associations.

**RESULTS:** Somatic NLRP3 mosaicism was identified in 18 of the 26 patients (69.2%). Estimates of the level of mosaicism ranged from 4.2% to 35.8% (mean  $\pm$  SD 12.1  $\pm$  7.9%). Mosaicism was not detected in any of the 19 healthy relatives (18 of 26 patients versus 0 of 19 relatives;  $P < 0.0001$ ). In vitro functional assays indicated that the detected somatic NLRP3 mutations had disease-causing functional effects. No differences in NLRP3 mosaicism were detected between

different cell lineages. Among nondescript clinical features, a lower incidence of mental retardation was noted in patients with somatic mosaicism. Genotype-matched comparison confirmed that patients with somatic NLRP3 mosaicism presented with milder neurologic symptoms.

CONCLUSION: Somatic NLRP3 mutations were identified in 69.2% of patients with mutation-negative NOMID/CINCA syndrome. This indicates that somatic NLRP3 mosaicism is a major cause of NOMID/CINCA syndrome.

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DOI: 10.1002/art.30512

PMCID: PMC3498501

PMID: 21702021 [Indexed for MEDLINE]

2981. Curr Rheumatol Rep. 2011 Oct;13(5):388-94. doi: 10.1007/s11926-011-0191-9.

Familial Mediterranean fever and seronegative arthritis.

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Familial Mediterranean fever (FMF) is characterized by recurrent, self-limited episodes of polyserositis, with articular involvement also being a common manifestation. The pattern and joint predilection of arthritis show many similarities to those of spondyloarthritis. Moreover, case series suggest an increased prevalence of ankylosing spondylitis or spondyloarthritis among FMF patients. FMF is caused by mutations in the MEFV gene encoding pyrin, which is believed to be involved in regulation of interleukin-1 $\beta$  activation. Recent studies conducted in populations with a high background carrier rate of MEFV variants have reported an increased frequency of M694V among AS patients with no personal or family history of FMF. These findings are of interest, as both candidate gene and genome-wide association studies suggest that the interleukin-1 cytokine pathway may be implicated in the pathogenesis of ankylosing spondylitis. Therefore, association of M694V with ankylosing spondylitis can be recognized as

a geographic region-specific risk factor affecting a common inflammatory pathway in the disease pathogenesis.

DOI: 10.1007/s11926-011-0191-9

PMID: 21695514 [Indexed for MEDLINE]

2982. J Pediatr Gastroenterol Nutr. 2011 Jul;53(1):102-5. doi: 10.1097/MPG.0b013e31820cfab1.

Infantile colitis as a novel presentation of familial Mediterranean fever responding to colchicine therapy.

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DOI: 10.1097/MPG.0b013e31820cfab1

PMID: 21694544 [Indexed for MEDLINE]

2983. Georgian Med News. 2011 May;(194):53-6.

[The role of interleukin-1 and interleukin-1-receptor antagonist in development of familial mediterranean fever and other autoinflammatory diseases].

[Article in Russian]

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Autoinflammatory diseases constitute a group of genetic disorders whose main clinical features are recurrent episodes of inflammatory lesions that can affect the skin, joints, bones, eyes, gastrointestinal tract and nervous system, in

association with signs of systemic inflammation. Example of these disorders is familial Mediterranean fever (FMF). FMF is an autosomal recessive disease characterized by recurrent episodes of fever and inflammation affecting serosal surfaces, joints and skin. The gene of FMF is expressed in granulocytes, monocytes, dendritic cells and serosal and sinovial fibroblasts, which result in formation of pyrin. A large percentage of FMF-associated pyrin mutations reside in C-terminal B30.2 domain. Pyrin normally suppresses IL-1 $\beta$ , but when mutated in case of FMF, it does not. Inhibition of the interaction between pyrin and caspase-1 leads to an increase in caspase-1 activity and subsequent increase in IL-1 $\beta$  secretion. The interleukin-1-receptor antagonist binds to the interleukin-1 receptor, thereby blocking access of interleukin-1 to the receptor. The outcome of an inflammatory process is likely to be affected by the relative amounts of interleukin-1 and interleukin-1-receptor antagonist.

PMID: 21685523 [Indexed for MEDLINE]

2984. Lancet. 2011 Jun 18;377(9783):2138-49. doi: 10.1016/S0140-6736(11)60244-4.

Juvenile idiopathic arthritis.

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Juvenile idiopathic arthritis is a heterogeneous group of diseases characterised by arthritis of unknown origin with onset before age of 16 years. Pivotal studies in the past 5 years have led to substantial progress in various areas, ranging from disease classification to new treatments. Gene expression profiling studies have identified different immune mechanisms in distinct subtypes of the disease, and can help to redefine disease classification criteria. Moreover, immunological studies have shown that systemic juvenile idiopathic arthritis is an acquired autoinflammatory disease, and have led to successful studies of both interleukin-1 and interleukin-6 blockade. In other forms of the disease, synovial inflammation is the consequence of a disturbed balance between proinflammatory effector cells (such as T-helper-17 cells), and anti-inflammatory regulatory

cells (such as FOXP3-positive regulatory T cells). Moreover, specific soluble biomarkers (S100 proteins) can guide individual treatment. Altogether these new developments in genetics, immunology, and imaging are instrumental to better define, classify, and treat patients with juvenile idiopathic arthritis.

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DOI: 10.1016/S0140-6736(11)60244-4

PMID: 21684384 [Indexed for MEDLINE]

2985. Rheumatology (Oxford). 2011 Aug;50(8):1525-6; author reply 1526-9. doi: 10.1093/rheumatology/ker145. Epub 2011 Jun 14.

Comment on: Low TNF-induced NF- $\kappa$ B and p38 phosphorylation levels in leucocytes in tumour necrosis factor receptor-associated periodic syndrome.

Turner MD, Chernajovsky Y.

Comment on

Rheumatology (Oxford). 2010 Feb;49(2):382-90.

DOI: 10.1093/rheumatology/ker145

PMID: 21672967 [Indexed for MEDLINE]

2986. Patholog Res Int. 2011;2011:936794. doi: 10.4061/2011/936794. Epub 2011 Jun 1.

Chronic Proliferative Dermatitis in Mice: NF $\kappa$ B Activation Autoinflammatory Disease.

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Autoinflammatory diseases are a heterogeneous group of congenital diseases characterized by the presence of recurrent inflammation, in the absence of



infectious agents, detectable autoantibodies or antigen-specific autoreactive T-cells. SHARPIN deficient mice presents multiorgan chronic inflammation without known autoantibodies or autoreactive T-cells, designated Sharpin(cpdm). Histological studies demonstrated epidermal hyperproliferation, Th-2 inflammation, and keratinocyte apoptosis in this mutant. The mutant mice have decreased behavioral mobility, slower growth, and loss of body weight. Epidermal thickness and mitotic epidermal cells increase along with disease development. K5/K14 expression is distributed through all layers of epidermis, along with K6 expression in interfollicular epidermis, suggesting epidermal hyperproliferation. K1/K10 is only detectable in outer layers of spinosum epidermis, reflecting accelerated keratinocyte migration. Alpha smooth muscle actin is overexpressed in skin blood vessels, which may release the elevated white blood cells to dermis. CD3(+)CD45(+) cells and granulocytes, especially eosinophils and mast cells, aggregate in the mutant skin. TUNEL assay, together with Annexin-V/propidium iodide FACS analysis, confirmed the increase of apoptotic keratinocytes in skin. These data validate and provide new lines of evidence of the proliferation-inflammation-apoptosis triad in Sharpin(cpdm) mice, an NFκB activation autoinflammatory disease.

DOI: 10.4061/2011/936794

PMCID: PMC3109521

PMID: 21660243

2987. Curr Opin Allergy Clin Immunol. 2011 Aug;11(4):355-60. doi: 10.1097/ACI.0b013e328348a882.

Biologic modulators in allergic and autoinflammatory diseases.

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**PURPOSE OF REVIEW:** The advent of molecular techniques has resulted in the ability to tailor medications to specific protein targets. This review will emphasize several biological therapies, specifically directed toward cytokine receptors and

inhibitors, and their role in the treatment of atopic and autoinflammatory diseases.

RECENT FINDINGS: Translational research and the identification of the molecular pathophysiology of diseases have led to more targeted treatment approaches. The biologic modulators encompassing monoclonal antibodies as cytokine inhibitors, receptor blocking antibodies, and new fusion receptors are now being applied to diseases beyond their original application.

SUMMARY: The expanded use of biological therapies has experienced success in the treatment of numerous disorders, especially in subsets of patients with disease that has been refractory to conventional therapies.

DOI: 10.1097/ACI.0b013e328348a882

PMCID: PMC3154953

PMID: 21659854 [Indexed for MEDLINE]

2988. Clin Lab Sci. 2011 Spring;24(2):93-8.

Immunoglobulin light chain levels can be used to determine disease stage in children with juvenile idiopathic arthritis.

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OBJECTIVE: Patients with some inflammatory diseases have been shown to have increased levels of immunoglobulin light chains. In this study, we measured the concentrations of immunoglobulin kappa and lambda light chains in sera of patients with juvenile idiopathic arthritis (JIA) (study group), familial mediterranean fever (FMF) (disease control group) and in healthy children. Our aim was to compare immunoglobulin light chain levels with other well-known markers of inflammation, such as the erythrocyte sedimentation rate (ESR) and the acute phase reactants (APRs), serum amyloid A (SAA) and C-reactive protein (CRP), to find out if immunoglobulin light chain determinations have any discriminating value in the follow-up of these patients.

RESULTS: ESR, CRP, SAA, kappa and lambda chain levels and lambda/IgG ratio showed a statistically significant difference between active and remission stages in JIA

patients. Kappa correlated very well with SAA and ESR in both stages. On the other hand, lambda correlated with SAA and ESR only in the remission period. There was no significant difference in kappa and lambda chain levels between active and remission stages in FMF patients. In addition, kappa and lambda chain concentrations showed no correlation with other markers of inflammation and immunoglobulin levels neither in entire FMF group nor in different subgroups with respect to clinical status. Immunoglobulin light chains kappa and lambda as well as levels of three markers of inflammation were found to be significantly higher in JIA patients who were in the active stage of disease when compared to data of healthy children

CONCLUSION: Ig light chains especially kappa chain concentrations are helpful to determine disease stage in JIA patients but with our current data, they do not exhibit superiority to any of the classical tests for inflammation.

PMID: 21657141 [Indexed for MEDLINE]

2989. Hautarzt. 2011 Jul;62(7):524-33. doi: 10.1007/s00105-010-2115-4.

[Autoinflammatory diseases as cause of wound healing defects].

[Article in German]

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Ulcerations of the skin and mucosal membranes are a common feature of autoinflammatory diseases. They can give raise to chronic wound healing defects and should be considered in the differential diagnosis of chronic skin ulcers. The increased activation of the innate immune system in the absence of an apparent provocation for inflammation is a hallmark of autoinflammatory diseases. Mutations and alterations of signaling pathways regulating the innate immune response to physical trauma/tissue damage result into an unrestrained activation of the inflammasome, which leads to increased activation of Interleukin-1. Uncontrolled recruitment and activation of myeloid effector cells within the

wound site lead to the release of potent proteases that cause the degradation of structural components of the skin. The majority of these diseases respond well to immunosuppressive and immunomodulatory treatment regimes. Therapeutic resistance converts the acute inflammatory response into a chronic and non-resolving inflammatory process that leads to tissue degeneration. In this article we will focus on the review of those autoinflammatory diseases that often display ulcerative cutaneous and aphthous lesions including pyoderma gangrenosum, Behçet disease, PAPA syndrome and hyperimmunoglobulinemia D with periodic fever syndrome (HIDS). Furthermore, the article will be complemented by an overview of those inflammatory diseases that are associated with non-ulcerative cutaneous manifestations.

DOI: 10.1007/s00105-010-2115-4

PMID: 21647771 [Indexed for MEDLINE]

2990. Nat Rev Rheumatol. 2011 Jun 7;7(7):416-26. doi: 10.1038/nrrheum.2011.68.

Pathogenesis of systemic juvenile idiopathic arthritis: some answers, more questions.

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Systemic juvenile idiopathic arthritis (sJIA) has long been recognized as unique among childhood arthritides, because of its distinctive clinical and epidemiological features, including an association with macrophage activation syndrome. Here, we summarize research into sJIA pathogenesis. The triggers of disease are unknown, although infections are suspects. Once initiated, sJIA seems to be driven by innate proinflammatory cytokines. Endogenous Toll-like receptor ligands, including S100 proteins, probably synergize with cytokines to perpetuate inflammation. These and other findings support the hypothesis that sJIA is an autoinflammatory condition. Indeed, IL-1 is implicated as a pivotal cytokine, but the source of excess IL-1 activity remains obscure and the role of IL-1 in chronic arthritis is less clear. Another hypothesis is that a form of hemophagocytic lymphohistiocytosis underlies sJIA, with varying degrees of its

expression across the spectrum of disease. Alternatively, sJIA with MAS might be a genetically distinct subtype. Yet another hypothesis proposes that inadequate downregulation of immune activation is central to sJIA, supporting evidence for which includes 'alternative activation' of monocyte and macrophages and possible deficiencies in IL-10 and T regulatory cells. Some altered immune phenotypes persist during clinically inactive disease, which suggests that this stage might represent compensated inflammation. Despite much progress being made, many questions remain, providing fertile ground for future research.

DOI: 10.1038/nrrheum.2011.68

PMCID: PMC4180659

PMID: 21647204 [Indexed for MEDLINE]

2991. Nihon Naika Gakkai Zasshi. 2011 Apr 10;100(4):1041-3.

[Case report; a case of familial Mediterranean fever diagnosed in adult].

[Article in Japanese]

Watanabe T(1), Sato M, Gohda F, Takahashi Y, Uchiyama T, Maezawa A, Nishikomori R, Tamura J.

Author information:

(1)Department of General Medicine, Takasaki General Medical Center, Japan.

PMID: 21626841 [Indexed for MEDLINE]

2992. Scand J Rheumatol. 2011;40(5):383-6. doi: 10.3109/03009742.2011.562532. Epub 2011 May 30.

Common MEFV mutations in Iranian Azeri Turkish patients with Behçet's disease.

Esmaeili M(1), Bonyadi M, Khabbazi A, Ebrahimi AA, Sharif SK, Hajjalilo M, Kolahi S, Dastgiri S.

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(1)Liver and Gastrointestinal Disease Research Centre, Drug Applied Research Centre, Tabriz University of Medical Sciences, Tabriz, Iran.

**OBJECTIVE:** Behçet's disease (BD) is an inflammatory disorder of unknown cause with higher prevalence along the ancient Silk Road. BD shares epidemiological and clinical features with familial Mediterranean fever (FMF). Moreover, association of BD and certain MEFV gene mutations has been described in recent decades. We studied the role of MEFV mutations in Iranian Azeri Turkish patients with BD.

**METHODS:** Fifty-three BD patients who met the International Study Group criteria for BD were analysed for five common MEFV mutations (M694V, V726A, M680I, M694I, and E148Q) using amplification refractory mutation system and polymerase chain reaction (PCR) restriction-digestion testing methods. A cohort of 200 healthy Azeri Turkish individuals who had been previously genotyped regarding the five common MEFV mutations served as the control group.

**RESULTS:** Eighteen patients were found to carry a single MEFV mutation and one additional patient was compound heterozygote. There was a statistically significant difference between the patient group and ethnically matched healthy individuals regarding M694V and M680I mutations ( $p = 0.01$  and  $p = 0.04$ , respectively). Both BD groups (carriers and non-carriers of MEFV mutations) were similar in their clinical symptoms.

**CONCLUSION:** Definite MEFV mutations seem to be a susceptibility factor for BD in our cohort of Iranian Azeri Turkish patients.

DOI: 10.3109/03009742.2011.562532

PMID: 21623663 [Indexed for MEDLINE]

2993. Iran J Pediatr. 2011 Jun;21(2):244-8.

A Case of Henoch-Schönlein Purpura with P369S Mutation in MEFV Gene.

Ertan P(1), Tekin G, Sahin GE, Kasirga E, Taneli F, Kandioğlu AR, Sözeri B.

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**BACKGROUND:** Henoch-Schönlein purpura (HSP) is the most common vasculitis of childhood. HSP can affect multiple organs presenting with a characteristic rash

in most of the patients. Familial Mediterranean Fever (FMF) is an inherited inflammatory disease common in mediterranean populations. HSP is the most common vasculitis seen in children with FMF.

CASE PRESENTATION: A 16 year old boy was referred with history of abdominal pain lasting for 20 days. He was hospitalized and had appendectomy. Due to the persistence of his abdominal pain after surgery he was admitted to our hospital. His physical examination showed palpable purpuric rashes symmetrically distributed on lower extremities. Abdominal examination revealed periumbilical tenderness. Laboratory tests showed elevated erythrocyte sedimentation rate, Creactive protein and fibrinogen. Urinalysis revealed microscopic hematuria and severe proteinuria. The fecal occult blood testing was positive. Based on these clinic findings, the patient was diagnosed as HSP with renal, gastrointestinal tract and skin involvement. We performed DNA analysis in our patient because he had diagnosis of vasculitis with severe symptoms and found that he was carrying heterozygote P369S mutation.

CONCLUSION: Our case is noteworthy as it indicates that it may be important not to overlook presence of FMF mutations in patients with a diagnosis of severe vasculitis.

PMCID: PMC3446153

PMID: 23056796

2994. Immunity. 2011 May 27;34(5):695-7. doi: 10.1016/j.immuni.2011.05.004.

A new twist on the PYRIN Mediterranean coast.

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Comment on

Immunity. 2011 May 27;34(5):755-68.

Familial Mediterranean fever is caused by mutations of the PYRIN protein. Chae et al. (2011) provide evidence for a ASC protein-dependent pathway of caspase-1

activation in which gain-of-function PYRIN mutations lead to IL-1 $\beta$  cytokine overproduction and inflammatory disease.

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DOI: 10.1016/j.immuni.2011.05.004

PMID: 21616439

2995. Immunity. 2011 May 27;34(5):665-79. doi: 10.1016/j.immuni.2011.05.007.

Regulation of the antimicrobial response by NLR proteins.

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Nucleotide-binding, oligomerization domain (NOD)-like receptor (NLR) proteins are a family of innate immune receptors that play a pivotal role in microbial sensing, leading to the initiation of antimicrobial immune responses.

Dysregulation of the function of multiple NLR family members has been linked, both in mice and humans, to a propensity for infection and autoinflammatory disease. Despite our increased understanding of NLR function and interactions, many aspects related to mechanisms of sensing, downstream signaling, and in vivo functions remain elusive. In this review, we focus on key members of the NLR family, describing their activation by diverse microbes, downstream effector functions, and interactions with each other and with other innate sensor protein families. Also discussed is the role of microbial sensing by NLR receptors leading to activation of the adaptive immune arm that collaborates in the antimicrobial defense.

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DOI: 10.1016/j.immuni.2011.05.007

PMID: 21616436 [Indexed for MEDLINE]



2996. Int J Immunogenet. 2011 Aug;38(4):327-9. doi: 10.1111/j.1744-313X.2011.01015.x. Epub 2011 May 25.

Increased expression of exon 2 deleted MEFV transcript in familial Mediterranean fever patients.

Kirectepe AK(1), Erdem GC, Senturk N, Arisoy N, Hatemi G, Ozdogan H, Kasapcopur O, Tahir Turanli E.

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A defect in MEFV gene expression regulation has been implicated in familial Mediterranean fever (FMF) etiopathophysiology. Here we show significantly higher expression level in second exon lacking MEFV transcript in FMF patients compared with healthy controls ( $P=0.026$ ). Our results also point out a possible role of exon 2 deleted MEFV transcript in FMF pathogenesis.

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DOI: 10.1111/j.1744-313X.2011.01015.x

PMID: 21615705 [Indexed for MEDLINE]

2997. Med Clin (Barc). 2011 Jan;136 Suppl 1:34-7. doi: 10.1016/S0025-7753(11)70007-0.

[Canakinumab, a monoclonal antibody against IL-1 $\beta$ , with potential utility in different inflammatory processes].

[Article in Spanish]

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Canakinumab is a fully human monoclonal antibody targeted at IL-1 $\beta$  which has shown to be effective in the control the symptoms of patients affected by CAPS and other autoinflammatory diseases. Its effect is rapid and sustained. In clinical trials conducted up until now, the most common adverse effects reported with the use of this drug have been different types of infections, migraines and vertigo.

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DOI: 10.1016/S0025-7753(11)70007-0

PMID: 21596185 [Indexed for MEDLINE]

2998. Med Clin (Barc). 2011 Jan;136 Suppl 1:22-8. doi: 10.1016/S0025-7753(11)70005-7.

[Pathophysiological mechanisms underlying cryopyrin-associated periodic syndromes: genetic and molecular basis and the inflammasome].

[Article in Spanish]

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NLRP3 gene (formerly known as CIAS1) encodes for cryopyrin (Nalp3) protein, which belongs to the Nod-like family of innate immune receptors. Cryopyrin recruits different adaptor and effectors proteins into a cytosolic macromolecular complex termed Nalp3-inflammasome, which senses both several pathogen-associated and damage-associated molecular patterns as well as inorganic particles (asbestos, silica), and triggers innate immune and inflammatory responses. Gain-of-function NLRP3 mutations are the common molecular basis of cryopyrin-associated periodic syndromes (CAPS), which encompasses three clinical entities along a spectrum of disease severity (familial cold autoinflammatory syndrome, Muckle-Wells syndrome and CINCA-NOMID syndrome). This hypermorphic cryopyrin provokes an increased, unregulated secretion of different inflammatory cytokines (IL-1 $\beta$ , IL-18, IL-33) in patients with CAPS, and in vivo administration of IL-1 blocking agents results in excellent therapeutic responses in these patients.

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DOI: 10.1016/S0025-7753(11)70005-7

PMID: 21596183 [Indexed for MEDLINE]

2999. Med Clin (Barc). 2011 Jan;136 Suppl 1:16-21. doi: 10.1016/S0025-7753(11)70004-5.

[Syndrome of Muckle-Wells and autoinflammatory familial syndrome induced by cold].

[Article in Spanish]

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Familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS) belong to the cryopyrin-associated periodic syndromes (CAPS) with CIAS1 gene mutations as a common molecular basis. Patients with FCAS have the least severe clinical phenotype but are characterized by the development of symptoms induced by a generalized exposure to cold appearing during the first months of childhood. It is important to make differential diagnosis between FCAS and acquired cold urticaria (ACU) and familial atypical cold urticaria (FACU). Muckle-Wells syndrome is characterized by recurrent fever and urticarial rash, progressive sensorineural deafness and the development of secondary amyloidosis, but it is not considered the most severe disease of this group. Sensorineural deafness and amyloidosis are the two major complications of MWS and determine poor prognosis of the disease.

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DOI: 10.1016/S0025-7753(11)70004-5

PMID: 21596182 [Indexed for MEDLINE]

3000. Med Clin (Barc). 2011 Jan;136 Suppl 1:10-5. doi: 10.1016/S0025-7753(11)70003-3.

[Syndrome CINCA/NOMID].

[Article in Spanish]

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CINCA/NOMID syndrome was first reported in 1981, identified as a new disease in 1987 and the main cause discovered in 2001, when mutations in the CIAS1 gene modifying the structure of the protein cryopirin were found in those patients (although other factors seem to play a role). Together with the major symptoms that characterized the syndrome, neurological, cutaneous and articular manifestations, others have been added which seem to be quite constant among CINCA/NOMID diagnosed patients: pre and perinatal symptoms, morfological changes, outbreaks of fever and biological abnormalities which reveal a persistent inflammatory background. The radiological studies have been able to identify the physis as the origin of the osteoarticular malformations seen in this syndrome. Diferential diagnosis includes diseases with similar onset at the neonatal period or infancy: systemic onset juvenile idiopathic athritis, periodic fever associated with mevalonate kinase deficiency, deficiency of IL-1 receptor antagonist (DIRA) and Muckle-Wells syndrome.

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DOI: 10.1016/S0025-7753(11)70003-3

PMID: 21596181 [Indexed for MEDLINE]

3001. Med Clin (Barc). 2011 Jan;136 Suppl 1:3-9. doi: 10.1016/S0025-7753(11)70002-1.

[Autoinflammatory syndromes].

[Article in Spanish]

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Autoinflammatory syndromes are characterised by recurrent or persistent inflammation with no increase in the antibody titers or antigen-specific T lymphocytes, and absence of infection. Initially, they included the hereditary periodic fever syndromes, a group of innate immune system monogenic diseases characterised by recurrent febrile episodes, with different characteristics, duration and interval, accompanied by other symptoms. Secondary amyloidosis is a complication in this group. The advances in the last few years has led to the identification of susceptible genes, new proteins, and characterising mechanisms and pathogenic routes that have led to an improvement in the diagnosis and establishing more effective treatments. Among these routes, are the changes in the inflammasome components, a group of cytoplasmic proteins that regulate the production of several inflammatory response mediators. The initial group of monogenic autoinflammatory diseases have increased in the last few years, due to including several polygenic hereditary diseases.

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DOI: 10.1016/S0025-7753(11)70002-1

PMID: 21596180 [Indexed for MEDLINE]

3002. Immunity. 2011 May 27;34(5):755-68. doi: 10.1016/j.immuni.2011.02.020. Epub 2011 May 19.

Gain-of-function Pyrin mutations induce NLRP3 protein-independent interleukin-1 $\beta$  activation and severe autoinflammation in mice.

Chae JJ(1), Cho YH, Lee GS, Cheng J, Liu PP, Feigenbaum L, Katz SI, Kastner DL.

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Comment in

Immunity. 2011 May 27;34(5):695-7.

Missense mutations in the C-terminal B30.2 domain of pyrin cause familial Mediterranean fever (FMF), the most common Mendelian autoinflammatory disease. However, it remains controversial as to whether FMF is due to the loss of an inhibitor of inflammation or to the activity of a proinflammatory molecule. We generated both pyrin-deficient mice and "knockin" mice harboring mutant human B30.2 domains. Homozygous knockin, but not pyrin-deficient, mice exhibited spontaneous bone marrow-dependent inflammation similar to but more severe than human FMF. Caspase-1 was constitutively activated in knockin macrophages and active IL-1 $\beta$  was secreted when stimulated with lipopolysaccharide alone, which is also observed in FMF patients. The inflammatory phenotype of knockin mice was completely ablated by crossing with IL-1 receptor-deficient or adaptor molecule ASC-deficient mice, but not NLRP3-deficient mice. Thus, our data provide evidence for an ASC-dependent NLRP3-independent inflammasome in which gain-of-function pyrin mutations cause autoinflammatory disease.

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DOI: 10.1016/j.immuni.2011.02.020

PMCID: PMC3129608

PMID: 21600797 [Indexed for MEDLINE]

3003. Isr Med Assoc J. 2011 Apr;13(4):234-5.

Is vitamin D a new therapeutic agent in autoinflammatory and pain syndromes?

Arnson Y, Amital H.

Comment on

Isr Med Assoc J. 2011 Apr;13(4):212-5.

PMID: 21598813 [Indexed for MEDLINE]

3004. Isr Med Assoc J. 2011 Apr;13(4):209-11.

Atypical Henoch-Schonlein purpura: a forerunner of familial Mediterranean fever.

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Intussusception is the most common cause of intestinal obstruction in early childhood. The cause of most intussusceptions is unknown but it can complicate the course of Henoch-Schonlein purpura (HSP) as a result of the vasculitic process. Familial Mediterranean fever (FMF), a common disease in Israel, is also associated with HSP. In a few patients, particularly in children, HSP has been reported to precede the diagnosis of FMF. We describe two patients with an unusual clinical course of severe abdominal pain as a result of intussusception. The correlation between intussusception, HSP and FMF are discussed.

PMID: 21598807 [Indexed for MEDLINE]

3005. Isr Med Assoc J. 2011 Apr;13(4):206-8.

Expanding the panel of MEFV mutations for routine testing of patients with a clinical diagnosis of familial Mediterranean fever.

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**BACKGROUND:** Since the identification of the MEFV gene 198 mutations have been identified, not all of which are pathologic. The screening methods used in Israel to test patients suspected of having FMF include a kit that tests for the five main mutations (M694V, V726A, M680Ic/g, M694I, E148Q), and the sequencing of MEFV

exon 10 in combination with restriction analysis for detecting additional mutations

**OBJECTIVES:** To determine the contribution of testing for five additional mutations - A744S, K695R, M680Ic/t, R761H and P369S - to the molecular diagnosis of patients clinically suspected of having FMF.

**METHODS:** A total of 1637 patients were tested for FMF mutations by sequencing exon 10 and performing restriction analysis for mutations E148Q and P369S.

**RESULTS:** Nearly half the patients (812, 49.6%) did not have any detectable mutations, 581 (35.5%) had one mutation, 241 (14.7%) had two mutations, of whom 122 were homozygous and 119 compound heterozygous, and 3 had three mutations. Testing for the additional five mutations enabled us to identify 46 patients who would have been missed by the molecular diagnosis kit and 22 patients in whom only one mutation would have been found. Altogether, 4.3% of the patients would not have been diagnosed correctly had only the kit that tests for the five main mutations been used.

**CONCLUSIONS:** This study suggests that testing for the additional five mutations as well as the five main mutations in patients with a clinical presentation of FMF adds significantly to the molecular diagnosis of FMF in the Israeli population.

PMID: 21598806 [Indexed for MEDLINE]

3006. Isr Med Assoc J. 2011 Apr;13(4):202-5.

Serum amyloid A levels in kidney-transplanted patients with familial Mediterranean fever-amyloidosis.

Kivity S(1), Danilesko I, Ben-Zvi I, Gilburd B, Kukuy OL, Rahamimov R, Livneh A.

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**BACKGROUND:** Amyloidosis of familial Mediterranean fever (FMF) may lead to end-stage renal failure, culminating in kidney transplantation. Since amyloidosis is prompted by high serum amyloid A (SAA) levels, increased SAA is expected to persist after transplantation. However, no data are available to confirm such an



assumption.

**OBJECTIVES:** To determine SAA levels in kidney-transplanted FMF-amyloidosis patients and evaluate risk factors for the expected high SAA levels in this patient group.

**METHODS:** SAA, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) values were obtained from 16 kidney-transplanted FMF-amyloidosis patients, 18 FMF patients without amyloidosis and 20 kidney-transplanted patients with non-inflammatory underlying disease. Demographic, clinical and genetic risk factors evaluation was based on data extracted from files, interviews and examination of the patients.

**RESULTS:** SAA level in FMF patients who underwent kidney transplantation due to amyloidosis was elevated with a mean of  $21.1 \pm 11.8$  mg/L (normal  $\leq 10$  mg/L). It was comparable to that of transplanted patients with non-inflammatory disorders, but tended to be higher than in FMF patients without amyloidosis ( $7.38 \pm 6.36$ ,  $P = 0.08$ ). Possible risk factors for the elevated SAA levels in kidney transplant patients that were excluded were ethnic origin, MEFV mutations, gender, age and disease duration.

**CONCLUSIONS:** Kidney-transplanted patients with FMF-amyloidosis and with other non-FMF causes displayed mildly elevated SAA levels, possibly resulting from exposure to foreign tissue rather than from various FMF-related factors.

PMID: 21598805 [Indexed for MEDLINE]

3007. Isr Med Assoc J. 2011 Apr;13(4):199-201.

The structural effect of the E148Q MEFV mutation on the pyrin protein: a study using a quantum chemistry model.

Naimushin A(1), Lidar M, Ben Zvi I, Livneh A.

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Comment in

Isr Med Assoc J. 2011 Nov;13(11):714; author reply 714.

**BACKGROUND:** Familial Mediterranean fever (FMF) is a recessively inherited disease

with a variety of clinical presentations. The disease is associated with mutations in the FMF gene (MEFV), which encodes for the pyrin protein. The role of the E148Q pyrin mutation in the FMF phenotype remains inconclusive, and some authors even view it as a disease-insignificant polymorphism. The calculated change imposed by this mutation on pyrin structure may help to understand the role of this mutation.

**OBJECTIVES:** To calculate the relative electrochemical effect of the E148Q mutation on the structure of pyrin protein.

**METHODS:** The electronic properties of the wild-type pyrin molecule and its common mutated forms were computed for the full-length molecule and its segments, encoded by exons 2 and 10, using the HyperChem 7.5 program with one of the molecular mechanical methods (MM+). The change in the structure of the molecule, expressed as a change in energy gain, conferred by the mutations was determined.

**RESULTS:** The E148Q mutation caused deviation from the wildtype pyrin segment encoded by exon 2 by 1.15% and from the whole pyrin molecule by 0.75%, which was comparable to the R202Q mutation and less than the M694V mutation which caused a deviation from the wild-type structure of the whole pyrin molecule by 1.5%.

**CONCLUSIONS:** A quantum chemistry-based model suggests that the structural effect of the E148Q mutation is indeed low but not zero.

PMID: 21598804 [Indexed for MEDLINE]

3008. Isr Med Assoc J. 2011 Apr;13(4):197-8.

Familial mediterranean fever: a continuously challenging disease.

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PMID: 21598803 [Indexed for MEDLINE]

3009. J AAPOS. 2011 Apr;15(2):205-7. doi: 10.1016/j.jaapos.2011.02.004.

Uveitis in Blau syndrome from a de novo mutation of the NOD2/CARD15 gene.

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Blau syndrome (MIM 186580) is a rare autoinflammatory, familial granulomatous condition that occurs secondary to a single amino acid mutation of the NOD2/CARD15 gene on chromosome 16p12-q21. We report the case of a 2.5-year-old girl who presented for ophthalmic examination in the setting of rash and synovitis. Initially, small, evanescent, ovoid corneal subepithelial opacities unique to Blau syndrome were observed. She later developed a fulminant panuveitis that responded to immunomodulatory therapy. Subsequent genetic testing confirmed the diagnosis of Blau syndrome. Despite immunosuppression, at almost 7 years of age, she continues to have persistent panuveitis with vision of 20/20.

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DOI: 10.1016/j.jaapos.2011.02.004

PMID: 21596301 [Indexed for MEDLINE]

3010. Rheumatology (Oxford). 2011 Jul;50(7):1348-9; author reply 1349. doi: 10.1093/rheumatology/ker155. Epub 2011 May 17.

Comment on: Familial Mediterranean fever caused by homozygous E148Q mutation complicated by Budd-Chiari syndrome and polyarteritis nodosa.

Konstantopoulos K, Kanta A.

Comment on

Rheumatology (Oxford). 2011 Mar;50(3):624-6.

DOI: 10.1093/rheumatology/ker155

PMID: 21586521 [Indexed for MEDLINE]

3011. J Parasitol Res. 2011;2011:942616. doi: 10.1155/2011/942616. Epub 2011 Apr 18.

Helminth parasites and the modulation of joint inflammation.

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There is an urgent need to develop better therapeutics for autoimmune and autoinflammatory diseases, of which musculoskeletal disorders such as rheumatoid arthritis are particularly prevalent and debilitating. Helminth parasites are accomplished masters at modifying their hosts' immune activity, and so attention has focused on rodent-helminth model systems to uncover the workings of the mammalian immune response to metazoan parasites, with the hope of revealing molecules and/or mechanisms that can be translated into better treatments for human autoimmune and idiopathic disorders. Substantial proof-of-principal data supporting the concept that infection with helminth parasites can reduce the severity of concomitant disease has been amassed from models of mucosal inflammation. Indeed, infection with helminth parasites has been tried as a therapy in inflammatory bowel disease, and there are case reports relating to other conditions (e.g., autism); however, the impact of infection with parasitic helminths on musculoskeletal diseases has not been extensively studied. Here, we present the view that such a strategy should be applied to the amelioration of joint inflammation and review the literature that supports this contention.

DOI: 10.1155/2011/942616

PMCID: PMC3092582

PMID: 21584243

3012. Clin Pract. 2011 May 6;1(2):e34. doi: 10.4081/cp.2011.e34. eCollection 2011 May 16.

Coexistence of Behçet's disease with ankylosing spondylitis and familial Mediterranean fever: a rare occurrence.

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Behçet's disease (BD) and familial Mediterranean fever (FMF), which are two separate diseases sharing some clinical features, may also coexist in the same patient. Further investigations are needed to understand whether this coexistence is due to either chance or geographical distribution patterns of these diseases or to common etiopathogenetic characteristics. Spondylarthritis as part of the clinical picture in these two diseases has been questioned and probably it is not a prominent characteristic of any of them. We report a 35-year-old Tunisian man who had an association of BD, FMF and Human Leukocyte Antigen (HLA) B27 positive ankylosing spondylitis. Although that spondylarthritis is an infrequent joint involvement of FMF and BD, it must be looked for in case of association of these diseases.

DOI: 10.4081/cp.2011.e34

PMCID: PMC3981244

PMID: 24765296

3013. Mod Rheumatol. 2011 Dec;21(6):684-90. doi: 10.1007/s10165-011-0463-2. Epub 2011 May 13.

Anti-TNF agents in familial Mediterranean fever: report of three cases and review of the literature.

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Familial Mediterranean fever (FMF) is an autoinflammatory disease characterized by recurrent fever, peritonitis/pleuritis, or arthritis attacks. Patients may have FMF-associated mutations of pyrin. The role of biologics such as anti-tumor necrosis factor (TNF) agents (infliximab, etanercept, adalimumab, golimumab) and anakinra, canakinumab, or rilonacept in the treatment of FMF needs to be clarified. Herein we present reports of three patients (all were positive for HLA B27) with typical spondylitis associated with FMF who were successfully managed with anti-TNF agents, along with a literature review. The patients were a 37-year-old man with concomitant Crohn's disease and amyloidosis who was treated with infliximab (INF, 5 mg/kg for 3 years) and switched to adalimumab (ADA), and two female patients (a 24-year-old and a 31-year-old) with FMF who developed severe spondylitis and who were also treated with ADA. Anti-TNF agents can control FMF attacks quite effectively and they reveal a promising role in the treatment of FMF-associated amyloidosis and spondylitis.

DOI: 10.1007/s10165-011-0463-2

PMID: 21567247 [Indexed for MEDLINE]

3014. Mol Biol Rep. 2012 Jan;39(1):117-21. doi: 10.1007/s11033-011-0716-3. Epub 2011 May 13.

TNFRSF1A [corrected] R92Q mutation, autoinflammatory symptoms and multiple sclerosis in a cohort from Argentina.

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Systemic autoinflammatory diseases are genetic disorders characterized by seemingly unprovoked inflammation, without major involvement of the adaptive immune system. Among them it is recognized the TNF receptor associated periodic syndrome (TRAPS) caused by mutations in the TNFRSF1A gene and characterized by symptoms such as recurrent high fevers, rash, abdominal pain, arthralgia and myalgia. Recent studies have recognized the potential role of TNFRSF1A mutations

in Multiple Sclerosis (MS). Our aim was to investigate the role of TNFRSF1A R92Q gene mutation in a cohort of 90 Argentinean MS patients, where we determined the frequency of the TNFRSF1A R92Q mutation. We also compared autoinflammatory symptoms, MS clinical characteristics and treatment response and tolerability in R92Q carriers and non-carriers. Also, we used a case-control study design to obtain the genotypes of 78 healthy controls and assess the role of this mutation as a risk factor for MS. We found that five patients (5.5%) carried the R92Q mutation, four reported autoinflammatory symptoms previous to MS onset. We found no differences in MS clinical features, treatment response and tolerability between carriers and non-carriers. R92Q mutation was more frequent in MS patients as compared to controls. This increases the risk to develop MS in about 4.5 times. The TNFRSF1A R92Q mutation is a common finding in Argentinean MS patients. This genetic variant might be a risk factor for MS.

DOI: 10.1007/s11033-011-0716-3

PMID: 21567205 [Indexed for MEDLINE]

3015. J Am Soc Nephrol. 2011 Jun;22(6):1007-18. doi: 10.1681/ASN.2010080798. Epub 2011 May 12.

The inflammasomes in kidney disease.

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Renal inflammation is a universal response to infectious and noninfectious triggers. Sensors of the innate immune system, such as Toll-like receptors or RIG-like receptors, provide danger recognition platforms on renal cells that integrate and translate the diverse triggers of renal inflammation by inducing cell activation and the secretion of proinflammatory cytokines and chemokines. As a new entry, the inflammasome-forming NLR genes integrate various danger signals into caspase-1-activating platforms that regulate the processing and secretion of pro-IL-1 $\beta$  and pro-IL-18 into the mature and active cytokines. Accumulating data now document a role for the NLRP3 inflammasome and IL-1 $\beta$ /IL-18 in many diseases, including atherosclerosis, diabetes, amyloidosis, malaria, crystal-related

diseases, and other autoinflammatory disorders, identifying this innate immune pathway as an attractive therapeutic target. Here we review the current knowledge regarding inflammasome signaling and outline existing evidence on the expression and functional role of the inflammasome-caspase-1-IL-1 $\beta$ /IL-18 axis in kidney disease. We further provide a perspective on the potential roles of the inflammasomes in the pathogenesis of acute and chronic kidney diseases.

DOI: 10.1681/ASN.2010080798

PMID: 21566058 [Indexed for MEDLINE]

3016. J Neuroimmunol. 2011 Jun;235(1-2):110-2. doi: 10.1016/j.jneuroim.2011.04.005. Epub 2011 May 11.

TNFRSF1A coding variants in multiple sclerosis.

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Patients with the autoinflammatory disease Tumour Necrosis Factor receptor-associated periodic syndrome (TRAPS) who suffer from demyelinating disease have been described, and one of the milder TRAPS mutations (R92Q in the TNFRSF1A gene) has been suggested as a risk factor for multiple sclerosis (MS). In a study population of 967 MS patients and 1022 controls, we replicate association [ $P=5\times 10^{-4}$ , 3% in patients versus 1% in controls, OR=2.26 (95% CI 1.41-3.61)], which appears independent of an established common risk variant in the same gene. No other non-synonymous variants in the same allele frequency range influencing risk of MS were observed.

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DOI: 10.1016/j.jneuroim.2011.04.005

PMID: 21565411 [Indexed for MEDLINE]



3017. *Mod Rheumatol*. 2012 Feb;22(1):45-51. doi: 10.1007/s10165-011-0461-4. Epub 2011 May 12.

Enhanced exon 2 skipping caused by c.910G>A variant and alternative splicing of MEFV genes in two independent cases of familial Mediterranean fever.

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Most reported cases of familial Mediterranean fever (FMF) involve missense mutations of MEFV concentrated within exon 10. We experienced two independent pedigrees of a unique variant in the MEFV gene that might cause excessive exon 2 skipping due to enhanced alternative splicing. In this study, we tried to elucidate the molecular mechanism of the MEFV variant as a cause of the FMF phenotype. Peripheral blood was obtained from volunteers and two patients with homozygous c.910G>A variant of the MEFV gene. MEFV messenger RNA (mRNA) expression patterns in mononuclear cells and granulocytes were compared using forward and reverse primers from exons 1 and 3, respectively. Expression profiles of pyrin were examined by transfecting wild-type and variant MEFV genes into HEK293T cells. Expression of normal-sized mRNA was extremely reduced in these patients, whereas that of aberrant short mRNA, deleting exon 2 ( $\Delta$ ex2), was significantly increased. Immunohistochemical and immunoblotting analyses revealed a truncated immunoreactive pyrin protein in cells transfected with  $\Delta$ ex2 cDNA. The MEFV gene c.910G>A variant results in accelerated aberrant splicing with abnormal protein size, presumably leading to anomalous pyrin function. This is the first report to show that an MEFV variant other than missense mutation is responsible for the FMF phenotype.

DOI: 10.1007/s10165-011-0461-4

PMID: 21562927 [Indexed for MEDLINE]

3018. *Arthritis Care Res (Hoboken)*. 2011 May;63(5):780-3. doi: 10.1002/acr.20418.

Macrophage activation syndrome revealing familial Mediterranean fever.

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DOI: 10.1002/acr.20418

PMID: 21557533 [Indexed for MEDLINE]

3019. Open Rheumatol J. 2011 Feb 4;5:13-7. doi: 10.2174/1874312901105010013.

Melatonin and its day and night rhythm of alterations in familial mediterranean Fever: a brief research letter.

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**OBJECTIVE:** The pineal hormone melatonin plays a crucial role in immunomodulation, mainly by effecting T cells. The aims of the present study were to compare the melatonin levels in patients with Familial Mediterranean Fever (FMF) and healthy controls and to find out if it associates with interferon(IFN) $\gamma$  and interleukin(IL)-10.

**MATERIALS AND METHODOLOGY:** Twenty five patients with FMF and 16 healthy donors were enrolled into the study. Melatonin, IFN  $\gamma$  and IL-10 measurements were assayed by using enzyme immunoassay (EIA) method.

**RESULTS:** Serum melatonin levels at 03.30 am in both patients during attack-free phase and healthy controls were significantly higher than those levels of corresponding groups measured at 10.00 am. The melatonin levels at 03.30 and 10.00 am in patients during attack-free phase were higher than those levels measured in healthy controls at the same time points. IFN $\gamma$  and IL-10 did not show any day and night rhythm in both patients and healthy controls. In addition, there was no association among day and night levels of melatonin, IFN $\gamma$  and IL-10.

**CONCLUSIONS:** We conclude that melatonin may play a role in FMF pathogenesis.

However, its modulatory effect on immune response most likely does not depend on T cells. Further comprehensive studies should be performed in order to reveal the role of melatonin in the pathogenesis of this disease.

DOI: 10.2174/1874312901105010013

PMCID: PMC3087213

PMID: 21552416

3020. Rheumatol Int. 2011 Oct;31(10):1263-74. doi: 10.1007/s00296-011-1840-z. Epub 2011 Mar 10.

Coexistence of vasculitides with familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is the most common autoinflammatory disease characterized by recurrent self-limited attacks of fever accompanied with peritonitis, pleuritis, or arthritis. FMF may coexist with various systemic inflammatory diseases including vasculitides, spondyloarthritis, multiple sclerosis, and inflammatory bowel disease. Among these coexistences, this review concentrates on vasculitic disorders, with the aim of increasing the awareness of FMF-vasculitis association. This association does not merely show a coincidentally increased frequency of vasculitic disorders in FMF; rather, it seems that FMF patients might be at increased risk of developing vasculitis. Indeed, as also suggested by some authors, vasculitis might be an essential feature of FMF. Among the vasculitic disorders reported to be associated with FMF, Henoch-Schönlein purpura, and classical polyarteritis nodosa come the first, possibly followed up by protracted febrile myalgia. There is also an ongoing debate whether Behçet's disease (BD) more frequently seen in FMF than expected by chance alone. In this review, the associations of various vasculitic disorders with FMF and the possible pathogenic mechanisms underlying these associations, as well as the frequencies and clinical significances of FMF-related MEFV mutations in various vasculitides including BD, are discussed in the context of the

available data.

DOI: 10.1007/s00296-011-1840-z

PMID: 21547384 [Indexed for MEDLINE]

3021. J Phys Chem B. 2011 May 26;115(20):6644-52. doi: 10.1021/jp201848c. Epub 2011 May 4.

Nanocavity effect on photophysical properties of colchicine: a proof by circular dichroism study and picosecond time-resolved analysis in various reverse micellar assemblies.

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In August 2009, colchicine won Food and Drug Administration (FDA) approval in the United States as a stand-alone drug for the treatment of acute flares of gout and familial Mediterranean fever. Recently, it is now the center of attraction in medicinal research. In this present paper, we have employed two other analogues of colchicine for exploring the photophysical properties inside nanocavity environment in details. Here we have a series of interesting results that have interesting similarity with the colchinoid-tubulin interaction. To monitor fluorescence properties of colchinoids, we have used absorption, emission, and time-resolved spectroscopy and to monitor structural properties we have measured circular dichroism. Steady-state anisotropy and dynamic light scattering results give an idea about the microenvironment sensed by the colchinoids molecules. A sharp increment for colchicine, very small increment for isocolchicine and no increment for colcemid in fluorescence and different circular dichroism (CD) spectra of all of these colchinoids upon embedment inside nanocavity of reverse micelle made a supposition that all these changes of fluorescence properties and CD results of colchinoids is not solely due to viscosity effect but also the constraint, that is, very narrow space to spread over, given by the nanocavity of reverse micelle. Moreover, we have noticed that the B ring of the colchinoids also have a pronounced effect on the interaction nature as well as on conformational change of these compounds after entrapment.

DOI: 10.1021/jp201848c

PMID: 21542580 [Indexed for MEDLINE]

3022. Hautarzt. 2011 May;62(5):389-401; quiz 402. doi: 10.1007/s00105-010-2124-3.

[Autoinflammatory syndromes/fever syndromes].

[Article in German]

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Hereditary periodic (fever) syndromes, also called autoinflammatory syndromes, are characterized by relapsing fever and additional manifestations such as skin rashes, mucosal manifestations, or joint symptoms. Some of these disorders present with organ involvement and serological signs of inflammation without fever. There is a strong serological inflammatory response with an elevation of serum amyloid A (SAA), resulting in an increased risk of secondary amyloidosis. There are monogenic disorders (familial mediterranean fever (FMF), hyper-IgD-syndrome (HIDS), cryopyrin-associated periodic syndromes (CAPS), "pyogenic arthritis, acne, pyoderma gangrenosum" (PAPA), and "pediatric granulomatous arthritis (PGA) where mutations in genes have been described, which in part by influencing the function of the inflammasome, in part by other means, lead to the induction of the production of IL-1 $\beta$ . In "early-onset of enterocolitis (IBD)", a functional IL-10 receptor is lacking. Therapeutically, above all, the IL-1 receptor antagonist anakinra is used. In case of TRAPS and PGA, TNF-antagonists (etanercept) may also be used; in FMF colchicine is first choice. As additional possible autoinflammatory syndromes, PFAPA syndrome (periodic fever with aphthous stomatitis, pharyngitis and adenitis), Schnitzler syndrome, Still's disease of adult and pediatric onset, Behçet disease, gout, chronic recurrent multifocal osteomyelitis (CRMO) and Crohn's disease also are mentioned.

DOI: 10.1007/s00105-010-2124-3  
PMID: 21541834 [Indexed for MEDLINE]

3023. Clin Rheumatol. 2011 Oct;30(10):1347-51. doi: 10.1007/s10067-011-1759-5. Epub 2011 May 4.

Normal autonomic nervous system responses in uncomplicated familial Mediterranean fever: a comparative case-control study.

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There is a paucity of knowledge regarding the autonomic nervous system function in patients with familial Mediterranean fever (FMF). Therefore, our aim was to evaluate autonomic responses in patients with FMF using complementary tests. The study groups included 33 patients with uncomplicated FMF and 39 control subjects. Autonomic function was evaluated by measuring responses to metronomic breathing, the Valsalva maneuver, and the Ewing maneuver. Autonomic parameters were computed from electrocardiograms with designated computer software. There were no statistically significant differences in any of the measured parameters of autonomic function between the patient and control group. The measured autonomic parameters of both groups were similar to those previously reported in healthy individuals. In conclusion, patients with FMF who did not develop amyloidosis due to continuous colchicine treatment appeared to have normal autonomic function, as reflected by the normal response to physiological autonomic stimuli.

DOI: 10.1007/s10067-011-1759-5  
PMID: 21541656 [Indexed for MEDLINE]

3024. Pediatr Rheumatol Online J. 2010 Dec 2;8:29. doi: 10.1186/1546-0096-8-29.

Periodic fever syndromes in Eastern and Central European countries: results of a pediatric multinational survey.

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**OBJECTIVE:** To analyze the prevalence of diagnosed and suspected autoinflammatory diseases in Eastern and Central European (ECE) countries, with a particular interest on the diagnostic facilities in these countries.

**METHODS:** Two different strategies were used to collect data on patients with periodic fever syndromes from ECE countries- the Eurofever survey and collection of data with the structured questionnaire.

**RESULTS:** Data from 35 centers in 14 ECE countries were collected. All together there were 11 patients reported with genetically confirmed familial Mediterranean fever (FMF), 14 with mevalonate-kinase deficiency (MKD), 11 with tumor necrosis factor receptor associated periodic syndrome (TRAPS) and 4 with chronic infantile neurological cutaneous and articular syndrome (CINCA). Significantly higher numbers were reported for suspected cases which were not genetically tested. All together there were 49 suspected FMF patients reported, 24 MKD, 16 TRAPS, 7 CINCA and 2 suspected Muckle-Wells syndrome (MWS) patients.

**CONCLUSIONS:** The number of genetically confirmed patients with periodic fever syndromes in ECE countries is very low. In order to identify more patients in the future, it is important to organize educational programs for increasing the knowledge on these diseases and to establish a network for genetic testing of periodic fever syndromes in ECE countries.

DOI: 10.1186/1546-0096-8-29

PMCID: PMC3014922

PMID: 21539753

3025. Arthritis Rheum. 2011 May;63(5):1459-64. doi: 10.1002/art.30241.

Identification and functional consequences of a recurrent NLRP12 missense

mutation in periodic fever syndromes.

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**OBJECTIVE:** To gain insight into the molecular bases of genetically unexplained periodic fever syndromes (PFS) by screening NLRP12, a gene in which only a nonsense and a splice site mutation have so far been identified, and to assess the functional consequences of the identified missense variation.

**METHODS:** NLRP12 was screened for mutations by direct sequencing. Functional assays were performed in HEK 293T cells stably expressing the proapoptotic protein ASC and procaspase 1, in order to determine the effects of normal and mutated NLRP12 proteins on speck formation, caspase 1 signaling, and NF- $\kappa$ B activation.

**RESULTS:** A heterozygous NLRP12 missense mutation involving a CpG site (c.1054C>T; p.Arg352Cys) was identified in exon 3, which encodes the nucleotide-binding site (NBS) of the protein, in 2 patients from different countries and carrying different NLRP12 haplotypes. The mutation, which does not alter the inhibitory effect of NLRP12 on NF- $\kappa$ B activation, increases speck formation and activates caspase 1 signaling. To define this new class of PFS, we propose the term NLRP12-associated disorders (NLRP12AD).

**CONCLUSION:** Given the rarity of known NLRP12-associated disorders, the identification of this NLRP12 molecular defect contributes to the delineation of the clinical spectrum associated with mutations in this gene and highlights the importance of screening NLRP12 in patients presenting with unexplained PFS. This study also demonstrates, by means of functional assays, the deleterious effect of this recurrent missense mutation; the gain of function for speck formation and caspase 1 signaling associated with this NBS mutation is consistent with the inflammatory phenotype of PFS.

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DOI: 10.1002/art.30241

PMID: 21538323 [Indexed for MEDLINE]



3026. Curr Rheumatol Rep. 2011 Apr;13(2):123-31. doi: 10.1007/s11926-011-0165-y.

Current status of understanding the pathogenesis and management of patients with NOMID/CINCA.

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Neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic, cutaneous, and arthritis (CINCA) syndrome is the most severe clinical phenotype in the spectrum of cryopyrin- (NLRP3/NALP3) associated periodic syndromes (CAPS). The study of patients with NOMID/CINCA has been instrumental in characterizing the extent of organ-specific inflammatory manifestations and damage that can occur with chronic interleukin (IL)-1 $\beta$  overproduction. Mutations in CIAS1/NLRP3 lead to constitutive activation of the "NLRP3 inflammasome," an intracellular platform that processes and secretes increased amounts of IL-1 $\beta$ . The pivotal role of IL-1 $\beta$  in NOMID/CINCA has been demonstrated in several clinical studies using IL-1--blocking agents that lead to rapid resolution of the inflammatory disease manifestations. NOMID/CINCA is a monogenic autoinflammatory syndrome; and the discovery of the role of IL-1 in NOMID has led to the exploration in the role of IL-1 in other disorders including gout and Type II diabetes. The inflammation in NOMID/CINCA is continuous with intermittent flares, and organ manifestations encompass the central nervous system, eye, inner ear, and bones. This review discusses updates on the pathogenesis of NOMID/CAPS, emerging long term-outcome data regarding IL-1--blocking agents that have influenced our considerations for optimal treatment, and a monitoring approach tailored to the patient's disease severity and organ manifestations.

DOI: 10.1007/s11926-011-0165-y

PMCID: PMC3195512

PMID: 21538043 [Indexed for MEDLINE]

3027. Eur J Pediatr. 2011 Dec;170(12):1563-8. doi: 10.1007/s00431-011-1479-5. Epub 2011

May 3.

PFAPA syndrome in siblings. Is there a genetic background?

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"PFAPA syndrome" is an autoinflammatory entity composed of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis. There have been many reports of children with the disease, but only occasionally have been described in siblings, and no specific genetic mutation has been determined yet. Corticosteroids are the mainstay in the treatment of the acute attacks. The role of surgery in long-term follow-up (tonsillectomy with or without adenoidectomy) is controversial. We report two brothers affected with the syndrome, in whom corticosteroids as the only treatment led to an improvement. A genetic work-up was performed, making very unlikely other possible syndromes of recurrent fever. CONCLUSION: PFAPA syndrome is the most common recurrent periodic fever disorder described in childhood. Its genetic background has not been elucidated yet. Our contribution with two siblings affected with PFAPA syndrome further support the genetic basis for the entity.

DOI: 10.1007/s00431-011-1479-5

PMID: 21537926 [Indexed for MEDLINE]

3028. Acta Paediatr. 2011 Aug;100(8):e49-50. doi: 10.1111/j.1651-2227.2011.02339.x. Epub 2011 Jun 1.

A case of Familial Mediterranean Fever at the Baltic Sea.

Glaserapp S, Klaunick G, Stuhldreier G, Lohse P, Wigger M, Haffner D.

DOI: 10.1111/j.1651-2227.2011.02339.x

PMID: 21535129 [Indexed for MEDLINE]

3029. Curr Infect Dis Rep. 2011 Aug;13(4):308-16. doi: 10.1007/s11908-011-0189-5.

Pericarditis: pathophysiology, diagnosis, and management.

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Pericarditis, the most common disease of the pericardium, may be isolated or a manifestation of a systemic disease. The etiology of pericarditis is varied and includes infectious (especially viral and tuberculosis) and noninfectious causes (autoimmune and autoinflammatory diseases, pericardial injury syndromes, and cancer [especially lung cancer, breast cancer, and lymphomas]). Most cases remain idiopathic with a conventional diagnostic evaluation. A targeted etiologic search should be directed to the most common cause on the basis of the patient's clinical background, epidemiologic issues, specific presentations, and high-risk features associated with specific etiologies or complications (fever higher than 38°C, subacute onset, large pericardial effusion, cardiac tamponade, lack of response to NSAIDs). The management of pericardial diseases is largely empiric because of the relative lack of randomized trials. NSAIDs are the mainstay of empiric anti-inflammatory therapy, with the possible addition of colchicine to prevent recurrences.

DOI: 10.1007/s11908-011-0189-5

PMID: 21534015

3030. Eur J Immunol. 2011 May;41(5):1203-17. doi: 10.1002/eji.201141550.

A clinical perspective of IL-1 $\beta$  as the gatekeeper of inflammation.

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An expanding spectrum of acute and chronic non-infectious inflammatory diseases is uniquely responsive to IL-1 $\beta$  neutralization. IL-1 $\beta$ -mediated diseases are often called "auto-inflammatory" and the dominant finding is the release of the active form of IL-1 $\beta$  driven by endogenous molecules acting on the monocyte/macrophage. IL-1 $\beta$  activity is tightly controlled and requires the conversion of the primary transcript, the inactive IL-1 $\beta$  precursor, to the active cytokine by limited proteolysis. Limited proteolysis can take place extracellularly by serine proteases, released in particular by infiltrating neutrophils or intracellularly by the cysteine protease caspase-1. Therefore, blocking IL-1 $\beta$  resolves inflammation regardless of how the cytokine is released from the cell or how the precursor is cleaved. Endogenous stimulants such as oxidized fatty acids and lipoproteins, high glucose concentrations, uric acid crystals, activated complement, contents of necrotic cells, and cytokines, particularly IL-1 itself, induce the synthesis of the inactive IL-1 $\beta$  precursor, which awaits processing to the active form. Although bursts of IL-1 $\beta$  precipitate acute attacks of systemic or local inflammation, IL-1 $\beta$  also contributes to several chronic diseases. For example, ischemic injury, such as myocardial infarction or stroke, causes acute and extensive damage, and slowly progressive inflammatory processes take place in atherosclerosis, type 2 diabetes, osteoarthritis and smoldering myeloma. Evidence for the involvement of IL-1 $\beta$  and the clinical results of reducing IL-1 $\beta$  activity in this broad spectrum of inflammatory diseases are the focus of this review.

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DOI: 10.1002/eji.201141550

PMID: 21523780 [Indexed for MEDLINE]

3031. Hautarzt. 2011 May;62(5):388. doi: 10.1007/s00105-011-2161-6.

[CME article: "Autoinflammatory syndromes/fever syndromes"].

[Article in German]

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DOI: 10.1007/s00105-011-2161-6

PMID: 21503781 [Indexed for MEDLINE]

3032. Clin J Am Soc Nephrol. 2011 May;6(5):1214-21. doi: 10.2215/CJN.09381010. Epub 2011 Apr 14.

Recurrence of secondary glomerular disease after renal transplantation.

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The risk of a posttransplant recurrence of secondary glomerulonephritis (GN) is quite variable. Histologic recurrence is frequent in lupus nephritis, but the lesions are rarely severe and usually do not impair the long-term graft outcome. Patients with Henoch-Schonlein nephritis have graft survival similar to that of other renal diseases, although recurrent Henoch-Schonlein nephritis with extensive crescents has a poor prognosis. Amyloid light-chain amyloidosis recurs frequently in renal allografts but it rarely causes graft failure. Amyloidosis secondary to chronic inflammation may also recur, but this is extremely rare in patients with Behcet's disease or in those with familial Mediterranean fever, when the latter are treated with colchicine. Double organ transplantation (liver/kidney; heart/kidney), chemotherapy, and autologous stem cell transplantation may be considered in particular cases of amyloidosis, such as hereditary amyloidosis or multiple myeloma. There is little experience with renal transplantation in light-chain deposition disease, fibrillary/immunotactoid GN, or mixed cryoglobulinemic nephritis but successful cases have been reported. Diabetic nephropathy often recurs but usually only after many years. Recurrence in patients with small vessel vasculitis is unpredictable but can cause graft failure. However, in spite of recurrence, patient and graft survival rates are similar in patients with small vessel vasculitis compared with those with other renal diseases. Many secondary forms of GN no longer represent a potential contraindication to renal transplantation. The main issues in transplantation of

patients with secondary GN are the infectious, cardiovascular, or hepatic complications associated with the original disease or its treatment.

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DOI: 10.2215/CJN.09381010

PMID: 21493742 [Indexed for MEDLINE]

3033. Otolaryngol Head Neck Surg. 2011 Aug;145(2):295-302. doi: 10.1177/0194599811402296.

Cryopyrin-associated periodic syndromes: otolaryngologic and audiologic manifestations.

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**OBJECTIVE:** Cryopyrin-associated periodic syndromes (CAPS) represent a spectrum of CIAS1 gene-mediated autoinflammatory diseases characterized by recurrent systemic inflammation. The clinical spectrum of CAPS varies from mild to severe and includes the syndromes historically described as familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID). This article presents the largest cohort of patients with CAPS. The objective is to describe the pathogenesis, otolaryngologic, and audiologic manifestations of CAPS.

**STUDY DESIGN:** Prospective (2003-2009).

**SETTING:** National Institutes of Health.

**SUBJECTS AND METHODS:** Fifty-seven patients with a diagnosis of CAPS were identified (31 NOMID, 11 NOMID/MWS, 9 MWS, and 6 FCAS). Comprehensive data regarding clinical manifestations, audiologic phenotype, and fluid attenuation inversion recovery MRI (FLAIR-MRI) of the brain and inner ear were obtained.

**RESULTS:** Complete audiologic data obtained on 70% of ears revealed conductive hearing loss in 4 (11%) NOMID ears and mixed hearing loss in 5 (13%) NOMID and 2 (14%) NOMID/MWS ears. Sensorineural hearing loss (SNHL), worse in higher frequencies, was the most common type of hearing loss and was present in 23 (61%)

NOMID, 10 (71%) NOMID/MWS, and 4 (33%) MWS ears. All of the patients with FCAS had normal hearing except 2, who had SNHL from 4 to 8 kHz. On FLAIR-MRI sequence, cochlear enhancement was noted in 26 of 29 (90%) NOMID, 6 of 11 (55%) NOMID/MWS, 3 of 9 (33%) MWS, and 1 of 6 (17%) FCAS patients and was significantly associated with the presence of hearing loss. Maxillary sinus hypoplasia and mucosal thickening were found in 39% and 86% of the cohort, respectively.

CONCLUSION: CIAS1 pathway-mediated CAPS is associated with unregulated autoinflammation mediated by interleukin-1 in the cochlea and hearing loss. Timely diagnosis is crucial to initiate early treatment with interleukin-1 receptor antagonists.

DOI: 10.1177/0194599811402296

PMCID: PMC3407887

PMID: 21493283 [Indexed for MEDLINE]

3034. Praxis (Bern 1994). 2011 Apr 13;100(8):483-6. doi: 10.1024/1661-8157/a000499.

[Arthritis, erythema nodosum and genital ulcerations. Behçet disease].

[Article in German]

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Behcet's disease is a disease of unknown etiology resting in between vasculitis, spondyloarthropathy and autoinflammatory diseases. If his predilection for the population originating from the Silk Road is well known, as are its cutaneous, ocular and vascular manifestations, this case illustrates the non-specificity of those manifestations, the diagnostic difficulties and the importance of routinely assessing for eyes and bowel diseases in this type of patient.

DOI: 10.1024/1661-8157/a000499

PMID: 21484713 [Indexed for MEDLINE]

3035. Clin Rheumatol. 2011 Oct;30(10):1295-8. doi: 10.1007/s10067-011-1745-y. Epub 2011

Apr 12.

P-wave dispersion in systemic AA amyloidosis of familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is a hereditary disease characterized by attacks of fever and polyserositis. Recent studies differ as to whether FMF is associated with an abnormally high P-wave duration and P-wave dispersion, markers for supraventricular arrhythmogenicity. The aim of our study was to further evaluate atrial dispersion in FMF patients with amyloidosis. The study groups consisted of 16 patients with FMF and amyloidosis, and 16 age- and sex-matched control subjects. All participants underwent 12-lead electrocardiography under strict standards. P-wave length and P-wave dispersion in each individual patient were computed from a randomly selected beat and an averaged beat constructed from 7 to 12 beats, included in a 10-s electrocardiogram. No statistically significant differences were found between the groups for minimal, maximal, and average P-wave duration and P-wave dispersion, calculated either from a random beat or averaged beats. In conclusion, although a small difference cannot be excluded because of the small study groups, FMF patients with amyloidosis appear to have atrial conduction parameters similar to those of healthy controls, and therefore apparently do not have an increased electrocardiographic risk for developing supraventricular arrhythmias.

DOI: 10.1007/s10067-011-1745-y

PMID: 21484223 [Indexed for MEDLINE]

3036. Acta Reumatol Port. 2011 Jan-Mar;36(1):69-74.

[Protracted Febrile Myalgia Syndrome with Henoch-Schönlein Purpura: an atypical presentation of Familial Mediterranean Fever].

[Article in Portuguese]



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Familial Mediterranean Fever (FMF) is an hereditary autosomal recessive disease characterized by recurrent attacks of fever, arthritis and serositis: peritonitis, pleurisy and/or pericarditis. Its main complication is systemic AA amyloidosis. The authors present a case of a 8-years-old female child with african ancestry, who was admitted three times since 5 years-old with abdominal pain, fever and high acute phase reactants. At the first admission appendectomy was made and at the third hospital admission the clinical picture was accompanied by myalgia, purpuric lesions and non nephrotic proteinuria. A renal biopsy was performed and was compatible with Henoch-Schönlein nephritis. Serum Amyloid A protein had high levels - 92 mg/L (> 6.8) and a diagnosis of Familial Mediterranean Fever was confirmed by genetic test (homozygote for M694V in MEFV gene). She started colchicine and is doing well, without any further complaints. FMF must be considered in the differential diagnosis of recurrent attacks of fever and abdominal pain in children, even with an atypical presentation (p.e. Protracted Febrile Myalgia Syndrome). Genetic study allows the confirmation of the diagnosis and has prognostic implications.

PMID: 21483284 [Indexed for MEDLINE]

3037. Arthritis Rheum. 2011 Jul;63(7):2142-8. doi: 10.1002/art.30378.

Role of interleukin-1 $\beta$  in NLRP12-associated autoinflammatory disorders and resistance to anti-interleukin-1 therapy.

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**OBJECTIVE:** A new class of autoinflammatory syndromes called NLRP12-associated disorders (NLRP12AD) has been associated with mutations in NLRP12. Conflicting data on the putative role of NLRP12 in interleukin-1 $\beta$  (IL-1 $\beta$ ) signaling have been found in in vitro analyses. This prospective study was undertaken to assess the secretion of IL-1 $\beta$  and 3 IL-1 $\beta$ -induced cytokines (IL-1 receptor antagonist [IL-1Ra], IL-6, and tumor necrosis factor  $\alpha$  [TNF $\alpha$ ]) in patients' peripheral blood mononuclear cells (PBMCs) cultured ex vivo and to evaluate the patients' response to IL-1Ra (anakinra), a major drug used in the treatment of autoinflammatory disorders.

**METHODS:** Patients' disease manifestations and cytokine measurements were recorded before anakinra treatment was started, during 14 months of therapy, and after discontinuation of anakinra treatment.

**RESULTS:** Spontaneous secretion of IL-1 $\beta$  by patients' PBMCs was found to be dramatically increased (80-175 fold) compared to healthy controls. Consistent with these findings, anakinra initially led to a marked clinical improvement and to a rapid near-normalization of IL-1 $\beta$  secretion. However, a progressive clinical relapse occurred secondarily, associated with an increase in TNF $\alpha$  secretion, persistent elevated levels of IL-1Ra and IL-6, and a reactivation of IL-1 $\beta$  secretion. Anakinra was discontinued after 14 months of therapy.

**CONCLUSION:** Our findings provide in vivo evidence of the crucial role of IL-1 $\beta$  in the pathophysiology of NLRP12AD. This is the first time anakinra has been used to treat this disorder. This study provides new insights into the mechanisms underlying resistance to anti-IL-1 therapy observed in a few patients with autoinflammatory syndromes. Our data also point to the potential of ex vivo cytokine measurements as predictors of response to treatment.

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DOI: 10.1002/art.30378

PMID: 21480187 [Indexed for MEDLINE]

3038. J Immunol. 2011 May 15;186(10):5738-48. doi: 10.4049/jimmunol.1003597. Epub 2011 Apr 6.

Caspase-1-processed cytokines IL-1 $\beta$  and IL-18 promote IL-17 production by  $\gamma\delta$  and CD4 T cells that mediate autoimmunity.

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IL-1 $\beta$  plays a critical role in promoting IL-17 production by  $\gamma\delta$  and CD4 T cells. However, IL-1-targeted drugs, although effective against autoinflammatory diseases, are less effective against autoimmune diseases. Conversely, gain-of-function mutations in the NLRP3 inflammasome complex are associated with enhanced IL-1 $\beta$  and IL-18 production and Th17 responses. In this study, we examined the role of caspase-1-processed cytokines in IL-17 production and in induction of experimental autoimmune encephalomyelitis (EAE). Killed *Mycobacterium tuberculosis*, the immunostimulatory component in CFA used for inducing EAE, stimulated IL-1 $\beta$  and IL-18 production by dendritic cells through activation of the inflammasome complex and caspase-1. Dendritic cells stimulated with *M. tuberculosis* and myelin oligodendrocyte glycoprotein promoted IL-17 production by T cells and induced EAE following transfer to naive mice, and this was suppressed by a caspase-1 inhibitor and reversed by administration of IL-1 $\beta$  or IL-18. Direct injection of the caspase-1 inhibitor suppressed IL-17 production by CD4 T cells and  $\gamma\delta$  T cells in vivo and attenuated the clinical signs of EAE.  $\gamma\delta$  T cells expressed high levels of IL-18R and the combination of IL-18 and IL-23, as with IL-1 $\beta$  and IL-23, stimulated IL-17 production by  $\gamma\delta$  T cells, but also from CD4 T cells, in the absence of TCR engagement. Our findings demonstrate that caspase-1-processed cytokines IL-1 $\beta$  and IL-18 not only promote autoimmunity by stimulating innate IL-17 production by T cells but also reveal redundancy in the functions of IL-1 $\beta$  and IL-18, suggesting that caspase-1 or the inflammasome may be an important drug target for autoimmune diseases.

DOI: 10.4049/jimmunol.1003597

PMID: 21471445 [Indexed for MEDLINE]

3039. Rheumatol Int. 2012 Jul;32(7):1955-62. doi: 10.1007/s00296-011-1894-y. Epub 2011 Apr 3.

Economic impact of juvenile idiopathic arthritis and familial Mediterranean fever.

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The aim of the study was to determine the economical impact of juvenile idiopathic arthritis (JIA) and familial Mediterranean fever (FMF) in Turkey. A total of 100 patients (69 F/31 M) with JIA and 100 with FMF (68 F/32 M) who were consecutively seen in the outpatient clinic of the pediatric rheumatology department at Cerrahpasa Medical School between August 2008 and January 2009 were studied. Cost data were collected through a questionnaire filled out by the parents. The mean age (JIA:  $11 \pm 5$  years; FMF:  $12 \pm 4$  years) and mean disease duration (JIA:  $5 \pm 3$  years; FMF:  $4 \pm 3$  years) of the patients were similar. JIA patients were assigned to 5 subtypes (polyarticular:  $n = 45$ , oligoarticular:  $n = 30$ , systemic onset:  $n = 13$ , psoriatic:  $n = 6$ , and enthesopathy-related JIA:  $n = 6$ ). Forty-nine percent of the patients with JIA were treated with anti-TNF drugs and 61% with DMARDs. All patients with FMF were using colchicine. The total annual cost of JIA ( $\text{€}3,994 \pm 4,101$ ) was considerably higher than that of FMF ( $\text{€}162 \pm 77$ ) ( $P < 0.001$ ). Medication fee was the major determinant of total costs in both diseases constituting 85% in JIA and 39% in FMF. Among the subtypes of JIA, total annual costs were the highest among patients with polyarticular type ( $\text{€}6,045 \pm 4,078$ ). Medications especially anti-TNF drugs were the major contributor among all determinants of costs in JIA. The low costs of health care system and prominent changes in the health care policies for the last 5 years in Turkey might have played role in our findings.

DOI: 10.1007/s00296-011-1894-y

PMCID: PMC3382642

PMID: 21461856 [Indexed for MEDLINE]

3040. Rheumatol Int. 2012 Jul;32(7):1945-8. doi: 10.1007/s00296-011-1896-9. Epub 2011 Apr 2.

QT dispersion in amyloidosis due to familial Mediterranean fever.

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Cardiac amyloid deposition in FMF may cause increased QT dispersion (QTd), a marker for cardiac arrhythmias. The aim of this study was to further evaluate repolarization dispersion in familial Mediterranean fever (FMF) with amyloidosis. Findings on 12-lead electrocardiography were compared between 18 patients with FMF-amyloidosis and 18 age- and sex-matched control subjects. Repolarization and dispersion parameters were computed with designated computer software, and results of the 5 beats were subsequently averaged. There were no statistically significant differences between the groups as to average corrected QT interval length, average QTd interval, average QT corrected dispersion, or QT dispersion ratio. JT dispersion and JT corrected dispersion were also similar in both groups. In conclusion, patients with FMF-amyloidosis seem to have QT and JT dispersion parameters similar to those of healthy subjects. Future research and longer follow-ups should be conducted in order to evaluate the prognostic importance of repolarization dispersion parameters in amyloidosis of FMF.

DOI: 10.1007/s00296-011-1896-9

PMID: 21461715 [Indexed for MEDLINE]

3041. J Rheumatol. 2011 Jul;38(7):1378-84. doi: 10.3899/jrheum.101260. Epub 2011 Apr 1.

Candidate genes in patients with autoinflammatory syndrome resembling tumor necrosis factor receptor-associated periodic syndrome without mutations in the TNFRSF1A gene.

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OBJECTIVE: Tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is an autosomal-dominant multisystemic autoinflammatory condition. Patients display different mutations of the TNF receptor superfamily 1A gene

(TNFRSF1A), coding for a nearly ubiquitous TNF receptor (TNFR1). No TNFRSF1A mutation has been identified in a proportion of patients with TRAPS-like phenotype.

**METHODS:** We investigated mechanisms downregulating the TNF-induced inflammatory response such as (1) receptor shedding, producing a secreted form acting as a TNF inhibitor; (2) receptor internalization with subsequent induction of apoptosis; and (3) negative regulation of nuclear factor- $\kappa$ B (NF- $\kappa$ B) transcription. We analyzed the sequence of genes known to play a pivotal role in these pathways, in 5 patients with TRAPS symptoms and showing shedding and/or apoptosis defects, but without mutations of the TNFRSF1A gene.

**RESULTS:** Sequence analysis of 3 genes involved in TNFR1 shedding (ERAP1, NUCB2, RBMX) and 3 genes involved in negative regulation of NF- $\kappa$ B signaling (TNFAIP3, CARP-2) or NF- $\kappa$ B transcription (ZFP36) revealed only a few unreported variants, apparently neutral.

**CONCLUSION:** Our study rules out any involvement in the pathogenesis of TRAPS of some of the genes known to regulate TNFR1 shedding and TNF-induced NF- $\kappa$ B signaling and transcription. Gene(s) responsible for TRAPS-like syndrome remain to be investigated among currently unidentified genes likely involved in these pathways, or by applying the genome-wide function-free sequencing approach.

DOI: 10.3899/jrheum.101260

PMID: 21459945 [Indexed for MEDLINE]

3042. Ugeskr Laeger. 2011 Mar 28;173(13):968-73.

[Hereditary periodical fever syndromes].

[Article in Danish]

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Autoinflammatory diseases are characterized by attacks of apparently unprovoked inflammation without significant levels of autoantibodies or antigen-specific T-cells. Within the past decade, a number of different genetic causes of fever

syndromes have been identified: familial Mediterranean fever (FMF), hyper IgD syndrome, cryopyrin-associated periodic syndromes and tumour necrosis factor receptor-associated periodic syndrome. The recent awareness and recognition of pathogenic mechanism of these diseases have led to new possibilities for medical treatment with targeted biological agents.

PMID: 21453638 [Indexed for MEDLINE]

3043. Joint Bone Spine. 2011 Dec;78(6):555-60. doi: 10.1016/j.jbspin.2011.02.010. Epub 2011 Mar 26.

Chronic recurrent multifocal osteomyelitis.

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Chronic recurrent multifocal osteomyelitis (CRMO), also known as chronic nonbacterial osteomyelitis, is an orphan disease that manifests as recurrent flares of inflammatory bone pain with or without a fever. The pain is related to one or more foci of nonbacterial osteomyelitis. To distinguish unifocal CRMO from a tumor or an infection, a bone biopsy is required in nearly all patients and a trial of antibiotic therapy in many. CRMO is now considered the pediatric equivalent of SAPHO syndrome, and recent data suggest that CRMO should be classified among the autoinflammatory diseases. The treatment of CRMO is not standardized. Although no randomized placebo-controlled trials are available, there is general agreement that nonsteroidal antiinflammatory drugs constitute the best first-line treatment and that bisphosphonates and biotherapies such as TNF $\alpha$  antagonists are effective in the most severe forms. Although CRMO is considered a benign disease, recent data suggest an up to 50% rate of residual impairments despite optimal management.

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3044. Clin Exp Immunol. 2011 Jun;164(3):365-72. doi: 10.1111/j.1365-2249.2011.04380.x.  
Epub 2011 Mar 25.

Expression of CD64 on polymorphonuclear neutrophils in patients with familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is an autoinflammatory disease characterized by recurrent episodes of fever and serosal or synovial inflammation. We examined the utility of CD64 (FcγRI) expression in polymorphonuclear neutrophils (PMNs) as clinical and biological parameters in patients with FMF. We studied 12 Japanese FMF patients (mean age;  $22.8 \pm 15.5$  years, male/female: 2/10), along with rheumatoid arthritis patients (RA,  $n = 38$  male/female: 6/32, mean age;  $52.2 \pm 15.3$  years), systemic lupus erythematosus (SLE,  $n = 15$  male/female: 0/15, mean age;  $38.5 \pm 15.9$  years) and 12 healthy subjects (male/female: 3/9, mean age;  $37.9 \pm 17.2$  years). CD64 expression on PMNs was determined using flow cytometry. The quantitative expression of CD64 in patients with FMF ( $2439.6 \pm 2215.8$  molecules per PMN) was significantly higher than in healthy subjects ( $547.8 \pm 229.5$ ,  $P = 0.003$ ) or in patients with RA ( $606.5 \pm 228.2$ ,  $P < 0.0001$ ) and SLE ( $681.3 \pm 281.1$ ,  $P = 0.004$ ). The increased CD64 expression on PMNs isolated from untreated FMF patients was down-regulated by colchicine treatment. NACHT-LRR-PYD-containing protein 3 (NLRP3) activation using MurNAc-L-Ala-D-isoGln (MDP) resulted in increased CD64 expression on PMNs from healthy subjects. Our results suggest that quantitative measurement of CD64 expression on PMNs can be a valuable tool to discriminate between FMF and autoimmune diseases.



DOI: 10.1111/j.1365-2249.2011.04380.x

PMCID: PMC3087932

PMID: 21438869 [Indexed for MEDLINE]

3045. Rheumatol Int. 2011 Oct;31(10):1275-81. doi: 10.1007/s00296-011-1845-7. Epub 2011 Mar 25.

Vascular comorbidities in familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is a common hereditary autoinflammatory disorder characterized by recurrent febrile attacks and polyserositis. The MEditerranean FeVer (MEFV) gene missense mutations altering the structure and function of pyrin protein play a significant role in the pathophysiology of the disease. Mutated pyrin is associated with the loss of delicate control of the inflammatory pathways, which results in a prolonged or augmented inflammation that predisposes these patients and carriers of the MEFV mutation to a pro-inflammatory state. This increased inflammation might lead to susceptibility to vascular comorbidities in FMF patients and even in carriers. In this review, we aim to discuss the vascular comorbidities seen in FMF patients. For this purpose, a thorough search was done in Web sites such as Pubmed, Web of Science, Scopus and Google Scholar, and the most relevant articles and case reports were evaluated. It seems that various vasculitides and the emerging problem of atherosclerosis have increasingly been recognized in these patients and, on the other hand, cardiac amyloidosis appears as a rare but devastating complication of FMF. Future studies will shed light on the unknown aspects of the emerging vascular problems in patients with FMF.

DOI: 10.1007/s00296-011-1845-7

PMID: 21437693 [Indexed for MEDLINE]

3046. Am J Pathol. 2011 Apr;178(4):1701-14. doi: 10.1016/j.ajpath.2010.12.053.

Spontaneous insertion of a b2 element in the ptpn6 gene drives a systemic autoinflammatory disease in mice resembling neutrophilic dermatosis in humans.

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We found a spontaneous autosomal mutation in a mouse leading to neutrophil infiltration with ulceration in the upper dermis of homozygous offspring. These animals had increased neutrophil numbers, associated with normal lymphocyte count, in peripheral blood and bone marrow, suggesting a myeloproliferative disorder; however, granulocyte precursor proliferation in bone marrow was actually reduced (because circulating neutrophils were less susceptible to apoptosis). Neutrophil infiltration of the skin and other organs and high serum levels of immunoglobulins and autoantibodies, cytokines, and acute-phase proteins were additional abnormalities, all of which could be reduced by high-dose corticosteroid treatment or neutrophil depletion by antibodies. Use of genome-wide screening localized the mutation within an 0.4-Mbp region on mouse chromosome 6. We identified insertion of a B2 element in exon 6 of the Ptpn6 gene (protein tyrosine phosphatase, non-receptor type 6; also known as Shp-1). This insertion involves amino acid substitutions that significantly reduced the enzyme activity in mice homozygous for the mutation. Disease onset was delayed, and the clinical phenotype was milder than the phenotypes of other Ptpn6-mutants described in motheaten (me, mev) mice; we designated this new genotype as Ptpn6(meB2/meB2) and the phenotype as meB2. This new phenotype encompasses an autoinflammatory disease showing similarities to many aspects of the so-called neutrophilic dermatoses, a heterogeneous group of skin diseases with unknown etiology in humans.

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DOI: 10.1016/j.ajpath.2010.12.053

PMCID: PMC3078426

PMID: 21435452 [Indexed for MEDLINE]

3047. Rheumatol Int. 2012 Apr;32(4):1095-7. doi: 10.1007/s00296-011-1855-5. Epub 2011 Mar 23.

Successful treatment with anti-tumor necrosis factor (anti-TNF)-alpha of proteinuria in a patient with familial mediterranean fever (FMF) resistant to colchicine: anti-TNF drugs and FMF.

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Familial mediterranean fever (FMF) is an autoinflammatory disease characterized by recurrent attacks of fever, peritonitis, pleuritis, and genetically by autosomal recessive inheritance. The major renal involvement in FMF is the occurrence of amyloidosis that can be prevented by a daily regimen of colchicine. About 5-10% of cases with familial mediterranean fever may be resistant to colchicine. In literature, there is a controversy about the treatment of FMF patients resistant to colchicine. We describe a case with FMF, proteinuria, and bilateral sacroiliitis, which responded to anti-TNF (tumor necrosis factor)-alpha therapy with infliximab and etanercept.

DOI: 10.1007/s00296-011-1855-5

PMID: 21431291 [Indexed for MEDLINE]

3048. Pediatr Res. 2011 Jul;70(1):78-82. doi: 10.1203/PDR.0b013e31821b581c.

The farnesyltransferase inhibitors tipifarnib and lonafarnib inhibit cytokines secretion in a cellular model of mevalonate kinase deficiency.

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The shortage of geranylgeranyl-pyrophosphate (GGPP) was associated to an increased IL-1 $\beta$  release in the autoinflammatory syndrome mevalonate kinase deficiency (MKD), a rare inherited disease that has no specific therapy.

Farnesyltransferase inhibitors (FTIs) act at the end of mevalonate pathway. Two FTIs, tipifarnib (Tip) and lonafarnib (Lon), were therefore evaluated as possible therapeutical choices for the treatment of MKD. FTIs could lead to a redirection of the limited available number of mevalonate intermediates preferentially to GGPP synthesis, eventually preventing the uncontrolled inflammatory response. The effect of Tip and Lon on intracellular cholesterol level (ICL) and on proinflammatory cytokines secretion was evaluated in a cellular model of MKD, chemically obtained treating RAW 264.7 cells with lovastatin (Lova) and alendronate (Ald). The combination of FTIs with the isoprenoid geraniol (GOH) was also tested both in this model and in monocytes isolated from MKD patients. Tip and Lon proved to revert the ICL lowering and to significantly reduce the lipopolysaccharide-induced cytokines secretion in Ald-Lova -RAW 264.7 cells. This anti-inflammatory effect was amplified combining the use of GOH with FTIs. The effect of GOH and Tip was successfully replicated in MKD patients' monocytes. Tip and Lon showed a dramatic anti-inflammatory effect in monocytes where mevalonate pathway was chemically or genetically impaired.

DOI: 10.1203/PDR.0b013e31821b581c

PMID: 21430599 [Indexed for MEDLINE]

3049. Biochem Soc Trans. 2011 Apr;39(2):669-73. doi: 10.1042/BST0390669.

Inflammasome activation: from inflammatory disease to infection.

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The recognition of pathogen-derived molecules by the innate immune system is mediated by a number of receptors, including members of the TLR (Toll-like receptor), RLH [RIG (retinoic acid-inducible gene)-like helicase] and the NLR (NOD-like receptor) families. NLRs in particular are also involved in the recognition of host-derived 'danger'-associated molecules which are produced under conditions of cellular stress or injury. Activation of these receptors leads to the assembly of high-molecular-mass complexes called inflammasomes which in turn leads to the generation of active caspase 1 and to the production of

mature IL-1 $\beta$  (interleukin 1 $\beta$ ). The discovery that NLRP3 (NLR-related protein 3) can recognize host-derived particulate matter such as uric acid and cholesterol crystals has led to this inflammasome being implicated in a number of inflammatory diseases, including gout, atherosclerosis and Type 2 diabetes. In addition, aberrant NLRP3 activation has also been observed in a number of heritable disorders now referred to as cryopyrinopathies. On the other hand, a number of studies have reported that recognition of both viral and bacterial products by NLRs is required for effective pathogen clearance. The present review discusses both aspects of NLR activation and will highlight the role of additional inflammasome complexes in sensing infection.

DOI: 10.1042/BST0390669

PMID: 21428959 [Indexed for MEDLINE]

3050. Turk J Pediatr. 2010 Nov-Dec;52(6):588-93.

Neuroendocrine immune system in familial Mediterranean fever.

Topaloğlu R(1), Bilginer Y, Alikışifoğlu A, Ozaltın F, Beşbaş N, Ozen S, Bakkaloğlu A.

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Familial Mediterranean fever (FMF) is an autoinflammatory disorder and is characterized by self-limited attacks of inflammation. Although mutations in the gene coding for pyrin are responsible for the inflammation seen in attacks, the question of whether the failure to mount an appropriate cortisol response to inflammation has any additive effects allowed us to plan this study. The aim was to determine the interactions between the neuroendocrine and immune system in patients with FMF and investigate the role of the neuroendocrine system in the acute inflammation process. Demographic characteristics, disease activity, mutation analysis, and duration of the disease were defined in 15 FMF patients (7 female, 8 male; mean age  $\pm$  SD: 9.1  $\pm$  4.2 years). The diagnosis was based on Tel-Hashomer criteria. Ten healthy volunteers and 21 active juvenile idiopathic arthritis (JIA) patients formed the control groups. Furthermore, 10 of these 15 patients with FMF were also studied during the attack-free period. Erythrocyte

sedimentation rate (ESR) C-reactive protein (CRP), fibrinogen, adrenocorticotrophic hormone (ACTH), cortisol, insulin-like growth factor-1 (IGF)-1, IGF binding protein (BP)-3, urinary cortisol levels, interleukin (IL)-1beta, IL-6, and tumor necrosis factor (TNF)-a were evaluated in FMF patients with attack and during the attack-free period. Although the median levels of ACTH (12.7 pg/ml) and cortisol (12 ug/dl) at 08:00 a.m. were lower in FMF patients during attack than in the attack-free period, these differences did not reach statistical significance. On the other hand, the median levels of ACTH were significantly lower during attack than in the healthy control group ( $p < 0.05$ ). Median levels of IGF-1 (118.5 ng/ml) were significantly lower during FMF attack than in the attack-free period ( $p < 0.05$ ). There was a negative correlation between IGF-1 and CRP ( $r = -0.47$ ). The median level of IL-6 was 18.1 pg/dl during FMF attack and was significantly higher than in the attack-free period and in the healthy control group ( $p < 0.05$ ). There was a negative correlation between cortisol level at 08:00 am and IL-6 ( $r = -0.45$ ). When we compared JIA with FMF patients during attack, inappropriately low secretion of adrenal cortisol and ACTH and low urine cortisol levels were more pronounced in JIA than FMF. Although it is more prominent in chronic inflammation, the neuroendocrine immune system seems to be impaired in relation to acute inflammation in FMF.

PMID: 21428190 [Indexed for MEDLINE]

3051. *Pediatr Dev Pathol*. 2011 Jul-Aug;14(4):301-6. doi: 10.2350/11-02-0985-OA.1. Epub 2011 Mar 22.

Perinatal onset mevalonate kinase deficiency.

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Defects in mevalonate kinase, a critical rate-limiting enzyme in cholesterol and isoprene metabolism, have been associated with 2 clinical phenotypes: mevalonic

aciduria, which presents in infancy or early childhood with growth failure, dysmorphic features, and neurologic disease; and hyperimmunoglobulinemia D and periodic fever syndrome, which usually presents outside the neonatal period as an autoinflammatory periodic fever syndrome. This report describes a kindred with 2 siblings affected by severe mevalonate kinase deficiency (mevalonic aciduria) with perinatal onset. Dysmorphic and central nervous system abnormalities, anemia, and cholestasis were prominent features in 1 sibling. Both cases were fatal, 1 in the immediate neonatal period and 1 in utero. The small number of cases of mevalonate kinase deficiency presenting in the perinatal period have typically been severely affected, with signs and symptoms of a severe multisystem disorder. Predominant features of perinatal onset mevalonate kinase deficiency include intrauterine growth restriction, cerebral ventriculomegaly, dysmorphic features, skeletal abnormalities, dyserythropoietic anemia with extramedullary erythropoiesis, thrombocytopenia, cholestatic liver disease, persistent diarrhea, renal failure, recurrent sepsis-like episodes, and failure to thrive. Clinical findings may mimic severe intrauterine viral infection, a chromosomal abnormality, or an acute sepsis syndrome, potentially contributing to delays in diagnosis of this rare condition. Perinatal onset mevalonate kinase deficiency is associated with a very poor prognosis, with death in utero or in early infancy. Detailed autopsy findings in mevalonate kinase deficiency have rarely been reported.

DOI: 10.2350/11-02-0985-OA.1

PMID: 21425920 [Indexed for MEDLINE]

3052. Cell Immunol. 2011;268(2):55-9. doi: 10.1016/j.cellimm.2011.02.007. Epub 2011 Mar 1.

Differential cytokine secretion results from p65 and c-Rel NF- $\kappa$ B subunit signaling in peripheral blood mononuclear cells of TNF receptor-associated periodic syndrome patients.

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Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is an autosomal dominant autoinflammatory condition caused by mutations in the TNFRSF1A gene which encodes the tumor necrosis factor (TNF) receptor, TNFR1. We investigated the effect of three high penetrance and three low penetrance TNFRSF1A mutations upon NF- $\kappa$ B transcription factor family subunit activity, and the resulting impact upon secretion of 25 different cytokines. Whilst certain mutations resulted in elevated NF- $\kappa$ B p65 subunit activity, others instead resulted in elevated c-Rel subunit activity. Interestingly, high p65 activity was associated with elevated IL-8 secretion, whereas high c-Rel activity increased IL-1 $\beta$  and IL-12 secretion. In conclusion, while all six TNFRSF1A mutations showed enhanced NF- $\kappa$ B activity, different mutations stimulated distinct NF- $\kappa$ B family subunit activities, and this in turn resulted in the generation of unique cytokine secretory profiles.

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DOI: 10.1016/j.cellimm.2011.02.007

PMID: 21420073 [Indexed for MEDLINE]

3053. Rheumatol Int. 2012 Jun;32(6):1675-8. doi: 10.1007/s00296-011-1853-7. Epub 2011 Mar 18.

Coexistence of Takayasu's arteritis with familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is the most common autoinflammatory disease characterized by recurrent self-limited attacks of fever, accompanied with peritonitis, pleuritis or arthritis. It is well known that FMF may coexist with vasculitic pathologies, especially with those involving small and medium vessels. Among the vasculitic pathologies reported to be associated with FMF, Henoch-Schönlein purpura and polyarteritis nodosa come the first, possibly followed up by protracted febrile myalgia. However, coexistence of FMF with any



large vessel vasculitis has not been reported to date. Here, we present a case with FMF who later developed Takayasu arteritis, with a severe disease course, being resistant to corticosteroids and conventional immunosuppressive agents, and requiring infliximab treatment.

DOI: 10.1007/s00296-011-1853-7

PMID: 21416236 [Indexed for MEDLINE]

3054. Genet Test Mol Biomarkers. 2011 Jul-Aug;15(7-8):475-82. doi: 10.1089/gtmb.2010.0146. Epub 2011 Mar 17.

Comprehensive analysis of a large-scale screen for MEFV gene mutations: do they truly provide a "heterozygote advantage" in Turkey?

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Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disorder characterized by episodes of inflammation in the absence of high-titer autoantibodies or antigen-specific T cells. The Mediterranean fever (MEFV) gene located on chromosome 16p13.3, which encodes the 781-amino-acid protein pyrin, is the causative gene for this monogenic Mendelian disease. This study presents the molecular analysis of an MEFV gene mutation screen of 5518 Turkish individuals with clinical diagnoses of FMF. Patients were genetically diagnosed using the FMF StripAssay and DNA sequencing analysis. Contrary to the results achieved by the FMF StripAssay, DNA sequencing analysis identified large-scale coding and noncoding novel sequence variants, together with a significant group (76%) of individuals who were receiving colchicine and had a single heterozygous mutation, despite the recessive inheritance of FMF. In conclusion, sequence analysis, unlike other routine laboratory techniques, may enable screening for a broad range of nucleotide variations and may prevent less common, population-restricted, novel sequence variants from being overlooked.

DOI: 10.1089/gtmb.2010.0146

PMID: 21413889 [Indexed for MEDLINE]

3055. *Dermatol Ther.* 2011 Mar-Apr;24(2):187-95. doi: 10.1111/j.1529-8019.2011.01394.x.

An approach to the hospitalized patient with urticaria and fever.

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Urticaria is a common skin disorder with a long differential diagnosis. Most cases are readily treated symptomatically and have no systemic implications. However, a number of diseases and syndromes, including vasculitides, immunologic disorders, infectious diseases, hematologic diseases, and autoinflammatory syndromes, can present with urticaria and systemic symptoms, which may lead to hospitalization of the patient. These urticarial syndromes are important to recognize as they often have significant health implications. A comprehensive history and physical exam is important in distinguishing cases of simple urticaria from these syndromes. The presence of atypical wheals, systemic symptoms such as fever or arthralgia, and a lack of response to antihistamine therapy are important diagnostic clues that should prompt further workup.

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DOI: 10.1111/j.1529-8019.2011.01394.x

PMID: 21410608 [Indexed for MEDLINE]

3056. *Am J Pathol.* 2011 Apr;178(4):1434-41. doi: 10.1016/j.ajpath.2010.12.035. Epub 2011 Mar 4.

Alteration in the gene encoding protein tyrosine phosphatase nonreceptor type 6 (PTPN6/SHP1) may contribute to neutrophilic dermatoses.

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We have found a B2 repeat insertion in the gene encoding protein tyrosine phosphatase nonreceptor type 6 (PTPN6) in a mouse that developed a skin disorder with clinical and histopathological features resembling those seen in human neutrophilic dermatoses. Neutrophilic dermatoses are a group of complex heterogeneous autoinflammatory diseases that all demonstrate excessive neutrophil infiltration of the skin. Therefore, we tested the cDNA and genomic DNA sequences of PTPN6 from patients with Sweet's syndrome (SW) and pyoderma gangrenosum and found numerous novel splice variants in different combinations. Isoforms resulting from deletions of exons 2, 5, 11, and 15 and retention of intron 1 or 5 were the most common in a patients with a familial case of SW, who had a neonatal onset of an inflammatory disorder with skin lesions and a biopsy specimen consistent with SW. These isoforms were associated with a heterozygous E441G mutation and a heterozygous 1.7-kbp deletion in the promoter region of the PTPN6 gene. Although full-length PTPN6 was detected in all other patients with either pyoderma gangrenosum or SW, it was always associated with splice variants: a partial deletion of exon 4 with the complete deletion of exon 5, alterations that were not detected in healthy controls. The defect in transcriptional regulation of the hematopoietic PTPN6 appears to be involved in the pathogenesis of certain subsets of the heterogeneous group of neutrophilic dermatoses.

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DOI: 10.1016/j.ajpath.2010.12.035

PMCID: PMC3078441

PMID: 21406173 [Indexed for MEDLINE]

3057. Clin Lab Sci. 2011 Winter;24(1):2-7.

Chronic familial Mediterranean fever with development of secondary amyloidosis.

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A 20-year-old Turkish male presented with fever, abdominal pain, and systemic lethargy. His clinical history revealed symptoms to be self-limiting but reoccurring over the past six months. Blood and urine specimens collected indicated renal amyloidosis. A kidney CT image indicated kidney inflammation. He was diagnosed with Familial Mediterranean Fever with the development of secondary amyloidosis and treated with colchicine.

PMID: 21404957 [Indexed for MEDLINE]

3058. ScientificWorldJournal. 2011 Mar 7;11:641-50. doi: 10.1100/tsw.2011.64.

Recent insights into the pathogenesis of type AA amyloidosis.

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The amyloidoses are a group of life-threatening diseases in which fibrils made of misfolded proteins are deposited in organs and tissues. The fibrils are stable, insoluble aggregates of precursor proteins that have adopted an antiparallel beta-sheet structure. In type AA, or reactive, amyloidosis, the precursor protein of the fibrils is serum amyloid A (SAA). SAA is a 104-amino-acid protein that is produced in the liver in response to proinflammatory cytokines. Although the protein that is produced by the liver contains 104 amino acids, only the N-terminal 66-76 amino acids are found in amyloid fibrils. Furthermore, SAA has been shown to have an alpha-helical structure primarily. Thus, for SAA to be incorporated into an amyloid fibril, two processes have to occur: C-terminal cleavage and conversion into a beta-sheet. Only a minority of patients with elevated SAA levels develop amyloidosis. Factors that contribute to the risk of amyloidosis include the duration and degree of SAA elevation, polymorphisms in SAA, and the type of autoinflammatory syndrome. In the Hyper-IgD syndrome, amyloidosis is less prevalent than in the other autoinflammatory diseases. In

vitro work has shown that the isoprenoid pathway influences amyloidogenesis by farnesylated proteins. Although many proteins contain domains that have a potential for self-aggregation, amyloidosis is only a very rare event. Heat shock proteins (HSPs) are chaperones that assist other proteins to attain, maintain, and regain a functional conformation. In this review, recent insights into the pathogenesis of amyloidosis are discussed, in addition to a new hypothesis for a role of HSPs in the pathogenesis of type AA.

DOI: 10.1100/tsw.2011.64

PMCID: PMC5720109

PMID: 21403980 [Indexed for MEDLINE]

3059. J Vis Exp. 2011 Mar 1;(49). pii: 2662. doi: 10.3791/2662.

Accurate and simple measurement of the pro-inflammatory cytokine IL-1 $\beta$  using a whole blood stimulation assay.

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Inflammatory processes resulting from the secretion of soluble mediators by immune cells, lead to various manifestations in skin, joints and other tissues as well as altered cytokine homeostasis. The innate immune system plays a crucial role in recognizing pathogens and other endogenous danger stimuli. One of the major cytokines released by innate immune cells is Interleukin (IL)-1. Therefore, we utilize a whole blood stimulation assay in order to measure the secretion of inflammatory cytokines and specifically of the pro-inflammatory cytokine IL-1 $\beta$ (1, 2, 3). Patients with genetic dysfunctions of the innate immune system causing autoinflammatory syndromes show an exaggerated release of mature IL-1 $\beta$  upon stimulation with LPS alone. In order to evaluate the innate immune component of patients who present with inflammatory-associated pathologies, we use a specific immunoassay to detect cellular immune responses to pathogen-associated molecular patterns (PAMPs), such as the gram-negative bacterial endotoxin, lipopolysaccharide (LPS). These PAMPs are recognized by pathogen recognition receptors (PRRs), which are found on the cells of the innate immune system (4, 5,

6, 7). A primary signal, LPS, in conjunction with a secondary signal, ATP, is necessary for the activation of the inflammasome, a multiprotein complex that processes pro-IL-1 $\beta$  to its mature, bioactive form (4, 5, 6, 8, 9, 10). The whole blood assay requires minimal sample manipulation to assess cytokine production when compared to other methods that require labor intensive isolation and culturing of specific cell populations. This method differs from other whole blood stimulation assays; rather than diluting samples with a ratio of RPMI media, we perform a white blood cell count directly from diluted whole blood and therefore, stimulate a known number of white blood cells in culture (2). The results of this particular whole blood assay demonstrate a novel technique useful in elucidating patient cohorts presenting with autoinflammatory pathophysiologies.

DOI: 10.3791/2662

PMCID: PMC3197325

PMID: 21403634 [Indexed for MEDLINE]

3060. Mod Rheumatol. 2011 Dec;21(6):641-5. doi: 10.1007/s10165-011-0442-7. Epub 2011 Mar 12.

Patient with neonatal-onset chronic hepatitis presenting with mevalonate kinase deficiency with a novel MVK gene mutation.

Tahara M(1), Sakai H, Nishikomori R, Yasumi T, Heike T, Nagata I, Inui A, Fujisawa T, Shigematsu Y, Nishijima K, Kuwakado K, Watabe S, Kameyama J.

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A Japanese girl with neonatal-onset chronic hepatitis and systemic inflammation was diagnosed with hyper-immunoglobulinemia D and periodic fever syndrome (HIDS). However, she lacked the typical HIDS features until the age of 32 months. She had compound heterozygous MVK mutations, H380R and A262P, the latter of which was novel. These findings suggest that HIDS patients could lack typical episodes of recurrent fever at the onset and that HIDS should be considered as a possible cause of neonatal-onset chronic hepatitis.

DOI: 10.1007/s10165-011-0442-7

PMID: 21399979 [Indexed for MEDLINE]

3061. Vestn Ross Akad Med Nauk. 2011;(1):42-50.

[Signal receptors of congenital immunity: a new molecular target for diagnostics and treatment of inflammatory diseases].

[Article in Russian]

Kozlov IG.

The discovery of signal receptors of congenital immunity (signal PRR) not only provided a novel view of basic aspects of pathogenesis of chronic inflammatory diseases but also created a basis for the development of additional diagnostic criteria for these pathologies and new pharmaceuticals for their treatment. Reduced expression and function of PRR due to mutations/polymorphisms or epigenetic disturbances of regulation can be regarded as immunodeficient conditions manifest as severe infectious inflammatory diseases. In contrast, excessive expression and activation of PRR as a rule leads to chronic autoinflammatory, autoimmune, and atopic diseases involving adaptive immunity and aggression against own tissues and cells. Assessment of certain mutations in PRR genes, their expression and activation provides a powerful tool for in-depth diagnostics of inflammatory diseases. Simultaneously, new lines of immunostimulating and anti-inflammatory therapy are developed based on the knowledge of molecular physiology of PRR with the use of synthetic agonists and antagonists of signal PRR.

PMID: 21395096 [Indexed for MEDLINE]

3062. Ann Rheum Dis. 2011 Sep;70(9):1692-3. doi: 10.1136/ard.2010.144279. Epub 2011 Mar 6.

Failure of sustained response to etanercept and refractoriness to anakinra in patients with T50M TNF-receptor-associated periodic syndrome.

Quillinan N, Mannion G, Mohammad A, Coughlan R, Dickie LJ, McDermott MF, McGonagle D.

DOI: 10.1136/ard.2010.144279

PMID: 21378401 [Indexed for MEDLINE]

3063. Nihon Rinsho Meneki Gakkai Kaishi. 2011;34(1):20-8.

[Inflammasomes and related diseases].

[Article in Japanese]

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Although inflammation is important for host defense, excessive inflammation sometimes causes serious consequences. IL-1 $\beta$  is one of major proinflammatory cytokines. Dysregulation of IL-1 $\beta$  promotes development of several diseases. Mature IL-1 $\beta$  is produced by cleavage of its proform by a protein complex named inflammasome. Inflammasome consists of NOD-LRRs containing family (NLR proteins), an adaptor protein, and a cysteine protease caspase-1. Several NLRs can be assembled into inflammasome in response to various stimulatory signals. Genetic disorder of inflammasome-IL-1 system cause autoinflammatory diseases such as cryopyrin-associated autoinflammatory disease, familial Mediterranean fever, deficiency of IL-1 receptor antagonist, and PAPA syndrome. This article reviews recent advances in the study of inflammasome and related diseases.

PMID: 21372510 [Indexed for MEDLINE]

3064. Arthritis Rheum. 2011 Mar;63(3):840-9. doi: 10.1002/art.30149.

Efficacy and safety of anakinra therapy in pediatric and adult patients with the autoinflammatory Muckle-Wells syndrome.



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**OBJECTIVE:** Muckle-Wells syndrome (MWS) is an inherited autoinflammatory disease caused by mutations in the NLRP3 gene that result in excessive interleukin-1 (IL-1) release. It is characterized by severe fevers, rashes, arthralgia, and conjunctivitis, leading to sensorineural deafness and amyloidosis. The recombinant IL-1 receptor antagonist anakinra blocks the biologic activity of IL-1. The aim of this study was to determine the short- and long-term efficacy and safety of anakinra therapy in children and adults with severe MWS.

**METHODS:** A single-center observational study was performed. Standardized assessments included clinical features, the Disease Activity Score (DAS) for MWS, classic and novel markers of inflammation, and patient-derived measures of health status. The primary outcome was a score of <10 on the DAS for MWS at 2 weeks and at the last followup visit. Measures of MWS disease activity were investigated using descriptive statistics and paired comparative analysis.

**RESULTS:** A total of 12 patients with severe MWS (5 children and 7 adults) received anakinra for a median of 11 months (range 5-14 months). The median followup was 11 months (range 5-14 months). Disease activity was significantly lower in all patients at 2 weeks ( $P = 0.0005$ ). Organ manifestations of MWS improved, as did all patient-derived measures of health status, markers of inflammation, and hearing loss in 2 of the patients. Levels of the novel neutrophil activation biomarker S100A12 followed clinical disease activity. Treatment was well tolerated, and no serious adverse events were observed.

**CONCLUSION:** Anakinra was found to be a safe and effective treatment of severe MWS, leading to a significant improvement in disease activity at 2 weeks as well as long-term. Anakinra therapy should therefore be considered in children and adults with severe MWS disease requiring IL-1 blockade.

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DOI: 10.1002/art.30149

PMID: 21360513 [Indexed for MEDLINE]

3065. Arthritis Rheum. 2011 Mar;63(3):830-9. doi: 10.1002/art.30170.

Clinical presentation and pathogenesis of cold-induced autoinflammatory disease in a family with recurrence of an NLRP12 mutation.

Borghini S(1), Tassi S, Chiesa S, Caroli F, Carta S, Caorsi R, Fiore M, Delfino L, Lasigliè D, Ferraris C, Traggiai E, Di Duca M, Santamaria G, D'Ossualdo A, Tosca M, Martini A, Ceccherini I, Rubartelli A, Gattorno M.

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**OBJECTIVE:** NLRP12 mutations have been described in patients affected with peculiar autoinflammatory symptoms. This study was undertaken to characterize NLRP12 mutations in patients with autoinflammatory syndromes, particularly a novel missense mutation, p.D294E, affecting a protein sequence crucial for ATP binding, which was identified in a Caucasian family with familial cold-induced autoinflammatory syndrome in some family members.

**METHODS:** Fifty patients were tested for NLRP12 mutations. A Caucasian family with the p.D294E missense mutation of NLRP12 in some family members was clinically characterized. In vitro analysis of the effects of the mutation on NF- $\kappa$ B activity was performed in HEK 293 cells after cotransfection of the cells with a luciferase NF- $\kappa$ B-responsive element and mutant or wild-type (WT) NLRP12 expression plasmids. NF- $\kappa$ B activity was also evaluated 24 hours after stimulation with tumor necrosis factor  $\alpha$  in monocytes from individual family members carrying the mutation. Furthermore, secretion of interleukin-1 $\beta$  (IL-1 $\beta$ ), production of reactive oxygen species (ROS), and activation of antioxidant systems in patient and healthy donor monocytes, under resting conditions and after stimulation with pathogen-associated molecular patterns (PAMPs), were also assessed.

**RESULTS:** In the family assessed, the p.D294E mutation segregated in association with a particular sensitivity to cold exposure (especially arthralgias and myalgia), but not always with an inflammatory phenotype (e.g., urticarial rash or fever). In vitro, the mutant protein maintained the same inhibitory activity as that shown by WT NLRP12. Consistently, NLRP12-mutated monocytes showed neither increased levels of p65-induced NF- $\kappa$ B activity nor higher secretion of IL-1 $\beta$ . However, the kinetics of PAMP-induced IL-1 $\beta$  secretion were significantly accelerated, and high production of ROS and up-regulation of antioxidant systems were demonstrated.

**CONCLUSION:** Even with a variable range of associated manifestations, the extreme

sensitivity to cold represents the main clinical hallmark in an individual carrying the p.D294E mutation of the NLRP12 gene. Although regulation of NF- $\kappa$ B activity is not affected in patients, redox alterations and accelerated secretion of IL-1 $\beta$  are associated with this mild autoinflammatory phenotype.

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DOI: 10.1002/art.30170

PMCID: PMC3112487

PMID: 21360512 [Indexed for MEDLINE]

3066. *Pediatr Nephrol.* 2011 Aug;26(8):1215-27. doi: 10.1007/s00467-011-1797-x. Epub 2011 Mar 1.

Renal amyloidosis in children.

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Renal amyloidosis is a detrimental disease caused by the deposition of amyloid fibrils. A child with renal amyloidosis may present with proteinuria or nephrotic syndrome. Chronic renal failure may follow. Amyloid fibrils may deposit in other organs as well. The diagnosis is through the typical appearance on histopathology. Although chronic infections and chronic inflammatory diseases used to be the causes of secondary amyloidosis in children, the most frequent cause is now autoinflammatory diseases. Among this group of diseases, the most frequent one throughout the world is familial Mediterranean fever (FMF). FMF is typically characterized by attacks of clinical inflammation in the form of fever and serositis and high acute-phase reactants. Persisting inflammation in inadequately treated disease is associated with the development of secondary amyloidosis. The main treatment is colchicine. A number of other monogenic autoinflammatory diseases have also been identified. Among them cryopyrin-associated periodic syndrome (CAPS) is outstanding with its clinical features and the predilection to develop secondary amyloidosis in untreated cases. The treatment of secondary amyloidosis mainly depends on the treatment of

the disease. However, a number of new treatments for amyloid per se are in the pipeline.

DOI: 10.1007/s00467-011-1797-x

PMCID: PMC3119800

PMID: 21360109 [Indexed for MEDLINE]

3067. Clin Rheumatol. 2011 Jul;30(7):987-91. doi: 10.1007/s10067-011-1718-1. Epub 2011 Mar 2.

Familial Mediterranean fever: an association with non-alcoholic fatty liver disease.

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The purpose of this study is to characterize the chronic liver disease (CLD) that may be associated with familial Mediterranean fever (FMF). Twenty-seven patients (mean age,  $48 \pm 18$  years; F/M, 16:11) with FMF who were referred for assessment of CLD were studied. Data regarding FMF and CLD were obtained from patient medical files. Liver biopsy was performed in 21 of 27 patients and deferred in six (cirrhotic coagulopathy in five and one who improved after colchicine dose reduction). Patients with FMF and non-alcoholic fatty liver disease (NAFLD) were compared to matched controls from a cohort of 150 patients with NAFLD per liver biopsy but without FMF. The mean Tel Hashomer severity score was  $1.7 \pm 0.9$ . The mean daily dose of colchicine was  $1.4 \pm 0.4$  mg over a mean duration of  $21 \text{ years} \pm 10$ . Seven of ten patients who underwent mutation analysis for FMF were homozygous for M694V. In 15 patients, there was evidence of NAFLD: five with "simple" steatosis, three with non-alcoholic steatohepatitis (NASH), and seven with NASH-cirrhosis. An additional five patients had "cryptogenic" cirrhosis, which in most patients represents the end result of unrecognized NASH, and one had normal liver tissue. Comparing FMF patients with NAFLD to matched controls with NAFLD did not reveal excess of metabolic syndrome in FMF patients. Of our FMF patients, 74% had evidence of NAFLD, 75% of which with severe manifestation. The extremely high proportion of NAFLD in our cohort of FMF patients without overt metabolic syndrome may indicate an unappreciated novel association between

FMF and NAFLD.

DOI: 10.1007/s10067-011-1718-1

PMID: 21360101 [Indexed for MEDLINE]

3068. Eur J Pediatr. 2011 Apr;170(4):445-52. doi: 10.1007/s00431-011-1411-z. Epub 2011 Mar 1.

The Eurofever Project: towards better care for autoinflammatory diseases.

Ozen S(1), Frenkel J, Ruperto N, Gattorno M; Eurofever Project.

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Autoinflammatory diseases are a group of diseases characterized by inflammatory attacks. The monogenic forms of these diseases are also classified as the hereditary periodic fever syndromes. All are characterized by attacks of fever along with certain clinical features and high acute phase reactants. Most of these monogenic diseases are associated with hereditary disorders of the interleukin-1 pathway. The most common autoinflammatory disease is familial Mediterranean fever. The other rather common monogenic diseases are the tumor necrosis factor receptor-associated periodic syndrome, hyperimmunoglobulinemia D with periodic fever syndrome, and cryopyrin-associated periodic fever syndromes (CAPS). However, a number of multifactorial diseases such as Behçet disease are now also categorized under the topic of autoinflammatory diseases. The main features and management of these diseases will be reviewed. Finally, we introduce the "Eurofever" project, aimed to increase awareness and education for the aforementioned diseases. We conclude that the pediatrician should be aware of the features and management of autoinflammatory diseases since all present with fever-the most common symptom of pediatric practice.

DOI: 10.1007/s00431-011-1411-z

PMID: 21360011 [Indexed for MEDLINE]

3069. Cell Mol Immunol. 2011 May;8(3):189-92. doi: 10.1038/cmi.2010.70. Epub 2011 Feb

28.

Explosion of autoimmune diseases and the mosaic of old and novel factors.

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In recent decades, an enormous effort has been made to elucidate the pathogenesis of autoimmune and autoinflammatory diseases. Autoimmunity is a multifactorial process in which genetic, immunological, environmental and hormonal factors play in concert, together representing what was termed years ago the 'mosaic of autoimmunity'. To date, more than 80 systemic and organ-specific autoimmune diseases have been defined, and their cumulative burden is substantial, both medically and financially. Furthermore, the burden of autoimmune and autoinflammatory diseases is rising, making these diseases a ubiquitous global phenomenon that is predicted to further increase in the coming decades. In this issue of the journal, additional aspects of autoimmunity are detailed. Immune dysregulation and loss of self-tolerance are the cornerstones of autoimmunity.

DOI: 10.1038/cmi.2010.70

PMCID: PMC4012881

PMID: 21358666 [Indexed for MEDLINE]

3070. Genet Med. 2011 Jun;13(6):487-98. doi: 10.1097/GIM.0b013e3182060456.

Familial Mediterranean fever--a review.

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Familial Mediterranean fever is inherited in an autosomal recessive manner. There are two phenotypes: types 1 and 2. Familial Mediterranean fever type 1 is

characterized by recurrent short episodes of inflammation and serositis, including fever, peritonitis, synovitis, pleuritis, and, rarely, pericarditis. The symptoms and severity vary among affected individuals, sometimes even among members of the same family. Amyloidosis, which can lead to renal failure, is the most severe complication. Familial Mediterranean fever type 2 is characterized by amyloidosis as the first clinical manifestation of familial Mediterranean fever in an otherwise asymptomatic individual. Routine treatment of end-stage renal disease, including renal transplantation, is advised. Lifelong treatment with colchicine is required for homozygotes for the p.Met694Val mutation or compound heterozygotes for p.Met694Val and another disease-causing allele; this prevents the inflammatory attacks and the deposition of amyloid. Individuals who do not have the p.Met694Val mutation and who are only mildly affected should be either treated with colchicine or monitored every 6 months for the presence of proteinuria. Molecular genetic testing of the MEFV gene, the only gene currently known to be associated with familial Mediterranean fever, can be offered to family members, especially when the p.Met694Val allele is present, because renal amyloidosis can be prevented by colchicine.

DOI: 10.1097/GIM.0b013e3182060456

PMID: 21358337 [Indexed for MEDLINE]

3071. Curr Opin Immunol. 2011 Jun;23(3):345-52. doi: 10.1016/j.coi.2011.01.006. Epub 2011 Feb 24.

The function and regulation of immunoglobulin D.

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Recent discoveries of IgD in ancient vertebrates suggest that IgD has been preserved in evolution from fish to human for important immunological functions. A non-canonical form of class switching from IgM to IgD occurs in the human upper respiratory mucosa to generate IgD-secreting B cells that bind respiratory bacteria and their products. In addition to enhancing mucosal immunity, IgD class-switched B cells enter the circulation to 'arm' basophils and other innate

immune cells with secreted IgD. Although the nature of the IgD receptor remains elusive, cross-linking of IgD on basophils stimulates release of immunoactivating, proinflammatory and antimicrobial mediators. This pathway is dysregulated in autoinflammatory disorders such as hyper-IgD syndrome, indicating that IgD orchestrates an ancestral surveillance system at the interface between immunity and inflammation.

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DOI: 10.1016/j.coi.2011.01.006

PMCID: PMC3109135

PMID: 21353515 [Indexed for MEDLINE]

3072. J Dermatol. 2011 May;38(5):513-5. doi: 10.1111/j.1346-8138.2010.01003.x. Epub 2010 Nov 3.

Erysipelas-like erythema with familial Mediterranean fever.

Aydin F, Ozcelik C, Akpolat I, Turanli AY, Akpolat T.

DOI: 10.1111/j.1346-8138.2010.01003.x

PMID: 21352275 [Indexed for MEDLINE]

3073. Middle East J Dig Dis. 2011 Mar;3(1):50-5.

Adult-onset familial mediterranean Fever in northwestern iran; clinical feature and treatment outcome.

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**BACKGROUND** Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by sporadic, paroxysmal attacks of fever and serosal inflammation. Although the disease usually begins before the age of 20 years, we aimed to evaluate the demography, clinical features and treatment outcome of familial Mediterranean fever in Iranian adult patients above 20 years old. **METHODS** In this cross-sectional study, adult patients (first attack at the age of >20 years) with a diagnosis of FMF who referred to the gastroenterology and rheumatology Clinics of Ardebil University of Medical Science (situated in north west of Iran) over the period of 2004-2009 were enrolled. FMF diagnosis was based on clinical criteria. **RESULTS** Forty four FMF patients (30 male and 14 female) with the mean [ $\pm$  Standard Deviation (SD)] age of first attack of  $29 \pm 7.8$  years were enrolled. Abdominal pain (95.5%) and fever (91%) were the most common clinical findings. All of the patients had satisfactorily responded to therapy. Response was complete in 76.7% and partial in 23.3% of the patients. There was no clinical or laboratory evidence of amyloidosis at the time of diagnosis or during follow-up. **CONCLUSION** Our findings demonstrated that adult-onset FMF in Iran has different characteristics (more common in males, lesser prevalence of arthritis and erysipelas-like erythema, less delay in diagnosis) and treatment outcome (favorable response even to low-dose colchicine) in comparison with the previous data on early onset patients.

PMCID: PMC4154930

PMID: 25197532

3074. Gac Med Mex. 2010 Sep-Oct;146(5):346-7.

[Twenty seven year old male with abdominal pain, "acute abdomen" and negative

laparotomy].

[Article in Spanish]

Halabe-Cherem J(1), Shuchleib-Cung A, Portilla-Demichelis A, Cherem-Arana S, Garciadiego-Fossas P.

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PMID: 21348292 [Indexed for MEDLINE]

3075. Ann Rheum Dis. 2011 Jul;70(7):1347-8. doi: 10.1136/ard.2010.146878. Epub 2011 Feb 22.

The efficacy of canakinumab in the treatment of a patient with familial Mediterranean fever and longstanding destructive arthritis.

Mitroulis I, Skendros P, Oikonomou A, Tzioufas AG, Ritis K.

DOI: 10.1136/ard.2010.146878

PMID: 21345814 [Indexed for MEDLINE]

3076. Arch Dermatol Res. 2011 Aug;303(6):375-80. doi: 10.1007/s00403-011-1134-z. Epub 2011 Feb 22.

Monogenic autoinflammatory syndromes at a dermatological level.

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Autoinflammatory syndromes include an expanding list of diseases characterized by

unprovoked recurrent attacks of systemic inflammation with lack of autoantibodies or autoreactive T-cells. This group of conditions encompasses monogenic diseases with Mendelian inheritance which are caused by specific mutations of different genes regulating the innate immunity: familial Mediterranean fever, mevalonate kinase deficiency syndrome, tumor necrosis factor receptor-associated periodic syndrome, cryopyrin-associated periodic syndromes, pyogenic disorders and deficiency of interleukin-1 receptor antagonist: all these diseases can present with dermatological manifestations, which often represent the prominent clinical features or, in some cases, the presenting sign. The purpose of this review is to increase the recognition among clinicians and mostly dermatologists of the monogenic autoinflammatory syndromes, highlighting the cutaneous signs of these conditions, in consideration of the possibility to prevent irreversible damages when their diagnosis and treatment are precociously established.

DOI: 10.1007/s00403-011-1134-z

PMID: 21340744 [Indexed for MEDLINE]

3077. J Leukoc Biol. 2011 Jul;90(1):37-47. doi: 10.1189/jlb.1110616. Epub 2011 Feb 17.

Autoinflammation: translating mechanism to therapy.

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Autoinflammatory syndromes are a clinically heterogeneous collection of diseases characterized by dysregulation of the innate immune system. The hereditary recurrent fever disorders were the first to be defined as autoinflammatory. Several of the responsible genes are now known to encode proteins forming multimeric complexes called inflammasomes, which are intracellular "danger sensors" that respond to a variety of different signals by activating caspase-1, responsible for cleavage and subsequent release of bioactive IL-1 $\beta$ . This discovery of the causative link between autoinflammation and IL-1 $\beta$  maturation has led to a significantly improved understanding of the mechanisms of innate immunity, as well as life-altering treatments for patients. Targeting IL-1 $\beta$  for the treatment of autoinflammatory syndromes is an excellent example of the power

of translational research. Given the central role of inflammation in many complex multigenic diseases, these treatments may benefit larger numbers of patients in the future. Here, we review current treatment strategies of autoinflammatory diseases with a focus on IL-1 antagonism.

DOI: 10.1189/jlb.1110616

PMCID: PMC3219035

PMID: 21330349 [Indexed for MEDLINE]

3078. Conn Med. 2011 Jan;75(1):17-9.

Familial Mediterranean fever presenting with pulmonary embolism.

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Familial Mediterranean fever (FMF) is the autoinflammatory disease and hereditary periodic fever syndrome that most commonly affects people of Eastern Mediterranean origin. It is characterized by recurrent self-limited attacks of fever and serositis, with an increase in acute-phase reactant markers, and is transmitted in an autosomal recessive pattern. Inflammation shifts the hemostatic mechanisms favoring thrombosis. There are few reports of an increased risk of hypercoagulability in patients with FMF in the absence of amyloidosis and nephrotic syndrome. In this case report, we describe a 43-year-old Turkish patient who presented with right-sided pleuritic chest pain and pulmonary embolism. The patient described having prior similar attacks of serositis, but had never been diagnosed with FMF. Further workup revealed an increase in acute phase reactants, negative hypercoagulability studies and heterozygosity for the M694V mutation in the pyrin (MEFV) gene. We identified untreated FMF and chronic inflammation as his only risk factor for pulmonary embolism. With this case report, we support recent studies that have demonstrated that inflammation may lead to prothrombotic states in patients with FMF.

PMID: 21329287 [Indexed for MEDLINE]

3079. J Rheumatol. 2011 May;38(5):810-20. doi: 10.3899/jrheum.100732. Epub 2011 Feb 15.

Expression of Toll-like receptors and their signaling pathways in rheumatoid synovitis.

Tamaki Y(1), Takakubo Y, Hirayama T, Konttinen YT, Goodman SB, Yamakawa M, Takagi M.

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**OBJECTIVE:** Toll-like receptors (TLR) recognizing endogenous and exogenous danger signals could play a role in rheumatoid arthritis (RA). Our aim was to describe the presence, localization, and extent of expression of TLR and their adapters.

**METHODS:** TLR 1, 2, 3, 4, 5, 6, and 9 receptors, and myeloid differentiation primary response protein 88, Toll/interleukin receptor (TIR) domain-containing adapter protein MyD88 adapter-like, and TIR domain-containing adapter-inducing interferon/TIR-containing adapter molecule-1 adapters were analyzed in RA (n = 10) and osteoarthritis (OA; n = 5) samples using real-time polymerase chain reaction (PCR). Their colocalization with cellular markers CD68, CD15, CD3, CD4, CD8, CD20, dendritic cell lysosomal-associated membrane protein (DC-LAMP), CD123, and 5B5 was analyzed in double immunofluorescence staining.

**RESULTS:** In RA,  $\beta$ -actin standardized messenger RNA of TLR 2, 3, and 9 ( $p < 0.001$ ) were particularly high. TLR 5 and 6 were also elevated ( $p < 0.05$ ), but TLR 1 and 4 and adapters did not differ between RA and OA. In double-staining, TLR and adapters were strongly labeled in myeloid and plasmacytoid dendritic cells (DC), moderately in CD68+ type A lining cells/macrophages, and weakly to moderately in 5B5+ type B lining cells/fibroblasts. CD3+/CD4+ and CD3+/CD8+ T cells and CD20+ B cells in perivenular areas and in lymphoid follicles were moderately TLR- and weakly adapter-positive. In OA, TLR and adapters were weakly immunolabeled in vascular, lining, and inflammatory cells.

**CONCLUSION:** RA synovium showed abundant expression of TLR. RA synovitis tissue seems to be responsive to TLR ligands. DC, type A cells/macrophages, and type B cells/fibroblasts are, in that order from highest to lowest, equipped with TLR, suggesting a hierarchical responsiveness. In RA, danger-associated molecular patterns to TLR interactions may particularly drive DC to autoinflammatory and

autoimmune cascades/synovitis.

DOI: 10.3899/jrheum.100732

PMID: 21324962 [Indexed for MEDLINE]

3080. Autoimmun Rev. 2011 Jun;10(8):482-9. doi: 10.1016/j.autrev.2011.02.001. Epub 2011 Feb 12.

The pathogenesis of oligoarticular/polyarticular vs systemic juvenile idiopathic arthritis.

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Juvenile idiopathic arthritis (JIA) has had a long and difficult problem with classification. It is clearly a heterogeneous and multi-factorial autoimmune disease but all too often the distinctions among subtypes were unclear. In fact, there is now increasing evidence of a distinct pathogenesis of oligo/polyarticular JIA compared to systemic JIA. Oligo/polyarticular JIA is an antigen-driven lymphocyte-mediated autoimmune disease with abnormality in the adaptive immune system. Cartilage-derived auto-antigens activate autoreactive T cells including Th1 and Th17 cells with production of pro-inflammatory cytokines IFN- $\gamma$  and IL-17. On the other hand, the inhibition of regulatory T (Treg) cells including natural Foxp3(+) Treg and self-heat shock protein-induced Treg cells with decreased anti-inflammatory cytokine IL-10 results in the loss of immune tolerance. Imbalance between autoreactive Th1/Th17 and Treg cells leads to the failure of T cell tolerance to self-antigens, which contributes to the synovial inflammation of oligo/polyarticular JIA. By contrast, systemic JIA is an autoinflammatory disease with abnormality in the innate immune system. A loss of control of the alternative secretory pathway leading to aberrant activation of phagocytes including monocytes, macrophages and neutrophils seems to be involved in the release of pro-inflammatory cytokines IL-1, IL-6, IL-18 and pro-inflammatory S100-proteins, which contribute to the multisystem inflammation of systemic JIA. Markedly distinct pathogenesis of oligo/polyarticular JIA and systemic JIA implies that they might need different treatment strategies.

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DOI: 10.1016/j.autrev.2011.02.001

PMID: 21320644 [Indexed for MEDLINE]

3081. Genet Med. 2011 Mar;13(3):263-9. doi: 10.1097/GIM.0b013e31820e27b1.

Diagnosis and management of familial Mediterranean fever: integrating medical genetics in a dedicated interdisciplinary clinic.

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Familial Mediterranean fever is an autosomal recessive genetic disorder characterized by recurrent febrile polyserositis, especially prevalent in individuals of Mediterranean descent. Familial Mediterranean fever can have nonspecific manifestations that mimic many common acquired disorders such as infections, acute appendicitis, cholecystitis, and arthritis, which can delay diagnosis for many years and subject patients to extensive evaluations and even unnecessary surgery. Untreated familial Mediterranean fever can result in serious complications such as end-stage renal disease and malabsorption secondary to amyloid deposition in the kidneys and digestive tract, male and female infertility, and growth retardation in children. These significant sequelae, along with the episodic acute attacks, are readily preventable by treatment with oral colchicine and underscore the necessity of early detection and treatment from a medical, psychosocial, and economic standpoint. We describe our comprehensive approach to the accurate diagnosis and effective management of this disorder by means of a dedicated familial Mediterranean fever clinic that incorporates medical genetics on equal footing with general medicine. In addition to providing the clinician with the presenting features of familial Mediterranean fever, methods of diagnosis including molecular testing, and current management based on our extensive experience with hundreds of affected individuals, we also advance this approach as a model for the incorporation of medical genetics practice into the more traditional domains of general medicine.

DOI: 10.1097/GIM.0b013e31820e27b1  
PMID: 21317656 [Indexed for MEDLINE]

3082. Br J Pharmacol. 2011 Jul;163(5):912-26. doi: 10.1111/j.1476-5381.2011.01254.x.

Colchicine inhibits cationic dye uptake induced by ATP in P2X2 and P2X7 receptor-expressing cells: implications for its therapeutic action.

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**BACKGROUND AND PURPOSE:** The two longest C-termini of the purinergic P2X receptors occur in the P2X2 and P2X7 receptors and are thought to interact with multiple cytoplasmic proteins, among which are members of the cytoskeleton, including microtubules. In this work we asked whether disrupting the microtubule cytoskeleton might affect the functions of these receptors.

**EXPERIMENTAL APPROACH:** Functions of heterologously expressed P2X2 and P2X7 receptors were evaluated with electrophysiology and dye uptake following ATP application. Permeabilization and secretion of pro-inflammatory agents were quantified from fresh or cultured peritoneal mouse macrophages, treated in vitro or in vivo with colchicine.

**KEY RESULTS:** Disrupting the microtubule network with colchicine did not affect currents generated by ATP in P2X2 and P2X7 receptor-expressing cells but inhibited uptake of the dye Yo-Pro-1 in *Xenopus* oocytes and HEK293 cells expressing these channels. Peritoneal mouse macrophages showed less ATP-induced permeabilization to ethidium bromide in the presence of colchicine, and less reactive oxygen species (ROS) formation, nitric oxide (NO) and interleukin (IL)-1 $\beta$  release. Colchicine treatment did not affect ATP-evoked currents in macrophages. Finally, in vivo assays with mice inoculated with lipopolysaccharide and ATP showed diminished ROS, IL-1 $\beta$ , interferon- $\gamma$  and NO production after colchicine treatment.

**CONCLUSIONS AND IMPLICATIONS:** Colchicine has known anti-inflammatory actions and is used to treat several conditions involving innate immunity, including gout and familial Mediterranean fever. Here we propose a new mechanism of action -



inhibition of pore formation induced by activation of P2X receptors - which could explain some of the anti-inflammatory effects of colchicine.

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DOI: 10.1111/j.1476-5381.2011.01254.x

PMCID: PMC3130939

PMID: 21306580 [Indexed for MEDLINE]

3083. Blood. 2011 Apr 7;117(14):3720-32. doi: 10.1182/blood-2010-07-273417. Epub 2011 Feb 8.

Interleukin-1 in the pathogenesis and treatment of inflammatory diseases.

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More than any other cytokine family, the IL-1 family of ligands and receptors is primarily associated with acute and chronic inflammation. The cytosolic segment of each IL-1 receptor family member contains the Toll-IL-1-receptor domain. This domain is also present in each Toll-like receptor, the receptors that respond to microbial products and viruses. Since Toll-IL-1-receptor domains are functional for both receptor families, responses to the IL-1 family are fundamental to innate immunity. Of the 11 members of the IL-1 family, IL-1 $\beta$  has emerged as a therapeutic target for an expanding number of systemic and local inflammatory conditions called autoinflammatory diseases. For these, neutralization of IL-1 $\beta$  results in a rapid and sustained reduction in disease severity. Treatment for autoimmune diseases often includes immunosuppressive drugs whereas neutralization of IL-1 $\beta$  is mostly anti-inflammatory. Although some autoinflammatory diseases are due to gain-of-function mutations for caspase-1 activity, common diseases such as gout, type 2 diabetes, heart failure, recurrent pericarditis, rheumatoid arthritis, and smoldering myeloma also are responsive to IL-1 $\beta$  neutralization. This review summarizes acute and chronic inflammatory diseases that are treated by reducing IL-1 $\beta$  activity and proposes that disease severity is affected by the

anti-inflammatory members of the IL-1 family of ligands and receptors.

DOI: 10.1182/blood-2010-07-273417

PMCID: PMC3083294

PMID: 21304099 [Indexed for MEDLINE]

3084. Eur J Neurol. 2011 Sep;18(9):1146-50. doi: 10.1111/j.1468-1331.2011.03356.x. Epub 2011 Feb 8.

Familial Mediterranean fever (FMF) and multiple sclerosis: an association study in one of the world's largest FMF cohorts.

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Comment in

Eur J Neurol. 2011 Aug;18(8):e96; author reply e97.

**BACKGROUND AND PURPOSE:** To describe and characterize the association between familial Mediterranean fever (FMF) and multiple sclerosis (MS).

**METHODS:** The patient registry of The National Center for FMF was screened for the coexistence of FMF and MS. Tel-Hashomer criteria were used for the diagnosis of FMF, and FMF severity was evaluated, using the simplified FMF severity scale. McDonald criteria were used for the diagnosis of MS, and neurologic disability was measured using the expanded disability status scale (EDSS).

**RESULTS:** We identified nine patients, affected with both FMF and MS. The onset of the FMF averaged 15.6 (3-37) years. Most patients suffered from abdominal and joint attacks, and 50% of the patients sustained a moderate to severe FMF. The onset of the MS was at an average age of 31.6 (17-50) years. Neurologic manifestations varied individually, without a dominant deficit, and the course was in a relapsing-remitting pattern in most. The median EDSS was in general of low score (3.0), apart from the patients who were homozygous for the M694V mutation, in whom the MS was more severe. Based on our case series, the frequency of MS in our FMF population is 0.075%, twice higher the expected rate in the general population (P=0.0057).

CONCLUSIONS: Multiple sclerosis is more common in FMF than in the general Israeli population. Homozygosity for the M694V MEFV mutation may aggravate the phenotype of MS and predispose FMF patients to develop MS.

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DOI: 10.1111/j.1468-1331.2011.03356.x

PMID: 21299735 [Indexed for MEDLINE]

3085. Rheumatology (Oxford). 2011 Jun;50(6):1171-3. doi: 10.1093/rheumatology/ker012. Epub 2011 Feb 4.

A Japanese case of familial Mediterranean fever presenting diffuse bone marrow uptake of FDG-PET and high levels of neutrophil membrane CD64 expression.

Koga T, Umeda M, Migita K, Yamasaki S, Nakamura H, Kawakami A.

DOI: 10.1093/rheumatology/ker012

PMID: 21296849 [Indexed for MEDLINE]

3086. Br J Biomed Sci. 2010;67(4):202-7.

Analysis of common MEFV mutations in Egyptian patients with familial Mediterranean fever: molecular characterisation of the disease.

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Familial Mediterranean fever (FMF) is a hereditary inflammatory disorder transmitted as an autosomal recessive trait. It predominantly affects people living in, or originating from, areas around the Mediterranean and was difficult to diagnose until mutations in the MEFV gene were identified. This study aims to analyse the five most common MEFV mutations in Egyptian patients diagnosed clinically as FME Thirty-eight unrelated patients were tested for the presence of

the MEFV gene mutations V726A, M694V, M694I, M680I and E148Q, using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and the amplification refractory mutation system (ARMS). Twenty-three patients (60.5%) had one or more mutations, whereas no mutation was found in the remaining 15 patients (39.5%). The most common mutation was M694I (42.5%), followed by V726A (22.5%), M680I (17.5%) and E148Q (17.5%). The M694V mutation was not detected. The profile of MEFV gene mutations in this study suggests that the origin of FMF in Egypt is heterogeneous, a finding in concordance with that for other Arab populations; however, some differences were observed as M694V, the most common mutation reported in Arabs, was not detected in this study.

PMID: 21294448 [Indexed for MEDLINE]

3087. Genet Couns. 2010;21(4):461-6.

Screening for the M694V mutation of the familial Mediterranean fever (FMF) gene in 604 French patients.

Bathelier C, Lenoir G, Lucotte G.

PMID: 21290976 [Indexed for MEDLINE]

3088. Nat Rev Rheumatol. 2011 Feb;7(2):82-4. doi: 10.1038/nrrheum.2010.229.

Autoinflammation in 2010: expanding clinical spectrum and broadening therapeutic horizons.

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DOI: 10.1038/nrrheum.2010.229

PMCID: PMC3393888

PMID: 21289614 [Indexed for MEDLINE]

3089. Eur J Pediatr. 2011 Aug;170(8):1055-7. doi: 10.1007/s00431-011-1404-y. Epub 2011 Feb 2.

Application of the new pediatric criteria and Tel Hashomer criteria in heterozygous patients with clinical features of FMF.

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Recently, a new set of criteria was established for the diagnosis of familial Mediterranean fever (FMF) in childhood. The aim of this study is to validate the new criteria set among heterozygous patients with clinical features of FMF. The study group consisted of FMF patients, who had a mutation at a single allele, who were followed in four pediatric nephrology-rheumatology centers in Turkey. Patients were evaluated by the new criteria set and also by the Tel Hashomer criteria. According to the new criteria, the diagnosis of FMF was established by the presence of two or more of five criteria (fever, abdominal pain, chest pain, arthritis, family history of FMF). The study group consisted of 110 FMF (54 male, 56 female) patients. Majority of the patients had heterozygous pM694V mutation (65%). The sensitivity of the new criteria set and that of the Tel Hashomer criteria in our study group were found to be 93% and 100%, respectively. In conclusion, this study designates that sensitivity of the new criteria set is also high in patients who had a mutation at a single allele.

DOI: 10.1007/s00431-011-1404-y

PMID: 21287357 [Indexed for MEDLINE]

3090. Ann Med. 2012 Mar;44(2):109-18. doi: 10.3109/07853890.2010.548399. Epub 2011 Feb 1.

Setting up TRAPS.

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Tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is a dominantly inherited autoinflammatory disease caused by heterozygous mutations in the TNFRSF1A gene encoding for the TNF receptor 1 (TNFR1). TRAPS is a multi-faceted and heterogeneous disease which commonly manifests as recurrent episodes of high fever accompanied by abdominal pain, pleurisy, migratory rash, and myalgia. Disease attacks occur spontaneously or may be elicited by minor triggers. Because of a vigorous and sustained acute-phase response it may be complicated by systemic AA amyloidosis. Therapeutically interleukin-1 blockade seems even more promising than TNF blockade. Studies on the pathogenesis of TRAPS have shown TNF $\alpha$ -dependent cellular signalling to be defective, an enigmatic finding considering the hyperinflammatory phenotype of the disease. Several studies indicate that most mutated receptors never reach the cell surface but are misfolded and trapped in the endoplasmic reticulum, where they may elicit an intracellular inflammatory response, and thus lead to constitutional expression of proinflammatory cytokines. The aim of this review is to describe the current understanding of the pathogenesis of TRAPS by integrating recent clinical and laboratory data.

DOI: 10.3109/07853890.2010.548399

PMID: 21284532 [Indexed for MEDLINE]

3091. Ann Med. 2011 Aug;43(5):341-6. doi: 10.3109/07853890.2010.547212. Epub 2011 Feb 1.

Autoinflammatory diseases and cardiovascular manifestations.

Rigante D(1), Cantarini L, Imazio M, Lucherini OM, Sacco E, Galeazzi M, Brizi MG, Brucato A.

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**Abstract** A host of clinical scenarios can be depicted in hereditary autoinflammatory diseases, and the cardiovascular system can also be involved especially in familial Mediterranean fever (FMF), caused by mutations in the MEFV gene, and tumour necrosis factor receptor-associated periodic syndrome (TRAPS), caused by mutations in the TNFRSF1A gene. Pericardial diseases are the most represented cardiovascular abnormalities, though the role of MEFV and TNFRSF1A in the initiation of heart involvement has not been demonstrated formally and will be discussed herein.

DOI: 10.3109/07853890.2010.547212

PMID: 21284530 [Indexed for MEDLINE]

3092. J Exp Med. 2011 Mar 14;208(3):519-33. doi: 10.1084/jem.20102049. Epub 2011 Jan 31.

Mitochondrial reactive oxygen species promote production of proinflammatory cytokines and are elevated in TNFR1-associated periodic syndrome (TRAPS).

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**Comment in**

Nat Rev Immunol. 2011 Mar;11(3):162.

Nat Rev Rheumatol. 2011 May;7(5):254.

Reactive oxygen species (ROS) have an established role in inflammation and host defense, as they kill intracellular bacteria and have been shown to activate the NLRP3 inflammasome. Here, we find that ROS generated by mitochondrial respiration are important for normal lipopolysaccharide (LPS)-driven production of several proinflammatory cytokines and for the enhanced responsiveness to LPS seen in

cells from patients with tumor necrosis factor receptor-associated periodic syndrome (TRAPS), an autoinflammatory disorder caused by missense mutations in the type 1 TNF receptor (TNFR1). We find elevated baseline ROS in both mouse embryonic fibroblasts and human immune cells harboring TRAPS-associated TNFR1 mutations. A variety of antioxidants dampen LPS-induced MAPK phosphorylation and inflammatory cytokine production. However, gp91(phox) and p22(phox) reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase subunits are dispensable for inflammatory cytokine production, indicating that NADPH oxidases are not the source of proinflammatory ROS. TNFR1 mutant cells exhibit altered mitochondrial function with enhanced oxidative capacity and mitochondrial ROS generation, and pharmacological blockade of mitochondrial ROS efficiently reduces inflammatory cytokine production after LPS stimulation in cells from TRAPS patients and healthy controls. These findings suggest that mitochondrial ROS may be a novel therapeutic target for TRAPS and other inflammatory diseases.

DOI: 10.1084/jem.20102049

PMCID: PMC3058571

PMID: 21282379 [Indexed for MEDLINE]

3093. Am J Pathol. 2011 Feb;178(2):580-90. doi: 10.1016/j.ajpath.2010.10.013.

The IL-27 receptor has biphasic effects in crescentic glomerulonephritis mediated through Th1 responses.

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Despite its initially defined role as a T-helper type 1 cell (Th1)-inducing cytokine, interleukin-27 (IL-27) has complex roles in vivo. The role of IL-27 receptor (IL-27R) was defined in experimental crescentic glomerulonephritis induced by a foreign antigen, sheep globulin, which is planted in glomeruli. This lesion is dependent on a Th1 effector cellular response. Twenty-one days after the administration of sheep anti-mouse glomerular basement membrane antibody, wild-type mice developed histologic and functional inflammatory renal injury. Injury was attenuated in the absence of IL-27R  $\alpha$  chain (IL-27R $\alpha$ ), the unique



component of the IL-27R complex. In contrast to the attenuated renal injury on day 21, IL27ra(-/-) mice exhibited enhanced systemic immune responses, including Th1 responses, with increased IL-2-dependent interferon- $\gamma$  (IFN- $\gamma$ ) production. However, earlier in the development of the nephritogenic immune response, IFN- $\gamma$  production was decreased, with reduced early immune responses translating into attenuated renal injury. Having demonstrated decreased early Th1 systemic immune responses, followed by enhanced nephritogenic Th1 immune responses, renal injury was studied at later time points. On days 28 and 35 after injection of the nephritogenic antigen, renal injury was enhanced in IL27ra(-/-) mice compared with wild-type mice in an at least partially IFN- $\gamma$ -dependent manner. In Th1-dependent autoinflammatory lesions, IL-27R $\alpha$  has a biphasic role in vivo, initially pathogenic, but ultimately playing a protective role by regulating immune responses and attenuating disease.

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DOI: 10.1016/j.ajpath.2010.10.013

PMCID: PMC3069896

PMID: 21281790 [Indexed for MEDLINE]

3094. *Sociol Health Illn*. 2011 May;33(4):618-33. doi: 10.1111/j.1467-9566.2010.01305.x. Epub 2011 Feb 1.

Shifting normalities: interactions of changing conceptions of a normal life and the normalisation of symptoms in rheumatoid arthritis.

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Biographical disruption and related concepts have been widely applied in chronic illness. Different conceptualisations of normalisation have also been proposed in order to explain individuals' diverse responses to illness on their biography, but as yet, not clearly related to changing bodily experience or normalisation of symptoms. This article aims to examine the relevance of these concepts in

rheumatoid arthritis (RA), an unpredictable autoinflammatory disease characterised by painful and swollen joints, disability, fatigue and joint damage. Interviews were conducted with 23 people living with RA, and analysed using Framework, to enable people's whole narratives and context to be considered. Six typologies of normality emerged from the data: disrupted; struggling to maintain; fluctuating; resetting; returning; and continuing normality. Multiple normalities were often present in individuals' narratives, with one normality typology usually dominating at the time of the interview. The typologies connect to several biographical concepts, and instances of 'biographical reinstatement' were also found, where participants described returning to normal life, through perceived effective medication rather than reconceptualisation of health. The concept of 'shifting normalities' is proposed, providing a dynamic explanatory model of chronic illness that captures the interaction of changing conceptions of a normal life and the normalisation of symptoms.

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DOI: 10.1111/j.1467-9566.2010.01305.x

PMID: 21281314 [Indexed for MEDLINE]

3095. *Semin Arthritis Rheum*. 2011 Oct;41(2):265-71. doi: 10.1016/j.semarthrit.2010.11.003. Epub 2011 Feb 1.

Interleukin-1 targeting drugs in familial Mediterranean fever: a case series and a review of the literature.

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**OBJECTIVES:** Familial Mediterranean fever (FMF) is an autosomal-recessive autoinflammatory disorder common in Mediterranean populations. FMF is associated with mutations of the MEFV gene, which encodes pyrin. Functional studies suggest that pyrin is implicated in the maturation and secretion of IL-1. The IL-1

receptor antagonist or anti-IL1 monoclonal antibody may therefore represent a new approach to treat FMF. The aim of this report was to evaluate and discuss treatment of FMF with interleukin-1 targeting drugs.

**METHODS:** Electronic mailing lists of French pediatric and adult rheumatologist associations were used to call for FMF patients treated with interleukin-1 antagonists. A search for published FMF patients treated with interleukin-1 targeting drugs was performed by screening PubMed.

**RESULTS:** Here, we report 7 cases of FMF patients treated with anakinra and/or canakinumab and discuss the clinical situations that may indicate the use of IL-1 blocking agents in FMF. The use of interleukin-1 targeting drugs was beneficial to all patients. The reasons for using interleukin-1 targeting drugs in FMF patients were as follows: (1) incomplete control of disease activity despite colchicine treatment; (2) high serum amyloid A levels despite colchicine treatment; (3) impossibility to use colchicine treatment because of severe side effects; (4) FMF in association with vasculitis.

**CONCLUSIONS:** Interleukin-1 targeting drugs may be good candidates when looking for an alternative or supplementary treatment to colchicine. These observations highlight the need for controlled trials to further evaluate the safety and efficacy of interleukin-1 antagonists in FMF patients.

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DOI: 10.1016/j.semarthrit.2010.11.003

PMID: 21277619 [Indexed for MEDLINE]

3096. Clin Chem Lab Med. 2011 May;49(5):783-91. doi: 10.1515/CCLM.2011.127. Epub 2011 Jan 31.

The plodding diagnosis of monogenic autoinflammatory diseases in childhood: from the clinical scenery to laboratory investigation.

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Autoinflammatory diseases (AID) are inherited errors of innate immunity which,

although individually uncommon, collectively set up an emerging chapter of medicine. Careful analysis and identification of AID is essential to prompt effective treatment and improve survival and quality of life in these patients. Research into pediatric AID is lagging behind studies in adults, though a better understanding of AID in infancy could lead to improved diagnostic protocols and reduce long-term disability. This review provides a detailed summary of monogenic AID in childhood to help pediatricians correctly recognize these conditions and also highlight recent developments in the laboratory diagnostic work-up.

DOI: 10.1515/CCLM.2011.127

PMID: 21275813 [Indexed for MEDLINE]

3097. Mol Med. 2011 May-Jun;17(5-6):363-8. doi: 10.2119/molmed.2011.00039. Epub 2011 Jan 25.

Effects of the histone deacetylase inhibitor ITF2357 in autoinflammatory syndromes.

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We explored the effects of the oral histone deacetylase (HDAC) inhibitor ITF2357 in patients with autoinflammatory syndrome. In this prospective open-label pilot study, eight patients were enrolled; one patient with tumor necrosis factor receptor-associated periodic syndrome (TRAPS), three patients with hyper-IgD and periodic fever syndrome (HIDS) and four patients with Schnitzler syndrome were closely followed during 90 d of ITF2357 treatment. Three patients with Schnitzler syndrome and one TRAPS patient experienced a partial remission. In four patients, there was no effect. In HIDS patients, there was a tendency toward a higher attack frequency and increasing attack severity. In two patients (one TRAPS and one HIDS), we observed a decrease of acute-phase response without signs of clinical improvement. One patient with Schnitzler syndrome showed a partial response despite an ongoing acute-phase response. In conclusion, ITF2357 monotherapy was able to induce partial response only in patients with Schnitzler

syndrome and no response in patients with AIDS.

DOI: 10.2119/molmed.2011.00039

PMCID: PMC3105134

PMID: 21274502 [Indexed for MEDLINE]

3098. Proc Natl Acad Sci U S A. 2011 Feb 15;108(7):2927-32. doi: 10.1073/pnas.1012455108. Epub 2011 Jan 26.

Inflammasome-independent role of the apoptosis-associated speck-like protein containing CARD (ASC) in the adjuvant effect of MF59.

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Erratum in

Proc Natl Acad Sci U S A. 2013 Mar 12;110(11):4429.

Clinical studies have indicated that subvirion inactivated vaccines against avian influenza viruses, particularly H5N1, are poorly immunogenic in humans. As a consequence, the use of adjuvants has been championed for the efficient vaccination of a naïve population against avian influenza. Aluminum salts (alum) and the oil-in-water emulsion MF59 are safe and effective adjuvants that are being used with influenza vaccines, but the mechanism underlying their stimulation of the immune system remains poorly understood. It was shown recently that activation of a cytosolic innate immune-sensing complex known as "NLR-Pyrin domain containing 3" (NLRP3) inflammasome, also known as "cryopyrin," "cold-induced autoinflammatory syndrome 1" (CIAS1), or NACHT domain-, leucine-rich repeat-, and PYD-containing protein 3 (Nalp3), is essential for the adjuvant effect of alum. Here we show that the inflammasome component apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), an adapter protein within the NLRP3 inflammasome, is a crucial element in the adjuvant effect of MF59 when combined with H5N1 subunit vaccines. In the absence of ASC, H5-specific IgG antibody responses are significantly reduced, whereas the responses are intact in NLRP3(-/-) and caspase-1(-/-) mice. This

defect is caused mainly by the failure of antigen-specific B cells to switch from IgM to IgG production. We conclude that ASC plays an inflammasome-independent role in the induction of antigen-specific humoral immunity after vaccination with MF59-adjuvanted influenza vaccines. These findings have important implications for the rational design of next-generation adjuvants.

DOI: 10.1073/pnas.1012455108

PMCID: PMC3041074

PMID: 21270336 [Indexed for MEDLINE]

3099. Clin Nephrol. 2011 Feb;75 Suppl 1:1-3.

Successful treatment of renal AA amyloidosis in familial Mediterranean fever with pegylated alpha-2a interferon.

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Renal AA amyloidosis is a severe consequence of chronic inflammatory diseases such as familial Mediterranean fever (FMF). FMF is caused by mutations in the MEFV gene, resulting in defective control of granulocyte-mediated inflammation. Interferon-alpha is known to induce MEFV expression in monocytes and granulocytes in vitro. We present the first case of colchicine-resistant FMF in which a durable disease remission and regression of renal amyloidosis was induced by chronic treatment with pegylated interferon-alpha.

PMID: 21269584 [Indexed for MEDLINE]

3100. Clin Exp Rheumatol. 2011 Jan-Feb;29(1):111-6. Epub 2011 Feb 23.

The distribution of juvenile idiopathic arthritis in the eastern Mediterranean: results from the registry of the Turkish Paediatric Rheumatology Association.

Demirkaya E(1), Ozen S, Bilginer Y, Ayaz NA, Makay BB, Unsal E, Erguven M, Poyrazoglu H, Kasapcopur O, Gok F, Akman S, Balat A, Cavkaytar O, Kaya B, Duzova A, Ozaltin F, Topaloglu R, Besbas N, Bakkaloglu A, Arisoy N, Ozdogan H, Bakkaloglu S, Turker T.

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**OBJECTIVES:** To analyse the demographics, main clinical and laboratory features and subtype distribution of juvenile idiopathic arthritis (JIA) in an eastern Mediterranean country, based on a multicentre registry.

**METHODS:** Between March 2008 and February 2009 with this cross-sectional study, consecutive patients seen with JIA in selected centres were registered through a web-based registry. All patients were classified according to the International League of Associations for Rheumatology (ILAR) criteria.

**RESULTS:** There were 634 patients with a mean age of  $11.84 \pm 4.66$  years and the female/male ratio was 1.2. The distributions of JIA patients according to onset of disease were as follows: systemic 92 (14.5%), oligoarticular extended 26 (4.1%), oligoarticular persistent 234 (36.9%), rheumatoid factor (RF) positive polyarthritis 20 (3.2%), RF negative polyarthritis 129 (20.3%), enthesitis-related 120 (18.9%), psoriatic 13(2.1%). The frequency of uveitis was 15.7% among all of the oligoarthritis patients. Anti-nuclear antibody (ANA) was positive mainly among the oligoarticular onset patients. Twenty-one patients also had Familial Mediterranean fever (FMF). Among systemic JIA patients, the frequency of macrophage activation syndrome (MAS) was 15.2% (n=14). At the end of the mean follow-up of  $7.6 \pm 4.4$  years, 305 (48.1%) patients were defined to have inactive disease on medication, and 106 (16.7%) were completely free of any disease symptoms without medication.

**CONCLUSIONS:** Enthesitis related arthritis had a high frequency whereas psoriatic arthritis was very rare compared to other series. We suggest that there are certain differences in the characteristics of JIA in our eastern Mediterranean population. Thus, genetic studies need to be assessed in these populations separately and findings of genome wide association studies need to be confirmed in different populations.

PMID: 21269582 [Indexed for MEDLINE]

3101. Rheumatol Int. 2012 May;32(5):1265-9. doi: 10.1007/s00296-010-1725-6. Epub 2011 Jan 26.

Rheumatoid arthritis risk associates with DNA repair gene XRCC1 Arg399Gln polymorphism in Turkish patients.

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Rheumatoid arthritis (RA) is an autoinflammatory disease with a genetic background. The synoviocytes in RA shows cellular transformation with tumor-like features, and RA patients have genomic instability and relaxation of DNA repair mechanisms. The polymorphisms in BER repair pathway genes, XRCC1 and OGG1, may change the response to inflammation via altered DNA repair capacity. In this study, we aimed to investigate the relationship between the risk of RA and XRCC1 Arg194Trp, Arg399Gln, and OGG1 Ser326Cys polymorphisms in a group of Turkish RA patients. XRCC1 Arg194Trp, Arg399Gln, and OGG1 Ser326Cys polymorphisms were investigated by PCR-RFLP method in 100 RA patients and 158 healthy control subjects. The results were statistically analyzed by calculating the odds ratios (OR) and their 95% confidence intervals (95% CI) using the  $\chi^2$ -tests. RA patients in this study had significantly higher frequencies of XRCC1 Arg399Gln polymorphism in both homozygote (GG) (35%, OR: 7.78 [95% CI: 3.65-16.59],  $P < 0.001$ ) and heterozygote (AG) forms (41%, OR: 2.17 [95% CI: 1.19-3.96],  $P < 0.01$ ) and also increased frequency of 399Gln (G) allele (55%, OR:2.99 [95% CI: 1.67-5.37],  $P < 0.001$ ). We conclude that XRCC1 Arg194Trp, and OGG1 Ser326Cys polymorphisms are not associated with RA; however, Arg399Gln polymorphism is a significant risk factor of RA, and carriers of 399Gln (G) allele have greater risk of RA.

DOI: 10.1007/s00296-010-1725-6

PMID: 21267572 [Indexed for MEDLINE]



3102. Rheumatol Int. 2012 Feb;32(2):529-33. doi: 10.1007/s00296-010-1766-x. Epub 2011 Jan 23.

Polyarteritis nodosa and Henoch-Schönlein purpura nephritis in a child with familial Mediterranean fever: a case report.

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Familial Mediterranean fever is an autosomal recessive disease characterized by recurrent self-limited attacks of fever accompanied by peritonitis, pleuritis, and arthritis. Approximately 5% of individuals with familial Mediterranean fever have been reported to have Henoch-Schönlein purpura and about 1% to have polyarteritis nodosa. A 7-year-old girl presenting with complaints of purpuric rash, abdominal pain, arthritis, hematuria, and proteinuria and having IgA depositions on renal biopsy was diagnosed as Henoch-Schönlein nephritis. She had a history of recurrent fever, abdominal and joint pain and M694 V compound homozygote mutation. Colchicine treatment was started for the diagnosis of FMF. When constitutional symptoms such as myalgia, weight loss, fatigue, fever, and hypertension were added to the clinical picture, the diagnosis of polyarteritis nodosa HSP was thought and confirmed by the demonstration of microaneurisms on renal arteries. There was no response to corticosteroid and cyclophosphamide treatments; however, the symptoms were rapidly and dramatically reduced after the administration of intravenous immunoglobulin. In conclusion, polyarteritis nodosa and Henoch-Schönlein purpura can be seen together with familial Mediterranean fever. It is also suggested that IVIG might be an important adjunct therapy in selected patients with polyarteritis nodosa, especially in the lack of response to steroids and immunosuppressive drugs.

DOI: 10.1007/s00296-010-1766-x

PMID: 21259007 [Indexed for MEDLINE]

3103. Cell Mol Immunol. 2011 Mar;8(2):135-45. doi: 10.1038/cmi.2010.81. Epub 2011 Jan 24.

The inflammasomes in health and disease: from genetics to molecular mechanisms of autoinflammation and beyond.

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Nucleotide-binding oligomerization domain (NOD)-containing protein-like receptors (NLRs) are a recently discovered class of innate immune receptors that play a crucial role in initiating the inflammatory response following pathogen recognition. Some NLRs form the framework for cytosolic platforms called inflammasomes, which orchestrate the early inflammatory process via IL-1 $\beta$  activation. Mutations and polymorphisms in NLR-coding genes or in genetic loci encoding inflammasome-related proteins correlate with a variety of autoinflammatory diseases. Moreover, the activity of certain inflammasomes is associated with susceptibility to infections as well as autoimmunity and tumorigenesis. In this review, we will discuss how identifying the genetic characteristics of inflammasomes is assisting our understanding of both autoinflammatory diseases as well as other immune system-driven disorders.

DOI: 10.1038/cmi.2010.81

PMCID: PMC4003142

PMID: 21258359 [Indexed for MEDLINE]

3104. Autoimmun Rev. 2011 May;10(7):404-9. doi: 10.1016/j.autrev.2011.01.003. Epub 2011 Jan 20.

Schnitzler syndrome, an autoimmune-autoinflammatory syndrome: report of two new cases and review of the literature.

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Schnitzler syndrome is a rare disorder characterized clinically by chronic

urticarial rash accompanied by fever, arthralgia or arthritis, bone pain and lymphadenopathy and biochemically by monoclonal gammopathy and elevation of inflammatory indices. The disorder is very likely under-recognized and its origin remains obscure although it may be included among the immune mediated inflammatory diseases with features of autoinflammation and autoimmunity. We describe here two patients affected by Schnitzler syndrome, both refractory to corticosteroids and immunosuppressive therapy, successfully treated with the interleukin-1 receptor antagonist Anakinra. Unfortunately after two weeks, one patient experienced an important local adverse reaction to the biological drug. We decided to discontinue Anakinra with flare of the disease after 24 h. We therefore switched to Rituximab obtaining a complete remission in two months. We searched MEDLINE in order to analyze the frequency of the disease, its pathogenesis and outcome. The electronic search was conducted using the following key words "Schnitzler syndrome" and "Treatment of Schnitzler syndrome". All the selected papers, except the clinical reviews, described at least one case of Schnitzler syndrome. The review of the literature highlighted that Schnitzler syndrome remains an enigmatic disorder hard to categorize and to treat.

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DOI: 10.1016/j.autrev.2011.01.003

PMID: 21256251 [Indexed for MEDLINE]

3105. J Membr Biol. 2011 Mar;240(1):55-62. doi: 10.1007/s00232-011-9342-1. Epub 2011 Jan 20.

Colchicine modulates oxidative stress in serum and leucocytes from remission patients with Family Mediterranean Fever through regulation of  $\text{Ca}^{2+}$  release and the antioxidant system.

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We investigated the effects of colchicine on oxidative stress and  $\text{Ca}^{2+}$  release in serum and polymorphonuclear leucocytes (PMNs) of Familial Mediterranean Fever

(FMF) patients with attack, remission and unremission periods. Eighteen FMF patients and six age-matched healthy subjects in four groups were used. The first group was a control. The second group included patients with active FMF. The third and fourth groups were patients with remission and unremission, respectively. Colchicine (1.5 mg/day) was given to the third and fourth groups for 1 month. PMN cells, serum lipid peroxidation and intracellular  $\text{Ca}^{2+}$ -release levels in the attack and unremission groups were higher than in those in controls, although they were lower in the remission group than in the attack group. Serum vitamin E and  $\beta$ -carotene concentrations were higher in the remission group than in the control and attack groups. However, PMN, serum lipid peroxidation and  $\text{Ca}^{2+}$ -release levels were further increased in the unremission group compared to the attack group. Glutathione peroxidase, reduced glutathione and vitamin A values in the four groups did not change by FMF and colchicine. In conclusion, we observed that colchicine induced protective effects on oxidative stress by modulating vitamin E,  $\beta$ -carotene and  $\text{Ca}^{2+}$ -release levels in FMF patients with a remission period.

DOI: 10.1007/s00232-011-9342-1

PMID: 21249347 [Indexed for MEDLINE]

3106. Curr Pharm Des. 2011;17(1):47-58.

Mean platelet volume: a link between thrombosis and inflammation?

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Platelet activation is a link in the pathophysiology of diseases prone to thrombosis and inflammation. Numerous platelet markers, including mean platelet volume (MPV), have been investigated in connection with both thrombosis and inflammation. This review considers MPV as a prognostic and therapeutic marker as well as the factors influencing its measurement. Established cardiovascular risk factors, such as smoking, hypertension, dyslipidemia, and diabetes, can influence MPV, depending on confounding factors. Low-grade inflammation is one such factor. Evidence, particularly derived from prospective studies and a meta-analysis,

suggest a correlation between an increase in MPV and the risk of thrombosis. High MPV associates with a variety of established risk factors, cardio- and cerebrovascular disorders, and low-grade inflammatory conditions prone to arterial and venous thromboses. High-grade inflammatory diseases, such as active rheumatoid arthritis or attacks of familial Mediterranean fever, present with low levels of MPV, which reverse in the course of anti-inflammatory therapy. Lifestyle modification, antihypertensive, lipid lowering and diet therapies can also affect MPV values, but these effects need to be investigated in large prospective studies with thrombotic endpoints.

PMID: 21247392 [Indexed for MEDLINE]

3107. Rheumatol Int. 2012 Apr;32(4):981-4. doi: 10.1007/s00296-010-1732-7. Epub 2011 Jan 19.

MEFV mutations in Moroccan patients suffering from familial Mediterranean Fever.

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Familial Mediterranean Fever (FMF, MIM 249100) is an autosomal recessive disease mainly affecting patients of the Mediterranean basin. It is an autoinflammatory periodic disorder characterised by recurrent episodes of fever and abdominal pain, synovitis and pleuritis. FMF is caused by mutations in the Mediterranean Fever (MEFV) gene located on chromosome 16p13.3. Several mutations in the MEFV gene have been characterised in different populations. However, very little is known about mutations in the MEFV gene in patients with Moroccan origin. The aim of this study is to determine the clinical components of FMF and characterise mutations in the MEFV gene in Moroccan patients. The study was carried out on 120 unrelated Moroccan patients referred to the department of medical genetics in Rabat for suspicious FMF over a period of 10 years. Patients were screened for the most common MEFV mutations by direct sequencing of exons 2 and 10. Of the 120 unrelated patients investigated, 56 patients (47%) were carriers of one or two MEFV mutations, and 64 patients (53%) had no detected mutations. Of those with

mutations, 24 were homozygous (44%), 13 were compound heterozygotes (24%), and 19 patients had only 1 identifiable mutation (32%). The most frequent mutation in Moroccan patients is M694V (47%), followed by M694I (32%), A744S (6.5%), M680L (4%), M694del (2%) and E148Q (6.5%). The R761H, K695R and I692del mutations were rarely encountered (less than 1%). The V726A mutation was not found in our study. Our data represent the first report of MEFV gene mutations causing FMF in Moroccan patients. The M694V and M694I mutations are the most common mutations found in MEFV gene in Moroccan population; while the most common mutation in Arabs from the Middle-East region, the V726A, was not found in our population.

DOI: 10.1007/s00296-010-1732-7

PMID: 21246368 [Indexed for MEDLINE]

3108. Int J Immunopathol Pharmacol. 2010 Oct-Dec;23(4):1133-41.

Development and preliminary validation of a diagnostic score for identifying patients affected with adult-onset autoinflammatory disorders.

Cantarini L(1), Lucherini OM, Iacoponi F, Cimaz R, Simonini G, Rigante D, Laghi Pasini F, Baldari CT, Capecchi PL, Brizi MG, Galeazzi M.

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To date, the rate of detection of autoinflammatory gene mutations in patients suspected of having an autoinflammatory disorder is very low. However, most of these data refer to pediatric populations. The relative rarity and lack of information on adult-onset autoinflammatory diseases make it likely that mutations will be found in an even smaller percentage of cases. Our aim was to develop and validate a set of variables for predicting the risk that a given adult patient presenting with recurrent fever episodes carries mutations in the MEFV or TNFRSF1A genes, in order to increase the probability of obtaining positive results on genetic testing. One hundred and ten consecutive patients with a clinical history of periodic fever attacks were screened for mutations in the TNFRSF1A and the MEFV genes. The mean age at disease onset was 27.85 years. Detailed information about each patient's family history, personal history, and

clinical manifestations were retrospectively collected. A diagnostic score was constructed based on univariate and multivariate analysis in a randomly-selected dataset (training set; n=40). The score was validated on an independent set of the remaining patients (validation set; n=70). Age at onset (odds ratio 0.958, P =0.050), positive family history of recurrent fever episodes (OR 5.738, P = 0.006), thoracic pain (OR 7.390, P = 0.002), abdominal pain (OR 2.853, P = 0.038) and skin involvement (OR 8.241, P = 0.003) were independently correlated with a positive genetic test result. A diagnostic score was calculated using the linear combination of the estimated coefficients of the logistic model (cut off equal to 0.24) revealing high sensitivity (0.94), high specificity (0.94) and high accuracy (0.94). We have identified variables that appear to be strongly related to the probability of detecting gene mutations in MEF and TNFRSF1A in adults, thus improving the evaluation of patients with suspected autoinflammatory disorders.

DOI: 10.1177/039463201002300417

PMID: 21244762 [Indexed for MEDLINE]

3109. Clin Rheumatol. 2011 May;30(5):711-3. doi: 10.1007/s10067-010-1673-2. Epub 2011 Jan 18.

Relapsing polychondritis and familial Mediterranean fever--an association.

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Relapsing polychondritis (RP) and familial Mediterranean fever (FMF) are systemic inflammatory disorders with seemingly distinct genetic and pathophysiologic mechanisms. An association between these disorders has been described based on a single case report with few clinical details available. We recently encountered a patient with biopsy-proven RP and genetically confirmed FMF. Following identification of this individual, we conducted a retrospective review of all cases of RP in our institution from 2000-2009 and identified one additional patient with RP who is also a genetic heterozygote for FMF. These cases highlight

the previously reported but sparsely documented relationship between these seemingly separate disorders.

DOI: 10.1007/s10067-010-1673-2

PMID: 21243389 [Indexed for MEDLINE]

3110. Open Access Rheumatol. 2011 Jan 18;3:9-18. eCollection 2011.

Interleukin-1 antagonists in the treatment of autoinflammatory syndromes, including cryopyrin-associated periodic syndrome.

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Cryopyrin-associated periodic syndrome (CAPS) include a group of rare autoinflammatory disorders, the spectrum of which ranges from the mildest form, ie, familial cold autoinflammatory syndrome to more severe phenotypes, ie, Muckle-Wells syndrome, and chronic infantile neurological cutaneous and articular syndrome, also known as neonatal-onset multisystem inflammatory disease. Three interleukin (IL)-1 antagonists have been tested in adults and children with CAPS, ie, anakinra, a recombinant homolog of the human IL-1 receptor antagonist; rilonacept, a fusion protein comprising the extracellular domains of IL-1 receptor I and the IL-1 adaptor protein, IL-1RAcP, attached to a human immunoglobulin G molecule; and canakinumab, the anti-IL-1 $\beta$  monoclonal antibody. Following rapid clinical development, rilonacept and canakinumab were approved by both the US Food and Drug Administration and the European Medicines Agency for use in adults and children. This review describes how the study of CAPS has helped us to understand better the way the innate immune system works, the pathogenesis of autoinflammatory syndromes, and the key role of IL-1. It also reviews the effects of IL-1 blockade in CAPS and other disorders, in particular systemic juvenile idiopathic arthritis, adult-onset Still's disease, and gout. Finally, this review covers some issues addressed by very recent and ongoing work regarding treatment indications, from orphan diseases to common disorders, continuous versus intermittent treatment, the pharmacokinetics, pharmacodynamics, and optimal dosages of the different drugs, as well as the need for Phase IV



trials, exhaustive registries, and long-term follow-up of several patient cohorts.

DOI: 10.2147/OARRR.S6696

PMCID: PMC5074783

PMID: 27790000

3111. Acta Paediatr. 2011 May;100(5):745-9. doi: 10.1111/j.1651-2227.2011.02143.x. Epub 2011 Mar 1.

Prevalence of MEFV gene mutations and their clinical correlations in Turkish children with Henoch-Schönlein purpura.

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AIM: To investigate the frequency of MEFV mutations and their associations with the clinical and laboratory findings in children with Henoch-Schönlein purpura (HSP).

METHODS: One hundred and seven children with HSP were investigated for 12 common MEFV mutations.

RESULTS: Forty-seven patients (43.9%) were found to have one of the MEFV mutations. Eight patients (7.5%) were homozygous for one mutation, 33 (30.8%) were heterozygous for one and six (5.6%) were compound heterozygous for two mutations. There were no age and sex differences between patients with or without mutations. Scrotal involvement was statistically more frequent in patients with mutations. Leucocyte counts, erythrocyte sedimentation rates, serum C-reactive protein (CRP) concentrations, number of patients with increased CRP levels and number of patients with increased immunoglobulin A concentrations were found to be higher in patients with MEFV mutations. p.M694V was the most frequent mutation and was found to have effects on clinical and laboratory findings in children with HSP. Fifteen patients were started on colchicine with the diagnosis of familial Mediterranean fever (FMF).

CONCLUSION: MEFV mutations are more frequent in HSP than in the general population, and mutation carriers may have more severe clinical findings with

higher inflammatory response, suggesting a dysregulation of the inflammatory response because of defective gene encoding the protein pyrine. Investigation of these mutations may be beneficial to follow-up the susceptible patients more closely leading to early diagnosis and treatment of FMF.

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DOI: 10.1111/j.1651-2227.2011.02143.x

PMID: 21231959 [Indexed for MEDLINE]

3112. Rheumatol Int. 2012 Apr;32(4):895-908. doi: 10.1007/s00296-010-1699-4. Epub 2011 Jan 13.

The prevalences of some rheumatic diseases in western Turkey: Havsa study.

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To study the prevalence major rheumatic diseases in western Turkey. This survey was conducted in Havsa which have a total population of 18,771. Physicians and interns visited every household, interviewed face to face a questionnaire about the symptoms of rheumatic disorders. The individuals replied positively to any question were examined at the nearest health center. Those have no objective findings related to any rheumatic diseases were excluded. People could not be clinically diagnosed were asked to come to the hospital for further evaluation. A total 17,835 of 18,771 residents participated. We estimated the prevalence of Behçet's Disease (BD) as 0.019%; ankylosing spondylitis: 0.120%; rheumatoid arthritis: 0.321%; knee osteoarthritis (OA): 5.351%; hand OA: 1.110%; hand and knee OA: 1.958%; total OA: 8.420%; primary Raynaud's: 1.192%; psoriasis: 0.424 %; psoriatic arthritis: 0.050%; rheumatic fever: 0.318%; rheumatic heart disease: 0.200%; inflammatory bowel disease: 0.023%; lupus: 0.059%; gout: 0.018%; systemic sclerosis: 0.022%; juvenile rheumatoid arthritis: 0.032%; temporal arteritis: 0.020%, and familial Mediterranean fever (FMF) as 0.006%. Figures were adjusted for age-sex of the general Turkish population. The prevalence's of BD and FMF are

considerably lower in Havsa as compared to other regions in Turkey.

DOI: 10.1007/s00296-010-1699-4

PMID: 21229358 [Indexed for MEDLINE]

3113. Arthritis Rheum. 2011 Apr;63(4):1141-50. doi: 10.1002/art.30237.

Long-term clinical profile of children with the low-penetrance R92Q mutation of the TNFRSF1A gene.

Pelagatti MA(1), Meini A, Caorsi R, Cattalini M, Federici S, Zulian F, Calcagno G, Tommasini A, Bossi G, Sormani MP, Caroli F, Plebani A, Ceccherini I, Martini A, Gattorno M.

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**OBJECTIVE:** To analyze the long-term impact of the R92Q mutation of TNFRSF1A in children with periodic fever, in comparison with children with tumor necrosis factor receptor-associated periodic syndrome (TRAPS) with TNFRSF1A structural mutations and children with periodic fever of unknown origin fulfilling the criteria for periodic fever, aphthosis, pharyngitis, and adenitis syndrome (PFAPA).

**METHODS:** The extracellular region of TNFRSF1A was analyzed in 720 consecutive children with periodic fever, using denaturing high-performance liquid chromatography and DNA sequencing. Followup data on 11 pediatric patients with TNFRSF1A structural mutations (cysteine or T50M), 23 pediatric patients with an R92Q substitution, and 64 pediatric patients with PFAPA were collected during routine clinic visits. The 50-item Child Health Questionnaire was used to assess health-related quality of life (HRQOL).

**RESULTS:** The frequency of typical TRAPS-related clinical manifestations was significantly lower and the impact of the disease on HRQOL was significantly reduced in patients with the R92Q mutation compared with TRAPS patients carrying structural mutations of TNFRSF1A. Followup data on 11 TRAPS patients with TNFRSF1A structural mutations (mean followup 7.9 years), 16 patients with the R92Q substitution (mean followup 7.3 years), and 64 patients with PFAPA (mean followup 5.2 years) were available. Patients with R92Q mutations and patients with PFAPA displayed a higher rate of self-resolution or amelioration of the fever episodes

than did TRAPS patients with structural mutations.

CONCLUSION: Although some cases may progress to a more chronic disease course, the majority of children with an R92Q mutation of the TNFRSFA1 gene show a milder disease course than that in children with TNFRSFA1 structural mutations and have a high rate of spontaneous resolution and amelioration of the recurrent fever episodes.

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DOI: 10.1002/art.30237

PMCID: PMC3112258

PMID: 21225694 [Indexed for MEDLINE]

3114. Arthritis Rheum. 2011 Apr;63(4):1151-5. doi: 10.1002/art.30215.

Role of interleukin-6 in a patient with tumor necrosis factor receptor-associated periodic syndrome: assessment of outcomes following treatment with the anti-interleukin-6 receptor monoclonal antibody tocilizumab.

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In this report, we describe treatment outcomes in the first case of a patient with tumor necrosis factor receptor-associated periodic syndrome (TRAPS) treated with the anti-interleukin-6 (anti-IL-6) receptor monoclonal antibody tocilizumab. Since IL-6 levels are elevated in TRAPS, we hypothesized that tocilizumab might be effective. The patient, a 52-year-old man with lifelong TRAPS in whom treatment with etanercept and anakinra had failed, was administered tocilizumab for 6 months, and the therapeutic response was assessed by measurement of monocyte CD16 expression and cytokine levels. Following treatment, the evolving acute attack was aborted and further attacks of TRAPS were prevented. The patient did not require corticosteroids and showed significant clinical improvement in scores for pain, stiffness, and well-being. Moreover, the acute-phase response diminished significantly with treatment. Monocyte CD16 expression was reduced and the numbers of circulating CD14+CD16+ and CD14++CD16- monocytes were transiently

decreased. However, cytokine levels were not reduced. This case supports the notion of a prominent role for IL-6 in mediating the inflammatory attacks in TRAPS, but blockade of IL-6 did not affect the underlying pathogenesis. These preliminary findings require confirmation.

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DOI: 10.1002/art.30215

PMID: 21225679 [Indexed for MEDLINE]

3115. Pediatrics. 2011 Feb;127(2):e489-93. doi: 10.1542/peds.2010-1218. Epub 2011 Jan 10.

Recurrent fever syndromes in patients after recovery from Kawasaki syndrome.

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The recurrence of fever in a child with a history of Kawasaki syndrome (KS) poses a dilemma for clinicians who must consider the possibility of recurrent KS. In this report we present the cases of 4 patients who presented with classical symptoms of KS, were successfully treated with intravenous immunoglobulin, and later experienced a reappearance of inflammatory symptoms in a pattern consistent with a recurrent fever syndrome. The association of these syndromes within the same patient suggests that some patients may have a genetic propensity toward altered immune responses and autoinflammatory syndromes. We propose that these 2 syndromes exist within a family of febrile disorders related to innate immune dysregulation.

DOI: 10.1542/peds.2010-1218

PMCID: PMC3025426

PMID: 21220401 [Indexed for MEDLINE]

3116. Annu Rev Immunol. 2011;29:185-214. doi: 10.1146/annurev-immunol-031210-101340.

Nucleic acid recognition by the innate immune system.

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Receptors of the innate immune system recognize conserved microbial features and provide key signals that initiate immune responses. Multiple transmembrane and cytosolic receptors have evolved to recognize RNA and DNA, including members of the Toll-like receptor and RIG-I-like receptor families and several DNA sensors. This strategy enables recognition of a broad range of pathogens; however, in some cases, this benefit is weighed against the cost of potential self recognition. Recognition of self nucleic acids by the innate immune system contributes to the pathology associated with several autoimmune or autoinflammatory diseases. In this review, we highlight our current understanding of nucleic acid sensing by innate immune receptors and discuss the regulatory mechanisms that normally prevent inappropriate responses to self.

DOI: 10.1146/annurev-immunol-031210-101340

PMID: 21219183 [Indexed for MEDLINE]

3117. Arthritis Res Ther. 2010;12(6):222. doi: 10.1186/ar3198. Epub 2010 Dec 17.

Spleen tyrosine kinase inhibition in the treatment of autoimmune, allergic and autoinflammatory diseases.

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Spleen tyrosine kinase (Syk) is involved in the development of the adaptive immune system and has been recognized as being important in the function of additional cell types, including platelets, phagocytes, fibroblasts, and

osteoclasts, and in the generation of the inflammasome. Preclinical studies presented compelling evidence that Syk inhibition may have therapeutic value in the treatment of rheumatoid arthritis and other forms of arthritis, systemic lupus erythematosus, autoimmune cytopenias, and allergic and autoinflammatory diseases. In addition, Syk inhibition may have a place in limiting tissue injury associated with organ transplant and revascularization procedures. Clinical trials have documented exciting success in the treatment of patients with rheumatoid arthritis, autoimmune cytopenias, and allergic rhinitis. While the extent and severity of side effects appear to be limited so far, larger studies will unravel the risk involved with the clinical benefit.

DOI: 10.1186/ar3198

PMCID: PMC3046528

PMID: 21211067 [Indexed for MEDLINE]

3118. *Pediatr Ann.* 2011 Jan;40(1):48-54. doi: 10.3928/00904481-20101214-10.

Periodic Fever syndromes.

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DOI: 10.3928/00904481-20101214-10

PMID: 21210600 [Indexed for MEDLINE]

3119. *World J Pediatr.* 2011 Nov;7(4):365-7. doi: 10.1007/s12519-011-0255-y. Epub 2011 Jan 5.

Familial Mediteranean fever with protein-losing enteropathy due to constrictive pericarditis.

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**BACKGROUND:** Constrictive pericarditis (CP) represents a rare cause of protein-losing enteropathy (PLE) resulting from intestinal lymphangiectasia (IL). In this report, we describe an 8-year-old Turkish boy with IL and PLE secondary to CP.

**METHODS:** The boy was introduced to our clinic due to bilateral pretibial edema and swelling of the eyelids caused by hypoproteinemia. Physical examination revealed a distended right jugular vein. Laboratory investigation revealed PLE with fecal concentration of alpha-1 antitrypsin of 4.87 mg/g. Histopathologic examination of random biopsies obtained from the duodenum revealed markedly dilated lymphatics compatible with IL. Constrictive pericarditis was diagnosed by tagged cine cardiac magnetic resonance imaging.

**RESULTS:** Pericardiectomy was performed for the patient. Genetic analysis was done and heterozygous mutation E148Q was detected as a disease-causing Mediterranean fever (MEFV) mutation. Colchicine was started after the operation. Six months after the initiation of regular colchicine therapy, echocardiography revealed disappearance of CP.

**CONCLUSION:** This is the first reported case of PLE with a distended right jugular vein due to CP secondary to familial Mediterranean fever associated with E148Q heterozygosity in the MEFV gene.

DOI: 10.1007/s12519-011-0255-y

PMID: 21210266 [Indexed for MEDLINE]

3120. Turk Kardiyol Dern Ars. 2010 Jul;38(5):379.

Case images: a pericardial cyst due to familial Mediterranean fever.

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PMID: 21200112 [Indexed for MEDLINE]



3121. Appl Clin Genet. 2011 Jan 26;4:21-7. doi: 10.2147/TACG.S8146. Print 2011.

Interleukin-1 $\beta$  inhibitors for the treatment of cryopyrin-associated periodic syndrome.

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Cryopyrin-associated periodic syndrome (CAPS) comprises a group of rare, but severe, inherited autoinflammatory disorders associated with aberrant secretion of interleukin (IL)-1. These distinct conditions of autoinflammatory origin include Muckle-Wells syndrome, familial cold autoinflammatory syndrome, and neonatal-onset multisystem inflammatory disease (NOMID), which is also referred to as chronic infantile neurologic cutaneous and articular syndrome. Recently, this group of diseases has been associated with mutations in the NLRP3 gene that encodes for the protein cryopyrin, a component of the inflammasome complex that regulates the maturation and secretion of inflammatory cytokine IL-1 $\beta$ . Immune cells from patients with NOMID secrete higher levels of active IL-1 $\beta$  compared with monocytes from healthy subjects. Overproduction of IL-1 is believed to promote aberrant inflammatory response in CAPS patients. Evidence supporting the clinical value of IL-1 $\beta$  in CAPS has been provided from the complete response of patients after treatment with IL-1 blocking agents.

DOI: 10.2147/TACG.S8146

PMCID: PMC3681175

PMID: 23776364

3122. Case Rep Rheumatol. 2011;2011:134106. doi: 10.1155/2011/134106. Epub 2012 Jan 15.

Etanercept-induced myelopathy in a pediatric case of blau syndrome.

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Blau syndrome is a rare autoinflammatory disorder within the group of pediatric granulomatous diseases. Mutations in nucleotide-binding oligomerization domain 2 (NOD2/CARD15) are responsible for this condition, which has an autosomal dominant pattern of inheritance and variable expressivity. The clinical picture includes arthritis, uveitis, skin rash, and granulomatous inflammation. Central nervous system involvement is seldom reported, although some isolated cases of seizures, neurosensorial hearing loss, and transient cranial nerve palsy have been described. Treatment consists of nonsteroidal anti-inflammatory drugs, corticosteroids, and immunosuppressive agents, among which anti-tumor-necrosis-factor-alpha (TNF- $\alpha$ ) biologic agents, such as etanercept, play an important role. Among the major adverse effects of TNF- $\alpha$  inhibitors, demyelinating disease, multiple sclerosis, and acute transverse myelitis have been reported in adults. We describe a case of pediatric Blau syndrome affected by etanercept-induced myelopathy, manifesting as a clinical syndrome of transverse myelitis. The patient experienced rapid recovery after etanercept was discontinued. To our knowledge, this is the first such case reported in the literature and, possibly, the one with the latest onset, following 8 years of treatment. We discuss the etiopathogenic mechanisms of this reaction and possible explanations for the imaging findings.

DOI: 10.1155/2011/134106

PMCID: PMC3420458

PMID: 22937436

3123. J Hum Genet. 2011 Feb;56(2):169-71. doi: 10.1038/jhg.2010.160. Epub 2010 Dec 23.

Familial Mediterranean fever with a single MEFV mutation: can a deletion resulting in  $\alpha$ -thalassemia be the cause?

Aslan D.

DOI: 10.1038/jhg.2010.160

PMID: 21179105 [Indexed for MEDLINE]

3124. J Dtsch Dermatol Ges. 2011 Mar;9(3):232-46. doi: 10.1111/j.1610-0387.2010.07580.x. Epub 2010 Dec 22.

Skin manifestations in autoinflammatory syndromes.

[Article in English, German]

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Autoinflammatory diseases encompass a group of inflammatory diseases that are non-infectious, non-allergic, non-autoimmune and non-immunodeficient. The term was initially coined for a small group of familial periodic fever syndromes of which familial Mediterranean fever (FMF) is the most common and best known. Genetic and molecular analyses demonstrated for the majority of these diseases an impairment of inflammasomes to cause an increased activity of an interleukin-1-dependent inflammatory response. Over the last years an increasing number of either rare hereditary syndromes or acquired common diseases could be summarized under the designation of autoinflammatory disease, thus creating an emerging new rubric of inflammatory diseases. Many of them display cutaneous manifestations as both concomitant or more rarely main symptoms. To name some of them like erysipelas-like erythema in FMF; urticaria-like rashes in tumor necrosis factor receptor 1- or cryopyrin-associated periodic syndromes (TRAPS, CAPS), hyperimmunoglobulin D syndrome (HIDS) or Schnitzler syndrome; pyoderma gangrenosum and acne in PAPA syndrome; or behçetoid aphthous ulcerations in HIDS and PFAPA syndrome. Based on the new insights into pathogenesis one increasingly realizes the good response of these diseases to IL-1 antagonist therapies.

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DOI: 10.1111/j.1610-0387.2010.07580.x

PMID: 21176105 [Indexed for MEDLINE]

3125. Ann Rheum Dis. 2011 Aug;70(8):1511-2. doi: 10.1136/ard.2010.143438. Epub 2010 Dec

Favourable and sustained response to anakinra in tumour necrosis factor receptor-associated periodic syndrome (TRAPS) with or without AA amyloidosis.

Obici L, Meini A, Cattalini M, Chicca S, Galliani M, Donadei S, Plebani A, Merlini G.

DOI: 10.1136/ard.2010.143438

PMID: 21173015 [Indexed for MEDLINE]

3126. Clin Rev Allergy Immunol. 2013 Feb;44(1):6-13. doi: 10.1007/s12016-010-8219-x.

Role of autoimmunity and autoinflammation in the pathogenesis of idiopathic recurrent pericarditis.

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Idiopathic recurrent pericarditis is the most common and troublesome complication of acute pericarditis affecting about one third of such patients. The pericardium may be involved in different systemic autoimmune diseases (i.e., systemic lupus erythematosus, rheumatoid arthritis, progressive systemic sclerosis, mixed connective tissue disease, Sjogren's Syndrome, polyarteritis, giant cell arteritis, other systemic vasculitides) either in a symptomatic form (usually during the active phase of the disease) or as asymptomatic pericardial effusion. Moreover, idiopathic recurrent pericarditis mimicks hereditary periodic fever syndromes (HPFSs). HPFSs are a group of disorders characterized by primary dysfunction of the innate immune system mostly caused by mutations of genes involved in the regulation or activation of the inflammatory response, without any apparent involvement of antigen-specific T cells or significant production of autoantibodies. These disorders usually manifest in the pediatric population, with onset ranging from the first hours to the first decade of life, however a limited number of patients experience disease onset during adulthood.

DOI: 10.1007/s12016-010-8219-x  
PMID: 21170606 [Indexed for MEDLINE]

3127. An Pediatr (Barc). 2011 Mar;74(3):194.e1-16. doi: 10.1016/j.anpedi.2010.09.022. Epub 2010 Dec 18.

[Consensus Document on the differential diagnosis and therapeutic approach to recurrent fever by the Paediatric Infectology Society and the Paediatric Rheumatology Society].

[Article in Spanish]

Calvo Rey C(1), Soler-Palacín P, Merino Muñoz R, Saavedra Lozano J, Antón López J, Aróstegui JI, Blázquez Gamero D, Martín-Nalda A, Juan M, Méndez M, Piñeiro Perez R, Calvo I; Sociedad de Infectología Pediátrica; Sociedad de Reumatología Pediátrica.

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Recurrent fever is a relatively common problem during childhood. Diagnosis is often easy and related to mild viral infections. However a small proportion of these cases originate from an underlying non-infectious process that is generally difficult to diagnose. In this paper we describe the differential diagnosis of recurrent or periodic fever versus other processes, with especial attention to autoinflammatory disorders (AD). AD are alterations of innate immunity, and they have been recently classified as an immunodeficiency. Anyhow, since infections are not present, these processes are different to the classic primary immunodeficiency. An important part of AD is of known genetic aetiology. The symptoms originate from an underlying inflammatory process and can have different clinical expressions. One of the most relevant groups is the hereditary syndromes of periodic fever. This group of diseases associates recurrent fever and several clinical symptoms with a relative periodicity, separated by intervals free or almost free of symptoms. We include the diagnostic criteria for some processes as well as the characteristics that should, eventually, lead to a genetic study. Although treatment should be individualised, we also include some general

recommendations.

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DOI: 10.1016/j.anpedi.2010.09.022

PMID: 21169071 [Indexed for MEDLINE]

3128. Hum Immunol. 2011 Mar;72(3):269-72. doi: 10.1016/j.humimm.2010.12.007. Epub 2010 Dec 14.

Association analysis of Toll-like receptor 7 gene polymorphisms and Behçet's disease in Japanese patients.

Sada T(1), Ota M, Katsuyama Y, Meguro A, Nomura E, Uemoto R, Nishide T, Okada E, Ohno S, Inoko H, Mizuki N.

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Action of Toll-like receptors (TLRs) is deeply associated with defense mechanisms of the innate and adaptive immune responses to microbial pathogens. There have been reports of genetic polymorphisms within the TLR7 gene being closely related to a variety of inflammatory and infectious diseases. Behçet's disease (BD) is an autoinflammatory disease, and the pathogenesis has yet to be fully discovered. We investigated whether polymorphisms of Toll-like receptor 7 (TLR7) are associated with BD by analyzing the frequency of eight single nucleotide polymorphisms (SNPs) within 200 Japanese BD patients and 102 randomized controls. We genotyped nine SNPs in the TLR7 gene and assessed the allele/genotype diversity between cases and controls for all SNPs. In all eight SNPs, statistically significant differences were not observed between cases and controls.

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DOI: 10.1016/j.humimm.2010.12.007

PMID: 21167247 [Indexed for MEDLINE]

3129. Trends Mol Med. 2011 Feb;17(2):57-64. doi: 10.1016/j.molmed.2010.11.001. Epub 2010 Dec 14.

Inflammasomes and autoimmunity.

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The NOD-like receptor (NLR) family members are cytosolic sensors of microbial components and danger signals. A subset of NLRs control inflammasome assembly that results in caspase-1 activation and, in turn, IL-1 $\beta$  and IL-18 production. Excessive inflammasome activation can cause autoinflammatory disorders, including the hereditary periodic fevers. Autoinflammatory and autoimmune diseases form a disease spectrum of aberrant, immune-mediated inflammation against self, through innate and adaptive immunity. However, the role of inflammasomes in autoimmune disease is less clear than in autoinflammation, despite the numerous effects IL-1 $\beta$  and IL-18 can have on shaping adaptive immunity. We summarize the role of inflammasomes in autoimmune disorders, highlight the need for a better understanding of inflammasomes in these conditions and offer suggestions for future research directions.

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DOI: 10.1016/j.molmed.2010.11.001

PMCID: PMC3057120

PMID: 21163704 [Indexed for MEDLINE]

3130. Clin Exp Rheumatol. 2010 Jul-Aug;28(4 Suppl 60):S103-4. Epub 2010 Sep 24.

Scleritis and sudden hearing loss associated with familial Mediterranean fever.

Akalin T, Demirag MD, Tezcan ME, Ozturk MA.

PMID: 20868588 [Indexed for MEDLINE]

3131. Clin Exp Rheumatol. 2010 Jul-Aug;28(4 Suppl 60):S101. Epub 2010 Sep 24.

Female reproductive dysfunction in familial Mediterranean fever patients with and without colchicine treatment.

Cerquaglia C, Verrecchia E, Fonnesu C, Giovinale G, Marinaro A, de Socio G, Manna R.

PMID: 20868586 [Indexed for MEDLINE]

3132. Clin Exp Rheumatol. 2010 Jul-Aug;28(4 Suppl 60):S99. Epub 2010 Sep 24.

Protracted synovitis without systemic manifestations in familial Mediterranean fever (FMF).

Migita K, Torigoshi T, Motokawa S, Ito M, Miyashita T, Izumi Y, Yasunami M.

PMID: 20868584 [Indexed for MEDLINE]

3133. Clin Exp Rheumatol. 2010 Jul-Aug;28(4 Suppl 60):S91. Epub 2010 Sep 24.

Familial Mediterranean fever diagnosed in an elderly patient.

Cantarini L, Capecchi PL, Lucherini OM, Laghi Pasini F, Galeazzi M.

PMID: 20868579 [Indexed for MEDLINE]

3134. Clin Exp Rheumatol. 2010 Jul-Aug;28(4 Suppl 60):S67-75. Epub 2010 Sep 24.



The prevalence of Behçet's syndrome, familial Mediterranean fever, HLA-B51 and MEFV gene mutations among ethnic Armenians living in Istanbul, Turkey.

Seyahi E(1), Tahir Turanli E, Mangan MS, Celikyapi G, Oktay V, Cevirgen D, Kuzuoglu D, Ozoglu S, Yazici H.

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**OBJECTIVES:** We investigated the prevalence of Behçet's syndrome (BS) among the ethnic Armenians in Istanbul using Familial Mediterranean Fever (FMF) as a comparator disease. We also studied HLA-B51 and MEFV mutations among a group of healthy Armenians and a non-Armenian population.

**METHODS:** The prevalence study was conducted in 2 parts in the Armenian primary schools in Istanbul, using the enrolled students as index cases to study the core family. In Part I, a questionnaire seeking only whether either parent had previously been diagnosed as having BS or FMF by a physician was distributed to a total of 1873 index students registered at 10 schools. A total of 1380 parents filled in the questionnaire, yielding a response rate of 37% (1380 / 3746). In Part II, eight schools participated with a response rate of 83 % (1183/1428). Also, genomic DNA samples of 108 healthy (14 M/94 F) Armenians and 97 (45 M/ 52 F) non-Armenians, were studied for HLAB51 and MEFV gene mutations.

**RESULTS:** In Part I, none of the parents turned out to have been diagnosed as BS, whereas a total of 12 / 1380 (870/105) had been diagnosed as FMF. In the second part the estimated prevalence of BS was 90 /105 and that of FMF was 760/ 105. HLA-B51 carrier rate was found to be similar between the Armenian (27%, 29/108) and the non-Armenian participants (19%, 18/97), ( $p=0.158$ ). Overall carrier rate of MEFV gene mutations was significantly higher in the Armenian group (36% vs. 20%,  $p=0.015$ ).

**CONCLUSIONS:** The genetic load for FMF is considerably higher among the Armenians when compared to the load for BS among the same ethnic group. On the other hand, the rather low frequency of BS among the Armenians when compared to the frequency among the general population living in the same environment is further evidence for a genetic predisposition to BS. HLA- B51 does not seem to play a dominant role in the said predisposition. Finally, as we have used an unorthodox epidemiological methodology in data collection our results might need to be further verified by more conventional methods.

PMID: 20868574 [Indexed for MEDLINE]

3135. Clin Exp Rheumatol. 2010 Jul-Aug;28(4 Suppl 60):S58-61. Epub 2010 Sep 24.

Anti-cyclic citrullinated peptides positivity rate in patients with familial Mediterranean fever.

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**OBJECTIVES:** To investigate the prevalence and levels of anti-cyclic citrullinated peptide antibodies (anti-CCP) in patients with familial Mediterranean fever (FMF) with and without arthritis.

**METHODS:** Eighty-three patients with FMF and 43 healthy controls were included in the study. Thirty seven FMF patients had a history of arthritis, and 46 patients did not. Serum antibodies directed to the anti-CCP were assessed with a commercial enzyme-linked immunosorbent assay (ELISA) kit. Values <20U were considered negative, between 20 and 39U low, 40-99U moderate, and >100U high positive.

**RESULTS:** Positivity rate of anti-CCP in the whole FMF group (14.5%) was three-fold higher than the control group (4.7%). However, the difference failed to achieve a statistically significant level ( $p=0.09$ ). Anti-CCP levels were  $21\pm30.1$  in patients with arthritis and  $13.1\pm10.3$  in the non arthritic group ( $p<0.05$ ). Anti-CCP positivity rates were 10/37 (27%) in patients with arthritis and 2/46 (4.3%) in patients without arthritis ( $p<0.005$ ). Five FMF patients with arthritis (13.5%) had moderate-high anti-CCP levels (>40U/ml). Anti-CCP levels were between 20-39U/ ml in 2FMF patients without arthritis and in 2 healthy controls. Anti-CCP positivity rate is higher in FMF patients with arthritis (27%) than healthy controls (4.7%) ( $p<0.005$ ).

**CONCLUSIONS:** Anti-CCP prevalence is higher in FMF patients with arthritis than without arthritis, and that a significant proportion of FMF patients with arthritis (13.5%) had moderate-high titers of anti-CCP. Therefore, anti-CCP antibodies may not be a reliable indicator to differentiate between FMF arthritis and rheumatoid arthritis.

PMID: 20868572 [Indexed for MEDLINE]

3136. Clin Exp Rheumatol. 2010 Jul-Aug;28(4 Suppl 60):S6-8. Epub 2010 Sep 23.

Behçet's disease and other autoinflammatory conditions: a brief account of a decade.

Talarico R, Marconcini L, Ben-Chetrit E, Yazici H.

PMID: 20868562 [Indexed for MEDLINE]

3137. J Rheumatol. 2011 Mar;38(3):516-8. doi: 10.3899/jrheum.100718. Epub 2010 Dec 15.

Anti-interleukin 1 treatment for patients with familial Mediterranean fever resistant to colchicine.

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**OBJECTIVE:** Familial Mediterranean fever (FMF) is a recessively inherited autoinflammatory disorder characterized by recurrent attacks of fever and serositis. Although colchicine is the standard therapy for preventing attacks and suppressing inflammation, 5%-10% of compliant patients are colchicine-resistant. We report the effect of anti-tumor necrosis factor therapy (etanercept) and anti-interleukin 1 (IL-1) treatment (anakinra) in 6 cases resistant to colchicine therapy.

**METHODS:** Five children and an adult patient (3 female, 3 male) who were experiencing at least 2 attacks per month and had consistently elevated C-reactive protein levels despite regular colchicine therapy were given either etanercept or anakinra.

**RESULTS:** Although etanercept lowered the number of attacks (from 3-4 attacks per

month to 2 attacks per month), attacks still recurred and acute-phase reactants remained high in 2 patients; thus etanercept was considered ineffective. All 4 patients were switched to anakinra. In 2 patients anakinra completely resolved clinical and laboratory findings. The other 4 patients have been switched to anakinra recently; to date anakinra has reduced the number of attacks (to < 1 per month) and lowered the levels of acute-phase reactants.

CONCLUSION: In this small series, anakinra was successful in suppressing inflammation and decreasing the number of attacks in FMF. This may be explained by the role of pyrin in the regulation of IL-1 $\beta$  activation.

DOI: 10.3899/jrheum.100718

PMID: 21159830 [Indexed for MEDLINE]

3138. J Intern Med. 2011 Jan;269(1):16-28. doi: 10.1111/j.1365-2796.2010.02313.x.

Blocking interleukin-1 $\beta$  in acute and chronic autoinflammatory diseases.

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An expanding spectrum of acute and chronic inflammatory diseases is considered 'autoinflammatory' diseases. This review considers autoinflammatory diseases as being distinct from 'autoimmune' diseases. Autoimmune diseases are associated with dysfunctional T cells and treated with 'biologicals', including antitumour necrosis factor $\alpha$ , CTLA-Ig, anti-IL-12/23, anti-CD20, anti-IL-17 and anti-IL-6 receptor. In contrast, autoinflammatory diseases are uniquely attributed to a dysfunctional monocyte caspase 1 activity and secretion of IL-1 $\beta$ ; indeed, blocking IL-1 $\beta$  results in a rapid and sustained reduction in the severity of most autoinflammatory diseases. Flares of gout, type 2 diabetes, heart failure and smouldering multiple myeloma are examples of seemingly unrelated diseases, which are uniquely responsive to IL 1 $\beta$  neutralization.

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DOI: 10.1111/j.1365-2796.2010.02313.x

PMCID: PMC3074355

PMID: 21158974 [Indexed for MEDLINE]

3139. Curr Opin Mol Ther. 2010 Dec;12(6):755-69.

Gevokizumab, an anti-IL-1 $\beta$  mAb for the potential treatment of type 1 and 2 diabetes, rheumatoid arthritis and cardiovascular disease.

Geiler J(1), McDermott MF.

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The inflammatory cytokine IL-1 $\beta$  has an essential role in the innate immune response. High levels of IL-1 $\beta$  have been implicated in the development of many diseases, including type 1 and 2 diabetes (T1D and T2D), rheumatoid arthritis (RA) and cardiovascular disease. XOMA is developing gevokizumab (XOMA-052), an IgG2 humanized mAb against human IL-1 $\beta$ , for the potential treatment of these diseases. Gevokizumab has a high affinity for IL-1 $\beta$  and a long t<sub>1/2</sub>, which would allow for once-monthly dosing and offer a considerable advantage for patients over agents requiring more frequent dosing. Data from preclinical studies and clinical trials suggest that gevokizumab is a potentially effective and well-tolerated treatment for the indicated diseases. At the time of publication, phase II clinical trials were ongoing in patients with T1D, T2D and RA, with the T2D trials assessing key cardiovascular markers. Following promising data from a recent pilot trial, XOMA was also planning a phase I/II trial of gevokizumab for the potential treatment of uveitis in patients with the vasculitic inflammatory disorder Behçet's disease and the autoinflammatory conditions familial cold autoinflammatory syndrome and Muckle-Wells syndrome.

PMID: 21154167 [Indexed for MEDLINE]

3140. Mol Biol Rep. 2011 Nov;38(8):5065-9. doi: 10.1007/s11033-010-0652-7. Epub 2010 Dec 14.

## Common Familial Mediterranean Fever gene mutations in a Turkish cohort.

Dundar M(1), Emirogullari EF, Kiraz A, Taheri S, Baskol M.

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Familial Mediterranean Fever (FMF) is an autosomal recessive autoinflammatory disorder with the responsible gene of MEFV which primarily affects Jewish, Armenian, Turkish and Arab populations. The FMF gene (MEFV) has recently been cloned to chromosome 16 p, which encodes pyrin. In the present study, we enrolled 2,067 unrelated patients with the suspicion of FMF in Middle Anatolia between the years 2006-2009 and identified the 12 MEFV mutations. DNA was amplified by PCR and subjected to reverse hybridization for the detection of MEFV gene mutations. Among the 2,067 patients, 866 (41.9%) were males and 1,201 (58.1%) were females. The mutations were homozygous in 176 (16.85%) patients, compound heterozygous in 314 (30.1%) patients, heterozygous in 546 (52.25%) patients and the other forms of mutations were found in 8 patients (0.76%). No mutation was detected in 1,023 (49.5%) patients. The most frequent mutations were M694V, M680I (G/C), E148Q and V726A. We could not find any significant differences between the two common mutations according to the gender. The high incidence of MEFV gene mutations in the Turkish population indicated that newborn screening may be discussed in the future. Because of the ethnic origin of Anatolia, larger serial analyses are necessary to investigate the rate and coexistence of these mutations.

DOI: 10.1007/s11033-010-0652-7

PMID: 21153919 [Indexed for MEDLINE]

3141. Adv Exp Med Biol. 2011;691:461-70. doi: 10.1007/978-1-4419-6612-4\_47.

Functional consequences of disease-associated mutations in TNFR1 elucidated by transcriptome analysis.

Rebelo SL(1), Radford PM, Bainbridge SE, Todd I, Tighe PJ.

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DOI: 10.1007/978-1-4419-6612-4\_47

PMID: 21153350 [Indexed for MEDLINE]

3142. Adv Exp Med Biol. 2011;691:409-19. doi: 10.1007/978-1-4419-6612-4\_43.

Lessons from anti-TNF biologics: infliximab failure in a TRAPS family with the T50M mutation in TNFRSF1A.

Nedjai B(1), Quillinan N, Coughlan RJ, Church L, McDermott MF, Hitman GA, Turner MD.

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DOI: 10.1007/978-1-4419-6612-4\_43

PMID: 21153346 [Indexed for MEDLINE]

3143. Rheumatology (Oxford). 2011 Mar;50(3):624-6. doi: 10.1093/rheumatology/keq405. Epub 2010 Dec 11.

Familial Mediterranean fever caused by homozygous E148Q mutation complicated by Budd-Chiari syndrome and polyarteritis nodosa.

Standing AS, Eleftheriou D, Lachmann HJ, Brogan PA.

Comment in

Rheumatology (Oxford). 2011 Jul;50(7):1348-9; author reply 1349.

DOI: 10.1093/rheumatology/keq405

PMID: 21149248 [Indexed for MEDLINE]

3144. Rheumatology (Oxford). 2011 Jan;50(1):237-42. doi: 10.1093/rheumatology/keq270.

Translational research network and patient registry for auto-inflammatory diseases.

Lainka E(1), Bielak M, Hilger V, Basu O, Neudorf U, Wittkowski H, Holzinger D, Roth J, Niehues T, Foell D.

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**OBJECTIVE:** Auto-inflammatory diseases (AIDs) are characterized by recurrent self-limiting systemic inflammation. In a multicentre effort, we set out to register genetic, epidemiological and clinical features as well as prognostic factors of these diseases by prospective longitudinal and long-term documentation, in order to define novel AIDs and to better understand treatment responses and outcome.

**METHODS:** In 2009, a federally funded clinical and research consortium (AID-Net) was established, including an online registry for AIDs (<http://www.aid-register.uk-essen.de>). Inclusion criteria are disease-associated mutations for hereditary periodic fever syndromes [FMF, hyperimmunoglobulinaemia D and periodic fever syndrome (HIDS), TNF receptor 1-associated periodic syndrome (TRAPS) and cryopyrin-associated periodic syndrome (CAPS)], or, alternatively, clinically confirmed AID, systemic-onset JIA (SoJIA) and periodic fever, aphthous stomatitis, pharyngitis and adenopathy (PFAPA) syndrome with unknown genetic background. Patients were recruited to the registry and patient material was deposited in biomaterial banks (DNA/serum). In addition, basic research projects were initiated that focus on molecular mechanisms of AID.

**RESULTS:** During the first 9 months, 117 patients (65 males, 52 females; age 1-21 years) have been recorded and classified as FMF (n=84), HIDS (n=1), TRAPS (n=3) and CAPS (n=1); clinically confirmed AID (n=5); SoJIA (n=22); and PFAPA (n=1). One hundred and fifty blood samples of 18 patients were included in biomaterial banks.

**CONCLUSION:** Recruitment and follow-up of patients with AID will enable us to comprehensively address the correlation between clinical and epidemiological data, genetics and biomarkers. The translational approach may help to identify genetic or inflammatory markers relevant for the course and outcome of diseases.



DOI: 10.1093/rheumatology/keq270  
PMID: 21148158 [Indexed for MEDLINE]

3145. Arch Argent Pediatr. 2010 Oct;108(5):445-8. doi: 10.1590/S0325-00752010000500011.

[Periodic fever: a description of twelve patients with periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA)].

[Article in Spanish]

De Cunto C(1), Britos M, Eymann A, Deltetto N, Liberatore D.

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PFAPA is a periodic fever syndrome characterized by: fever, aphthous stomatitis, pharyngitis and cervical adenitis. It is one of the autoinflammatory syndromes, but yet of unknown etiology. Our aim is to report our experience, describe clinical manifestations, laboratory findings, relapses occurrence and response to treatment. We present 12 PFAPA patients. Median age at onset: 1.15 years, mean duration of febrile episodes: 4 days, and relapses at regular intervals. All children received prednisone (1-2 mg/kg/dose) one to two doses, 9 patients responded immediately after the first dose and all experienced a lower periodicity of attacks. PFAPA is the most frequent periodic fever syndrome. To our knowledge, there are no other local series of PFAPA patients published. Recognizing this syndrome will prevent from ordering unnecessary studies and will favor family coping.

DOI: 10.1590/S0325-00752010000500011  
PMID: 21132234 [Indexed for MEDLINE]

3146. Am J Hum Genet. 2010 Dec 10;87(6):866-72. doi: 10.1016/j.ajhg.2010.10.031.

PSMB8 encoding the  $\beta 5i$  proteasome subunit is mutated in joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy syndrome.

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We performed homozygosity mapping in two recently reported pedigrees from Portugal and Mexico with an autosomal-recessive autoinflammatory syndrome characterized by joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy (JMP). This revealed only one homozygous region spanning 2.4 Mb (5818 SNPs) on chromosome 6p21 shared by all three affected individuals from both families. We directly sequenced genes involved in immune response located in this critical region, excluding the HLA complex genes. We found a homozygous missense mutation c.224C>T (p.Thr75Met) in the proteasome subunit, beta-type, 8 (PSMB8) gene in affected patients from both pedigrees. The mutation segregated in an autosomal-recessive fashion and was not detected in 275 unrelated ethnically matched healthy subjects. PSMB8 encodes a catalytic subunit of the 20S immunoproteasomes called  $\beta 5i$ . Immunoproteasome-mediated proteolysis generates immunogenic epitopes presented by major histocompatibility complex (MHC) class I molecules. Threonine at position 75 is highly conserved and its substitution with methionine disrupts the tertiary structure of PSMB8. As compared to normal lymphoblasts, those from an affected patient showed significantly reduced chymotrypsin-like proteolytic activity mediated by immunoproteasomes. We conclude that mutations in PSMB8 cause JMP syndrome, most probably by affecting MHC class I antigen processing.

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DOI: 10.1016/j.ajhg.2010.10.031

PMCID: PMC2997366

PMID: 21129723 [Indexed for MEDLINE]

3147. PLoS One. 2010 Nov 23;5(11):e14096. doi: 10.1371/journal.pone.0014096.

Combined mutation and rearrangement screening by quantitative PCR high-resolution

melting: is it relevant for hereditary recurrent Fever genes?

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The recent identification of genes implicated in hereditary recurrent fevers has allowed their specific diagnosis. So far however, only punctual mutations have been identified and a significant number of patients remain with no genetic confirmation of their disease after routine molecular approaches such as sequencing. The possible involvement of sequence rearrangements in these patients has only been examined in familial Mediterranean fever and was found to be unlikely. To assess the existence of larger genetic alterations in 3 other concerned genes, MVK (Mevalonate kinase), NLRP3 (Nod like receptor family, pyrin domain containing 3) and TNFRSF1A (TNF receptor superfamily 1A), we adapted the qPCR-HRM method to study possible intragenic deletions and duplications. This single-tube approach, combining both qualitative (mutations) and quantitative (rearrangement) screening, has proven effective in Lynch syndrome diagnosis. Using this approach, we studied 113 unselected (prospective group) and 88 selected (retrospective group) patients and identified no intragenic rearrangements in the 3 genes. Only qualitative alterations were found with a sensitivity similar to that obtained using classical molecular techniques for screening punctual mutations. Our results support that deleterious copy number alterations in MVK, NLRP3 and TNFRSF1A are rare or absent from the mutational spectrum of hereditary recurrent fevers, and demonstrate that a routine combined method such as qPCR-HRM provides no further help in genetic diagnosis. However, quantitative approaches such as qPCR or SQF-PCR did prove to be quick and effective and could still be useful after non contributory punctual mutation screening in the presence of clinically evocative signs.

DOI: 10.1371/journal.pone.0014096

PMCID: PMC2990815

PMID: 21124859 [Indexed for MEDLINE]

2010 Jan 6.

Hemophagocytic syndrome in a child with severe Crohn's disease and familial Mediterranean fever.

Uslu N(1), Demir H, Balta G, Saltik-Temizel IN, Ozen H, Gürakan F, Yüce A.

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Hemophagocytic lymphohistiocytosis (HLH) is a rare, potentially fatal, severe condition of hyperinflammation caused by the uncontrolled proliferation of activated lymphocytes and histiocytes secreting high amounts of inflammatory cytokines. Here we report a fatal hemophagocytic syndrome in a 11-year-old boy with a diagnosis of both Crohn's disease receiving immunosuppressive therapy and familial Mediterranean fever. It is important to evaluate the patients with inflammatory bowel disease receiving immunosuppressive therapy presenting with unexplained fever, cytopenia, progression of organomegaly and biochemical changes for the investigation of HLH for diagnosis and treatment.

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DOI: 10.1016/j.crohns.2009.12.005

PMID: 21122524 [Indexed for MEDLINE]

3149. N Engl J Med. 2010 Dec 2;363(23):2267-8. doi: 10.1056/NEJMc1009918.

Colchicine's other indication--effect of FDA action.

Grody WW, Getzug T.

Comment on

N Engl J Med. 2010 Jun 3;362(22):2045-7.

DOI: 10.1056/NEJMc1009918

PMID: 21121853 [Indexed for MEDLINE]

3150. Curr Opin Chem Biol. 2011 Feb;15(1):149-55. doi: 10.1016/j.cbpa.2010.10.015. Epub 2010 Nov 4.

Redox active secondary metabolites.

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Various secondary metabolites from plants, bacteria and fungi are redox active and able to modulate the intracellular redox equilibrium in living cells. Many of these compounds behave as antioxidants, yet some of them also cause oxidative modifications, which may ultimately result in cell death. Natural isothiocyanates and xanthohumol, for instance, appear to act specifically in and against cells with a disturbed redox balance, such as certain cancer cells. Similarly, polysulfane and pyocyanin derivatives employ the glutathione antioxidant defense system of cells to generate a lethal cocktail of reactive oxygen species. Together, these redox-modulating metabolites provide promising new leads to target selectively certain cancer cells. They may also be useful in the treatment of autoinflammatory diseases.

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DOI: 10.1016/j.cbpa.2010.10.015

PMID: 21115388 [Indexed for MEDLINE]

3151. Scand J Gastroenterol. 2011 May;46(5):577-82. doi: 10.3109/00365521.2010.539254. Epub 2010 Nov 30.

F-18 FDG-PET/CT in aseptic abscesses with recurrent febrile abdominal pain.

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**OBJECTIVE:** Mendelian and complex autoinflammatory disorders frequently manifest as recurrent abdominal pain and fever. Diagnosis may be difficult and scant data are available about the interest of 2-deoxy-2-[18F]fluoro-D-glucose-positron emission tomography/computed tomography (FDG-PET/CT) in such conditions, particularly aseptic abscesses (AA).

**MATERIAL AND METHODS:** We analyzed five cases of AA in which FDG-PET/CT was performed at diagnosis (n = 2) and after a suspected relapse (n = 5). Follow-up FDG-PET/CT was performed in two patients 9 days and 6 weeks after the initiation of oral corticosteroids.

**RESULTS:** FDG-PET/CT showed intense uptake foci in the abdominal lymph nodes (n = 4), liver (n = 2) and spleen (n = 4) before treatment. A marked metabolic response was observed while patients were being treated. In a relapsing patient with abdominal pain but no raised CRP, although CT scan was unchanged, abnormal uptake of FDG was observed. By contrast, some lesions previously observed on CT scan displayed no fixation on new FDG-PET/CT and were suggestive of sequelae in three patients.

**CONCLUSION:** Although nonspecific, FDG-PET/CT may be an interesting tool for the diagnosis and management of recurrent and febrile abdominal pain in AA. At the time of relapse, it can differentiate between a sequela of previous flares and a new localization. It can be used for whole-body screening to look for other asymptomatic disease localizations.

DOI: 10.3109/00365521.2010.539254

PMID: 21114433 [Indexed for MEDLINE]

3152. NDT Plus. 2010 Dec;3(6):599-600. doi: 10.1093/ndtplus/sfq171. Epub 2010 Oct 4.

Proteinuria-associated nutcracker syndrome: an amyloid-negative familial Mediterranean fever patient.

Deger SM(1), Karakaya F(2), Derici U(1), Arinsoy T(1), Sindel S(1).

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DOI: 10.1093/ndtplus/sfq171

PMCID: PMC4421433

PMID: 25949484

3153. Inflamm Bowel Dis. 2011 Jun;17(6):1445-6. doi: 10.1002/ibd.21523. Epub 2010 Nov 28.

Missense mutation V20A in the tumor necrosis factor receptor superfamily 1A (TNFRSF1A) gene is associated with tumor necrosis factor receptor-associated periodic syndrome (TRAPS) presenting with periodic gastrointestinal symptoms.

Yao Q, Yerian L, Shen B.

DOI: 10.1002/ibd.21523

PMID: 21113948 [Indexed for MEDLINE]

3154. Eur J Intern Med. 2010 Dec;21(6):503-8. doi: 10.1016/j.ejim.2010.09.010. Epub 2010 Nov 5.

Colchicine in clinical medicine. A guide for internists.

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Colchicine (COL) has been used in medicine for a long time. It is well recognized as a valid therapy in acute flares of gouty arthritis, familial Mediterranean fever (FMF), Behçet's disease, and recurring pericarditis with effusion. It has also been used to treat many inflammatory disorders prone to fibrosis, mostly with disappointing therapeutic results. The pharmacotherapeutic mechanism of action of COL in diverse diseases is not fully understood, though it is known

that the drug accumulates preferentially in neutrophils, and this effect is useful in FMF. COL shows a large interindividual bioavailability. Furthermore, interactions with drugs interfering with CYP3A4 dependent enzymes and P-glycoprotein occur and are clinically important. The dosage of COL must be reduced in patients with relevant hepatic and/or renal dysfunction. However, when appropriately used and contraindications have been excluded, oral COL is a safe treatment.

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DOI: 10.1016/j.ejim.2010.09.010

PMID: 21111934 [Indexed for MEDLINE]

3155. Ann Rheum Dis. 2011 Mar;70(3):495-9. doi: 10.1136/ard.2010.138420. Epub 2010 Nov 24.

Mutations in the autoinflammatory cryopyrin-associated periodic syndrome gene: epidemiological study and lessons from eight years of genetic analysis in France.

Cuisset L(1), Jeru I, Dumont B, Fabre A, Cochet E, Le Bozec J, Delpech M, Amselem S, Touitou I; French CAPS study group.

Collaborators: Bader-Meunier B, Berthelot JM, Cartault F, Caux F, Chevrant-Breton J, Cordier MP, Dhote R, Duquesne A, Frances C, Frange P, Gaillard D, Granel B, Grateau G, Hachulla E, Hatron PY, Hentgen V, Jorgensen C, Kacet N, Kaplanski G, Koné-Paut I, Lacombe D, Lejeune C, Lemelle I, Marlin S, Meyrier A, Morell-Dubois S, Neven B, Ninet J, Philit JB, Quartier P, Stirnemann J, Touraine R.

Author information:

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Erratum in

Ann Rheum Dis. 2012 Jul;71(7):1264. Lemelle, C [corrected to Lemelle, I].

BACKGROUND: Cryopyrin-associated periodic syndromes (CAPS) consist of a continuum



of autoinflammatory diseases caused by a defect in interleukin 1 $\beta$  regulation. Although symptoms may vary widely, the discovery, in 2001, of the gene involved (NLRP3) has dramatically helped diagnosis.

**OBJECTIVES:** To define the spectrum and prevalence of NLRP3 mutations in France and to delineate initial criteria before molecular analysis.

**METHODS:** Retrospective review (2001-9) of genetic analysis data and request forms of patients living in France with an NLRP3 mutation since the set up of CAPS molecular diagnosis by the three French laboratories providing this test (GenMAI network).

**RESULTS:** Over 800 analyses of this gene have been conducted, identifying 135 cases with an NLRP3 mutation (55 probands; 33 multiplex families); the estimated prevalence in France was equal to 1/360 000. A total of 21 different sequence variants were detected, among which four are common and nine are new mutations.

**CONCLUSIONS:** Although the number of NLRP3 test requests has doubled over the past 5 years, genetic screening has not contributed to enhanced detection of new index cases each year. There are two possible reasons for this: (i) no clinical prerequisite for genetic diagnosis and (ii) few new large families are now identified (unlike the initial study based on a selection by linkage). A set of initial clinical criteria have been drawn up which it is recommended should be fulfilled before a patient is tested: at least three recurrent bouts, age at disease onset < 20 years and elevated levels of C-reactive protein, especially in individuals with urticaria and moderate fever.

DOI: 10.1136/ard.2010.138420

PMID: 21109514 [Indexed for MEDLINE]

3156. Curr Allergy Asthma Rep. 2011 Feb;11(1):12-20. doi: 10.1007/s11882-010-0160-9.

Cryopyrin-associated periodic syndrome: an update on diagnosis and treatment response.

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Cryopyrin-associated periodic syndrome (CAPS) is a rare hereditary inflammatory

disorder encompassing a continuum of three phenotypes: familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease. Distinguishing features include cutaneous, neurological, ophthalmologic, and rheumatologic manifestations. CAPS results from a gain-of-function mutation of the NLRP3 gene coding for cryopyrin, which forms intracellular protein complexes known as inflammasomes. Defects of the inflammasomes lead to overproduction of interleukin-1, resulting in inflammatory symptoms seen in CAPS. Diagnosis is often delayed and requires a thorough review of clinical symptoms. Remarkable advances in our understanding of the genetics and the molecular pathway that is responsible for the clinical phenotype of CAPS has led to the development of effective treatments. It also has become clear that the NLRP3 inflammasome plays a critical role in innate immune defense and therefore has wider implications for other inflammatory disease states.

DOI: 10.1007/s11882-010-0160-9

PMCID: PMC3020304

PMID: 21104172 [Indexed for MEDLINE]

3157. J Inflamm (Lond). 2010 Nov 23;7:55. doi: 10.1186/1476-9255-7-55.

Increased levels of circulating Annexin A5 in Familial Mediterranean fever.

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**BACKGROUND:** Familial Mediterranean fever is a genetic autoinflammatory disease most commonly affecting the ethnic groups originating from around the Mediterranean Sea. Apoptosis plays an important role in down-regulation of the inflammatory response by reducing the lifespan of activated immunocompetent cells. Thus, increased apoptosis may be associated with pathogenesis of familial Mediterranean fever.

**METHODS:** In the present study we determined the serum levels of apoptotic marker, Annexin A5, in familial Mediterranean fever patients, within an attack and attack-free, in comparison to healthy subjects and assessed the influence of colchicine treatment on this parameter. In addition, in all study subjects serum

levels of C-reactive protein and interleukine-1 $\beta$ , and the total leukocyte count were also determined.

**RESULTS:** Our results demonstrated that pathogenesis of familial Mediterranean fever is characterized by the increased levels of circulating Annexin A5, which is higher in patients within the attack and which associate with the increased levels of C-reactive protein and interleukine-1 $\beta$  and total leukocyte count.

**CONCLUSIONS:** The results obtained indicate elevated rates of apoptosis of subpopulations of leukocytes involved in autoinflammation and recurrent episodes of fever in familial Mediterranean fever. It was also revealed that regular colchicine treatment sufficiently decreases the rate of apoptosis in familial Mediterranean fever patients by affecting the intensity of autoinflammatory reactions.

DOI: 10.1186/1476-9255-7-55

PMCID: PMC3002897

PMID: 21092278

3158. Hybridoma (Larchmt). 2010 Dec;29(6):501-9. doi: 10.1089/hyb.2010.0059. Epub 2010 Nov 18.

Interleukin-32 gamma specific monoclonal antibody and developing IL-32 specific ELISA.

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Cytokines are essential coordinators of defensive immune responses for resolving the invasion of pathogens such as bacteria, virus, and fungi. However, dysregulated cytokines are the main cause of various autoinflammatory immune disorders such as rheumatoid arthritis, inflammatory bowel disease, and psoriasis. Interleukin-32 (IL-32) is a recently described cytokine and characterized as a proinflammatory cytokine. IL-32 stimulates monocytes and macrophages to induce important proinflammatory cytokines (IL-1 $\beta$ , IL-6, and TNF $\alpha$ ) and chemokines (IL-8 and MIP-2) by activating the NF- $\kappa$ B and p38 mitogen-activated

protein (MAP) kinase pathways. The biological activities of IL-32 are associated with epidemic pathogens, *Mycobacterium tuberculosis*, influenza A virus, and human immunodeficiency virus (HIV). IL-32 is transcribed as six alternative splice variants ( $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ,  $\epsilon$ , and  $\zeta$ ), with IL-32 $\gamma$  being the most active isoform. However, it is unclear which isoform is related to specific disease activities since there are no high quality antibodies available to measure circulating IL-32 in biological samples of patients. Therefore, we developed specific anti-human IL-32 $\gamma$  monoclonal antibodies from recombinant human IL-32 $\gamma$ , which was expressed in *Escherichia coli*. The IL-32 $\gamma$  specific monoclonal antibodies recognized IL-32 in cell culture supernatants and serum of IL-32 $\gamma$  transgenic mice. The newly developed IL-32 $\gamma$  monoclonal antibodies will be a useful tool to measure IL-32 level in serum samples of various inflammatory diseases. These monoclonal antibodies will be helpful in investigating the precise function of IL-32 in immune responses and in autoinflammatory diseases.

DOI: 10.1089/hyb.2010.0059

PMID: 21087097 [Indexed for MEDLINE]

3159. *Ann Rheum Dis*. 2011 Feb;70(2):309-14. doi: 10.1136/ard.2010.132613. Epub 2010 Nov 15.

A preliminary score for the assessment of disease activity in hereditary recurrent fevers: results from the AIDAI (Auto-Inflammatory Diseases Activity Index) Consensus Conference.

Piram M(1), Frenkel J, Gattorno M, Ozen S, Lachmann HJ, Goldbach-Mansky R, Hentgen V, Neven B, Stojanovic KS, Simon A, Kuemmerle-Deschner J, Hoffman H, Stojanov S, Duquesne A, Pillet P, Martini A, Pouchot J, Koné-Paut I; EUROFEVER and EUROTRAPS networks.

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**BACKGROUND:** The systemic autoinflammatory disorders (SAID) share many clinical manifestations, albeit with variable patterns, intensity and frequency. A common definition of disease activity would be rational and useful in the management of

these lifelong diseases. Moreover, standardised disease activity scores are required for the assessment of new therapies in constant development. The aim of this study was to develop preliminary activity scores for familial Mediterranean fever, mevalonate kinase deficiency, tumour necrosis factor receptor-1-associated periodic syndrome and cryopyrin-associated periodic syndromes (CAPS).

**METHODS:** The study was conducted using two well-recognised consensus formation methods: the Delphi technique and the nominal group technique. The results from a two-step survey and data from parent/patient interviews were used as preliminary data to develop the agenda for a consensus conference to build a provisional scoring system.

**RESULTS:** 24 of 65 experts in SAID from 20 countries answered the web questionnaire and 16 attended the consensus conference. There was consensus agreement to develop separate activity scores for each disease but with a common format based on patient diaries. Fever and disease-specific clinical variables were scored according to their severity. A final score was generated by summing the score of all the variables divided by the number of days over which the diary was completed. Scores varied from 0 to 16 (0-13 in CAPS). These scores were developed for the purpose of clinical studies but could be used in clinical practice.

**CONCLUSION:** Using widely recognised consensus formation techniques, preliminary scores were obtained to measure disease activity in four main SAID. Further prospective validation study of this instrument will follow.

DOI: 10.1136/ard.2010.132613

PMCID: PMC3463866

PMID: 21081528 [Indexed for MEDLINE]

3160. Hum Immunol. 2011 Feb;72(2):135-8. doi: 10.1016/j.humimm.2010.11.006. Epub 2010 Dec 7.

Evidence for the involvement of mTOR inhibition and basal autophagy in familial Mediterranean fever phenotype.

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Familial Mediterranean fever (FMF) inflammatory attacks are often triggered by metabolic or physical stress. mTOR signaling and autophagy modulate cellular responses to metabolic danger signals. In this study, we investigated the implication of mTOR inhibition and autophagy in FMF pathophysiology. mTOR inhibition induced MEFV gene expression in polymorphonuclear cells (PMNs) from healthy individuals, whereas it had no effect on PMNs from attack-free FMF patients. A significant reduction in pyrin levels in PMNs from FMF patients after mTOR inhibition was also observed. Pyrin levels in control PMNs remained unaffected. Moreover, the basal autophagic status in PMNs from FMF patients was reduced, as indicated by the lower LC3B-II/I ratio and ATG mRNA expression levels. However, mTOR inhibition had similar effects on the induction of autophagy in the two groups. The differential pyrin expression after metabolic stress induction and the impaired basal autophagy suggest a potential role in the triggering of FMF attacks.

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DOI: 10.1016/j.humimm.2010.11.006

PMID: 21081147 [Indexed for MEDLINE]

3161. Joint Bone Spine. 2011 Mar;78(2):111-4. doi: 10.1016/j.jbspin.2010.09.021. Epub 2010 Nov 11.

Current data on familial Mediterranean fever.

Koné-Paut I, Hentgen V, Touitou I.

DOI: 10.1016/j.jbspin.2010.09.021

PMID: 21074474 [Indexed for MEDLINE]

3162. J Pediatr. 2011 Jan;158(1):155-9. doi: 10.1016/j.jpeds.2010.09.054. Epub 2010 Nov 11.

Familial cases of periodic fever with aphthous stomatitis, pharyngitis, and cervical adenitis syndrome.

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We report three familial cases of periodic fever with aphthous stomatitis, pharyngitis, and cervical adenitis syndrome, including a pair of monozygotic twins and their mother. It suggests that periodic fever with aphthous stomatitis, pharyngitis, and cervical adenitis syndrome may have a certain monogenetic background.

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DOI: 10.1016/j.jpeds.2010.09.054

PMID: 21074183 [Indexed for MEDLINE]

3163. J Cutan Pathol. 2011 Feb;38(2):202-8. doi: 10.1111/j.1600-0560.2010.01638.x. Epub 2010 Nov 10.

Cryopyrin-associated periodic syndrome: an autoinflammatory disease manifested as neutrophilic urticarial dermatosis with additional perieccrine involvement.

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A female newborn presented with a congenital urticarial rash that consisted of fluctuating well-demarcated pink or pale reddish macules or slightly raised papules and plaques. In addition, purulent cerebrospinal fluid was present in the absence of evidence of congenital infection. Skin biopsy revealed a sparse infiltrate throughout the entire dermis, including the eccrine adventitia. The infiltrate was composed mostly of neutrophils, but rarely lymphocytes and

eosinophils could also be seen. No vasculitis was present. Because of the presenting attributes, a diagnosis of cryopyrin-associated periodic syndrome (CAPS) was considered and the neonatal-onset multisystem inflammatory disorder (NOMID) that represents the most severe expression of the CAPS clinical spectrum was favored. Diagnosis was confirmed by identification of a mutation in the cold-induced autoinflammatory syndrome-1 gene and by an observed response to treatment with the interleukin-1 receptor antagonist anakinra. Both the clinical and histopathological findings of the presented case may represent a distinct entity within the spectrum of aseptic neutrophilic dermatitis. We refer to this spectrum as neutrophilic urticarial dermatosis (NUD), which may serve as a cutaneous marker of autoinflammation. NUD with perieccrine involvement should prompt consideration of CAPS, especially NOMID, in the context of neonatal multisystem disease.

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DOI: 10.1111/j.1600-0560.2010.01638.x

PMID: 21062341 [Indexed for MEDLINE]

3164. Nat Rev Rheumatol. 2011 Feb;7(2):105-12. doi: 10.1038/nrrheum.2010.181. Epub 2010 Nov 9.

Chronic inflammation in FMF: markers, risk factors, outcomes and therapy.

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Familial Mediterranean fever (FMF) is the most common of the hereditary periodic fever syndromes. Although the typical clinical course of FMF is characterized by bouts of painful inflammation, this presentation represents only the tip of the iceberg. In many patients inflammation can persist in attack-free periods, as shown by high levels of acute-phase proteins, cytokines and inflammation-induced proteins. This subclinical inflammation puts patients at risk of developing complications such as anemia, splenomegaly, decreased bone mineral density, heart disease and life-threatening amyloid A amyloidosis, among others. In this article, we review the published data on markers and other factors involved in



the persistence of inflammation in patients with FMF during attack-free periods, examine the risk factors for the development of this subclinical inflammation, summarize the complications of chronic inflammation in FMF and propose a new strategy for treatment, based on these data.

DOI: 10.1038/nrrheum.2010.181

PMID: 21060333 [Indexed for MEDLINE]

3165. Clin Rheumatol. 2011 Feb;30(2):255-7. doi: 10.1007/s10067-010-1609-x. Epub 2010 Oct 30.

Evaluation of nailfold capillaries in familial Mediterranean fever patients.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent inflammatory febrile attacks, abdominal, chest or joint pain, myalgia, and erysipelas-like skin lesions. Several types of vasculitis are associated with FMF such as polyarteritis nodosa and Henoch-Schönlein purpura. We aimed to determine microvascular abnormalities in FMF patients via nailfold capillaroscopy using a dermoscope. Thirty-one FMF patients were assessed; capillary enlargement, tortuosity, avascular areas and microhemorrhages were investigated. Capillary enlargement was found in five patients and microhemorrhages in one patient. Our study supports that nailfold capillary abnormalities, which are nonspecific, can be seen in FMF patients, but more studies are needed to clarify the importance of these findings.

DOI: 10.1007/s10067-010-1609-x

PMID: 21053037 [Indexed for MEDLINE]

3166. J Periodontol. 2011 Apr;82(4):566-74. doi: 10.1902/jop.2010.100439. Epub 2010 Nov 2.

Interaction between periodontal disease and systemic secondary amyloidosis: from inflammation to amyloidosis.

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Comment in

J Periodontol. 2012 Feb;83(2):140-2.

**BACKGROUND:** It has become increasingly clear in recent years that periodontal disease can cause a dramatic increase in the levels of markers of systemic inflammation, and that periodontal treatment can result in reduction in the levels of these markers. We have previously shown that the prevalence of moderate to severe periodontitis was significantly higher in patients with familial Mediterranean fever (FMF) with amyloidosis than in patients with FMF without amyloidosis. Thus, the aim of this study is to investigate if chronic periodontitis is associated with secondary amyloidosis in the Black Sea region of Turkey.

**METHODS:** A total of 112 patients with biopsy-proven secondary amyloidosis (59 patients with FMF, 40 patients who were either chronically infected or had malignant disease, 13 patients with periodontitis) and 22 healthy subjects, were included in this study. Periodontal health and disease were evaluated using gingival index (GI), papillary bleeding index (PBI), plaque index (PI), and periodontal disease index (PDI). The concentrations of serum acute phase reactants (APRs) were measured at baseline and at 4 to 6 weeks after completion of the non-surgical periodontal therapy.

**RESULTS:** The prevalence of moderate to severe periodontitis was 47.5% in patients with FMF, 72.5% in patients who were either chronically infected or had malignant disease, and 84.6% in patients with periodontitis. Serum levels of APRs in patients with amyloidosis were reduced significantly after non-surgical periodontal therapy ( $P < 0.01$ ).

**CONCLUSIONS:** Periodontitis can increase the levels of APRs and potentiate the development of amyloidosis either by themselves or association with traditional factors, such as FMF and other chronic inflammatory diseases. Thus, preventing or treating periodontitis might prevent or at least alleviate the progression of amyloidosis. Periodontal evaluation should be performed as part of a medical

assessment and considered as an etiologic factor for secondary amyloidosis.

DOI: 10.1902/jop.2010.100439

PMID: 21043797 [Indexed for MEDLINE]

3167. Blood. 2011 Jan 20;117(3):960-70. doi: 10.1182/blood-2010-08-303115. Epub 2010 Nov 1.

Tumor suppressor death-associated protein kinase is required for full IL-1 $\beta$  production.

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Interleukin-1 $\beta$  (IL-1 $\beta$ ) is critical for inflammation and control of infection. The production of IL-1 $\beta$  depends on expression of pro-IL-1 $\beta$  and inflammasome component induced by inflammatory stimuli, followed by assembly of inflammasome to generate caspase-1 for cleavage of pro-IL-1 $\beta$ . Here we show that tumor suppressor death-associated protein kinase (DAPK) deficiency impaired IL-1 $\beta$  production in macrophages. Generation of tumor necrosis factor- $\alpha$  in macrophages, in contrast, was not affected by DAPK knockout. Two tiers of defects in IL-1 $\beta$  generation were found in DAPK-deficient macrophages: decreased pro-IL-1 $\beta$  induction by some stimuli and reduced caspase-1 activation by all inflammatory stimuli examined. With a normal NLRP3 induction in DAPK-deficient macrophages, the diminished caspase-1 generation is attributed to impaired inflammasome assembly. There is a direct binding of DAPK to NLRP3, suggesting an involvement of DAPK in inflammasome formation. We further illustrated that the formation of NLRP3 inflammasome in situ induced by inflammatory signals was impaired by DAPK deficiency. Taken together, our results identify DAPK as a molecule required for full production of IL-1 $\beta$  and functional assembly of the NLRP3 inflammasome. In addition, DAPK knockout reduced uric acid crystal-triggered peritonitis, suggesting that DAPK may serve as a target in the treatment of IL-1 $\beta$ -associated autoinflammatory diseases.

DOI: 10.1182/blood-2010-08-303115  
PMID: 21041719 [Indexed for MEDLINE]

3168. Leg Med (Tokyo). 2011 Jan;13(1):44-6. doi: 10.1016/j.legalmed.2010.09.004. Epub 2010 Oct 28.

Distribution of 42-bp variable tandem repeat polymorphism of the cold-induced autoinflammatory syndrome 1 (CIAS1) gene in eight human populations.

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We recently identified a 42bp Variable Number of Tandem Repeats polymorphism in intron 4 of Cold-induced autoinflammatory syndrome 1 gene (CIAS1 42bp-VNTR), which are associated with CIAS1 gene expression and some inflammatory disease. The aim of our study is to investigate whether variability of CIAS1 42bp-VNTR allele is difference among races. A total of 1291 subjects from 7 populations (178 Chinese, 95 Korean, 614 Mongolian, 49 Bangladesh, 72 Sri Lanka, 192 African and 91 European) was genotyped on CIAS1 42bp-VNTR polymorphism, which was also compared to previous genotyping data from 508 Japanese subjects. A total of 11 genotypes and 5 alleles were found in 8 populations. The range of allele frequencies of CIAS1\*6, CIAS1\*7, CIAS1\*9, CIAS1\*12, and CIAS1\*13 were 0.000-0.167, 0.056-0.248, 0.008-0.203, 0.570-0.923, and 0.000-0.104 in eight populations. The CIAS1\*12 was the most common allele among all populations. The longest allele CIAS1\*13 in African population was extremely high frequent at 0.104 compared to other population. While shortest allele CIAS1\*6 was not observed Sri Lankan and African. Frequency (0.924) in the Sri Lankan population. These results showed that the CIAS1 42bp-VNTR polymorphism could represent genetic diversity among different human populations.

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DOI: 10.1016/j.legalmed.2010.09.004  
PMID: 21035374 [Indexed for MEDLINE]

3169. Dtsch Med Wochenschr. 2010 Nov;135(44):2186. doi: 10.1055/s-0030-1247618. Epub 2010 Oct 26.

[Two autopsy cases with systemic amyloidosis--case 11/2010].

[Article in German]

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**HISTORY AND ADMISSION FINDINGS:** A 37-year old patient was admitted with upper abdominal pain, vomiting and diarrhea. A 38-year-old patient was admitted for liver failure.

**INVESTIGATIONS:** Case 1 was diagnosed with an AL amyloidosis due to deposition of the immunoglobulin light chain kappa in all tissues analyzed. In the bone marrow plasma cells were increased to 20-30%. Case 2 suffered from AA amyloidosis secondary to familial mediterranean fever and underwent dialysis treatment for years. He was positive for hepatitis B and C.

**DIAGNOSIS, TREATMENT AND COURSE:** Patient 1 developed refractory nephrotic syndrome and low blood pressure. During hemodialysis circulatory failure occurred and she died during resuscitation. In patient 2 a flare of chronic hepatitis B was found and treated with antiviral therapy. He was referred to ICU for rectal bleeding and developed pulmonary arrest. After resuscitation he died because of lactate acidosis and refractory circulatory failure. Both cases were subjected to autopsy.

**CONCLUSIONS:** The vast majority (90%) of amyloidoses are due to acquired AA or AL amyloidosis. Prognosis remains poor, in particular when cardiac and vascular involvement occurs.

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DOI: 10.1055/s-0030-1247618

PMID: 20979003 [Indexed for MEDLINE]

3170. Endocrine. 2010 Dec;38(3):386-90. doi: 10.1007/s12020-010-9396-3. Epub 2010 Oct 23.

Effects of sex steroid hormones, thyroid hormone levels, and insulin regulation on thyrotoxic periodic paralysis in Chinese men.

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Our study is to determine the expression of thyroid hormone, sex hormone, insulin, and C-peptide in Chinese male patients with thyrotoxic periodic paralysis (TPP). This study covered 102 patients with hyperthyroidism from Xijing Hospital. According to whether occurrence of TPP or not, patients were divided into two groups (those that were hyperthyroid with and without TPP) that were matched with age, blood pressure, urea, and creatinine. We found the body mass index (BMI) in patients with TPP was higher than that in pure hyperthyroidism patients. The levels of the total thyroxine (T4), free triiodothyronine (FT3), and free thyroxine (FT4) were significantly lower in patients with TPP compared with pure hyperthyroidism patients, while serum testosterone levels were higher compared with pure hyperthyroidism patients. Moreover, after glucose administration, the concentration of insulin at 60, 120, and 180 min were significantly higher in patients with TPP than those in pure hyperthyroidism patients. The insulin area under the curve (AUC) was significantly increased in patients with TPP compared with pure hyperthyroidism patients. The levels of thyroid hormone, sex hormone, and insulin were different in Chinese male patients with TPP compared to those with only hyperthyroidism.

DOI: 10.1007/s12020-010-9396-3

PMCID: PMC5454485

PMID: 20972724 [Indexed for MEDLINE]

3171. Arthritis Rheum. 2011 Feb;63(2):314-24. doi: 10.1002/art.30105.

The emerging role of interleukin-1 $\beta$  in autoinflammatory diseases.

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DOI: 10.1002/art.30105

PMID: 20967858 [Indexed for MEDLINE]

3172. Curr Opin Pediatr. 2010 Dec;22(6):771-8. doi: 10.1097/MOP.0b013e3283404598.

Treatment of autoinflammatory syndromes.

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**PURPOSE OF REVIEW:** Inherited autoinflammatory diseases are experiments in nature in which mutations of proteins playing a pivotal role in the regulation of the innate immunity lead to unprovoked episodes of inflammation. The understanding of the molecular pathways involved in these disorders has shed a new light on the pattern of activation and maintenance of the inflammatory response and disclosed new molecular therapeutic targets. In this review, we outline the more recent novelties in the treatment of autoinflammatory diseases and their possible implications for some multifactorial pediatric conditions.

**RECENT FINDINGS:** Cryopyrin-associated periodic syndrome (CAPS) represents the prototype of autoinflammatory diseases. The study of the pathophysiological consequence of mutations of the cryopyrin gene (NLRP3) allowed the identification of the intracellular pathways thought to play a pivotal part in the activation and secretion of the potent inflammatory cytokine interleukin (IL)-1 $\beta$ . The dramatic effect of IL-1 blockade in CAPS opens new perspectives for the treatment of other inherited and multifactorial inflammatory disorders. A number of IL-1 blockers are now available on the market.

**SUMMARY:** Studies on the pathogenesis and treatment of inherited autoinflammatory diseases are also changing the approach to some multifactorial inflammatory conditions.

DOI: 10.1097/MOP.0b013e3283404598  
PMID: 20966753 [Indexed for MEDLINE]

3173. Intern Med. 2010;49(20):2259-62. Epub 2010 Oct 15.

Periodic peritonitis due to familial Mediterranean fever in a patient with systemic lupus erythematosus.

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We report a patient with systemic lupus erythematosus (SLE) who showed periodic peritonitis with spontaneous remission. She showed compound heterozygous mutations in the MEFV gene, leading to the diagnosis of familial Mediterranean fever (FMF). Oral colchicine successfully reduced the severity and frequency of her peritonitis. SLE occasionally manifests abdominal symptoms, but in cases with periodic peritonitis, associated FMF should be considered as a possible cause.

PMID: 20962446 [Indexed for MEDLINE]

3174. Expert Opin Biol Ther. 2010 Nov;10(11):1631-6. doi: 10.1517/14712598.2010.530653.

Canakinumab for treatment of cryopyrin-associated periodic syndrome.

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**IMPORTANCE OF THE FIELD:** Autoinflammatory syndromes such as cryopyrin-associated periodic syndromes (CAPS) place a heavy burden on affected individuals as well as on their families due to significant morbidity and increased mortality. The inflammatory response in CAPS is caused by an overwhelming activation of the pro-inflammatory cytokine IL-1, which was identified as a promising treatment target.

**AREAS COVERED IN THIS REVIEW:** This article focuses on the pathogenic background and different clinical manifestations in CAPS. Furthermore, the development program and characteristics of canakinumab, a recently approved fully human anti-IL-1 $\beta$  mAb for the treatment of CAPS, are described and compared to other available IL-1 blocking agents.

**WHAT THE READER WILL GAIN:** Canakinumab targets selectively human IL-1 $\beta$  with high affinity and prevents the cytokine from interaction to its receptor and, thus, effectively blocks the inflammatory response in CAPS. In all studies performed, canakinumab showed a rapid improvement of symptoms of CAPS and a complete clinical response was achieved in most patients. Inflammatory markers such as C-reactive protein and serum amyloid-A protein were reduced to normal levels within few days. In comparison to other IL-1 blockers, canakinumab provides a longer plasma half-life and less injection site reactions.

**TAKE HOME MESSAGE:** Canakinumab offers the possibility of permanent disease control, almost symptom-free life, and hopefully less long-term morbidity and mortality in patients with CAPS.

DOI: 10.1517/14712598.2010.530653

PMID: 20955115 [Indexed for MEDLINE]

3175. Ren Fail. 2010;32(10):1230-2. doi: 10.3109/0886022X.2010.517344.

AA type renal amyloidosis secondary to FMF: a long-term follow-up in two patients.

Aybal Kutlugün A(1), Yildirim T, Altindal M, Arici M, Yasavul U, Turgan C.

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Renal amyloidosis, which leads to renal failure, is the most important long-term

complication of familial Mediterranean fever (FMF). Resolution of nephrotic syndrome secondary to amyloidosis in FMF following colchicine treatment has rarely been reported. We describe two patients with FMF and nephrotic syndrome. These patients were treated with colchicine 1.5 mg/day and had a complete remission of nephrotic syndrome with a stable clinical course over 30 years. To our knowledge, our patients have the longest follow-up time without proteinuria.

DOI: 10.3109/0886022X.2010.517344

PMID: 20954987 [Indexed for MEDLINE]

3176. Indian J Pediatr. 2010 Oct;77(10):1173-81. doi: 10.1007/s12098-010-0206-y. Epub 2010 Oct 16.

Fevers and the rheumatologist.

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Fevers in children are mainly due to infection, malignancy or inflammatory conditions. Rheumatologists have an important role in the care of inflammatory conditions, many of which are associated with fevers. Seven conditions, the hereditary recurrent fever syndromes, have been defined with the presenting symptom of recurring fever, and for which mutation of a single gene has been defined: Chronic infantile neurological articular syndrome (CINCA), Familial cold autoinflammatory syndrome (FACS), Familial Mediterranean fever (FMF), hyperimmunoglobulinemia D (HIDS), Muckle-Wells syndrome (MWS), Pyogenic sterile arthritis and Pyoderma gangrenosum (PAPA) and Tumour necrosis factor receptor-associated periodic syndrome (TRAPS) . These conditions will be discussed in detail in regard to how they fit into the wider picture of pediatric rheumatological conditions, how the diagnoses may be established and the current recommended treatments for each condition.

DOI: 10.1007/s12098-010-0206-y

PMID: 20953850 [Indexed for MEDLINE]

3177. F1000 Med Rep. 2010 Jan 18;2. pii: 3. doi: 10.3410/M2-3.

Periodic fever syndrome and autoinflammatory diseases.

Dickie LJ(1), Savic S, Aziz A, Sprakes M, McDermott MF.

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The concept of autoinflammatory disease as a new disease classification has resulted in a paradigm shift in our understanding of the the broad spectrum of immunological diseases. The effectiveness of interleukin-1 blockade in a variety of disorders has resulted in a marked reduction in suffering for many of these patients.

DOI: 10.3410/M2-3

PMCID: PMC2948378

PMID: 20948856

3178. Stroke. 2010 Nov;41(11):2687-9. doi: 10.1161/STROKEAHA.110.592725. Epub 2010 Oct 14.

Autoantibodies against oxidized low-density lipoprotein in cerebral small vessel disease.

Rouhl RP(1), van Oostenbrugge RJ, Theunissen RO, Kottnerus IL, Staals J, Henskens LH, Kroon AA, de Leeuw PW, Lodder J, Tervaert JW, Damoiseaux JG.

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BACKGROUND AND PURPOSE: Oxidized low-density lipoprotein (oxLDL) induces endothelial dysfunction and antibody formation. Because endothelial dysfunction

is involved in cerebral small vessel disease (CSVD) (dilated Virchow Robin spaces, lacunar infarcts, and white matter lesions), oxLDL antibodies could play a role in CSVD pathogenesis. Therefore, we studied oxLDL antibodies in patients with high prevalence of CSVD: lacunar stroke patients and essential hypertensive patients.

**METHODS:** A total of 158 lacunar stroke patients, 158 hypertensive patients, and 43 healthy controls were included. We determined levels of IgG and IgM against hypochlorite (HOCl) and malondialdehyde (MDA) oxLDL using ELISA (values in optical density).

**RESULTS:** Patients with CSVD had higher levels of IgG-HOCl-oxLDL (0.77 versus 0.70;  $P < 0.01$ ), as well as lower levels of IgM-MDA-oxLDL (0.55 versus 0.65;  $P < 0.05$ ) than patients without such lesions. Higher IgG-HOCl-oxLDL levels were only independently associated with higher numbers of Virchow Robin spaces at the level of the basal ganglia ( $\beta = 0.218$ ;  $P < 0.001$ ).

**CONCLUSIONS:** An autoinflammatory process with lower levels of IgM antibodies and higher levels of IgG antibodies against oxLDL may be involved in CSVD.

DOI: 10.1161/STROKEAHA.110.592725

PMID: 20947847 [Indexed for MEDLINE]

3179. Arch Dis Child Educ Pract Ed. 2010 Dec;95(6):178-82. doi: 10.1136/adc.2009.169961. Epub 2010 Oct 13.

Getting to the bones of the matter.

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DOI: 10.1136/adc.2009.169961

PMID: 20943805 [Indexed for MEDLINE]

3180. Int J Immunopathol Pharmacol. 2010 Jul-Sep;23(3):701-7.

Role of etanercept in the treatment of tumor necrosis factor receptor-associated

periodic syndrome: personal experience and review of the literature.

Cantarini L, Rigante D, Lucherini OM, Cimaz R, Laghi Pasini F, Baldari CT, Benucci M, Simonini G, Di Sabatino V, Brizi MG, Galeazzi M.

Tumor necrosis factor-alpha receptor (TNFR1)-associated periodic syndrome (TRAPS) is the most common autosomal-dominant autoinflammatory condition and is caused by mutations in the TNFRSF1A gene. TRAPS is characterized by recurrent attacks of fever typically lasting from 1 to 3 weeks; in addition to fever, common clinical features include mainly periorbital oedema, conjunctivitis, a migratory erythematous plaque simulating erysipela with underlying myalgia, and arthritis or arthralgia; serosal membrane inflammation is also possible. The identification of TNFRSF1A mutations as the genetic cause of TRAPS coincided with the wider use of biological agents in medicine and raised the possibility that blocking TNF could potentially represent the primary therapeutic goal in TRAPS, thus disclosing new treatment choices for this complex disease. In the past few years, isolated reports and case-series have been published suggesting that inhibition of TNF-alpha might represent a promising therapeutic approach in TRAPS. We present here our experience with etanercept in the treatment of patients affected with TRAPS, and we also add a review of the literature.

DOI: 10.1177/039463201002300303

PMID: 20943039 [Indexed for MEDLINE]

3181. J Pediatr (Rio J). 2010 Sep-Oct;86(5):353-66.doi:10.2223/JPED.2015.

Pediatric hereditary autoinflammatory syndromes.

[Article in English, Portuguese]

Jesus AA(1), Oliveira JB, Hilário MO, Terreri MT, Fujihira E, Watase M, Carneiro-Sampaio M, Silva CA.

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OBJECTIVE: To describe the most prevalent pediatric hereditary autoinflammatory

syndromes.

SOURCES: A review of the literature including relevant references from the PubMed and SciELO was carried out using the keywords autoinflammatory syndromes and child.

SUMMARY OF THE FINDINGS: The hereditary autoinflammatory syndromes are caused by monogenic defects of innate immunity and are classified as primary immunodeficiencies. These syndromes are characterized by recurrent or persistent systemic inflammatory symptoms and must be distinguished from infectious diseases, autoimmune diseases, and other primary immunodeficiencies. This review describes the epidemiological, clinical and laboratory features, prognosis, and treatment of the main autoinflammatory syndromes, namely: familial Mediterranean fever; TNF receptor associated periodic syndrome; the cryopyrinopathies; mevalonate kinase deficiency; pediatric granulomatous arthritis; pyogenic arthritis, pyoderma gangrenosum and acne syndrome; Majeed syndrome; and deficiency of interleukin 1 receptor antagonist. The cryopyrinopathies discussed include neonatal-onset multisystem inflammatory disease (also known as chronic infantile neurologic, cutaneous and articular syndrome), Muckle-Wells syndrome, and familial cold autoinflammatory syndrome.

CONCLUSIONS: Pediatricians must recognize the clinical features of the most prevalent autoinflammatory syndromes. Early referral to a pediatric rheumatologist may allow early diagnosis and institution of treatment, with improvement in the quality of life of these patients.

DOI: doi:10.2223/JPED.2015

PMID: 20938587 [Indexed for MEDLINE]

3182. Eur J Med Genet. 2011 Jan-Feb;54(1):50-4. doi: 10.1016/j.ejmg.2010.10.001. Epub 2010 Oct 15.

Familial Mediterranean fever in a large Lebanese family: multiple MEFV mutations and evidence for a Founder effect of the p.[M694I] mutation.

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Familial Mediterranean fever (FMF) is an autoinflammatory autosomal recessive disease characterized by recurrent fever crises and serous inflammation. The MEFV gene responsible for the disease was identified on chromosome 16, and 5 of the mutations discovered so far in the gene are most frequently encountered in FMF patients: p.[M694V], p.[V726A], p.[M680I] and p.[M694I] in exon 10, and p.[E148Q] in exon 2. The present work describes multiple MEFV mutations and the corresponding haplotypes for 31 FMF patients as well as 32 "healthy" individuals of a large consanguineous Lebanese family. The DNAs were screened for MEFV mutations, and determination of the corresponding haplotypes was performed for all individuals by genotyping 4 microsatellites surrounding the gene. Five different mutations were detected in this one family, which is unexpected in such a genetic isolate. A phenotypic variability was also observed. The haplotype carrying the p.[M694I] allele, detected in all the family branches, was well conserved and therefore seems to be the ancestral one.

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DOI: 10.1016/j.ejmg.2010.10.001

PMID: 20937419 [Indexed for MEDLINE]

3183. Biochem Biophys Res Commun. 2010 Nov 5;402(1):141-6. doi: 10.1016/j.bbrc.2010.10.004. Epub 2010 Oct 8.

The role of the pro-apoptotic protein Siva in the pathogenesis of Familial Mediterranean fever: A structural and functional analysis.

Goulielmos GN(1), Petraki E, Vassou D, Eliopoulos E, Iliopoulos D, Sidiropoulos P, Aksentijevich I, Kardassis D, Boumpas DT.

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Familial Mediterranean fever (FMF) is an autosomal, recessive disease, attributed to mutations in MEFV gene encoding pyrin, which is characterized by recurrent, acute and self-limiting attacks of fever as well as an increased neutrophil and

monocyte apoptosis. Most disease-associated mutations in MEFV gene reside on the C-terminal PRYSPRY (B30.2) domain of pyrin, an area found to interact with the pro-apoptotic protein Siva. Because apoptotic events may be contributing to endogenous inflammation we hypothesized that mutations in pyrin may affect Siva-mediated apoptosis. The confirmation of this hypothesis would be of a great biological significance since it would be demonstrated a connection between apoptosis and inflammation. We used homology modeling to construct a 3-D model of Siva protein and the constructed model of Siva defined structural elements with potential of binding other proteins to induce apoptosis. Given that Siva protein binds pyrin as shown by transfection and immunoprecipitation experiments, apoptosis was assessed by FACS and Western blotting. No differences in rates of apoptosis in myeloid cells (THP-1) upon transfection with either wt pyrin or mutant forms of pyrin were found. Patients with FMF did not display any mutations in the Siva-1 (full length) gene. Siva-1 was not linked to pyrin in the major predicted FMF gene network constructed using a literature-curated gene signature for FMF. These results suggest that Siva-mediated unprovoked apoptosis is not likely to be involved in the pathogenesis of FMF.

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DOI: 10.1016/j.bbrc.2010.10.004

PMID: 20934406 [Indexed for MEDLINE]

3184. South Med J. 2010 Nov;103(11):1170-2. doi: 10.1097/SMJ.0b013e3181f468b4.

MEFV gene mutations in a patient with eosinophilic gastroenteritis.

Kocak G(1), Kocak E, Yilmaz SR, Koklu S, Duranay M, Yalcin F, Albayrak Y.

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Eosinophilic gastroenteritis (EG) is an uncommon gastrointestinal disease affecting both children and adults. The underlying molecular mechanism predisposing to the clinical manifestation of eosinophilic gastroenteritis is unknown. A 39-year-old man who was followed up with the diagnosis of familial Mediterranean fever (FMF) was admitted to our clinic with diarrhea, abdominal



pain, and weight loss. After endoscopic and colonoscopic examinations EG was diagnosed by histopathological examination. Symptoms were resolved with the treatment of budesonide. To our knowledge, this is the first reported case of EG with the MEFV gene mutations in the literature.

DOI: 10.1097/SMJ.0b013e3181f468b4

PMID: 20890251 [Indexed for MEDLINE]

3185. J Rheumatol. 2010 Oct;37(10):2190; author reply 2190-1. doi: 10.3899/jrheum.100485.

Familial Mediterranean fever in Ashkenazi Jews.

Kahn MF.

Comment on

J Rheumatol. 2010 Feb;37(2):422-5.

DOI: 10.3899/jrheum.100485

PMID: 20889614 [Indexed for MEDLINE]

3186. J Autoimmun. 2010 Dec;35(4):414-23. doi: 10.1016/j.jaut.2010.09.001.

Successful modulation of type 2 diabetes in db/db mice with intra-bone marrow--bone marrow transplantation plus concurrent thymic transplantation.

Li M(1), Abraham NG, Vanella L, Zhang Y, Inaba M, Hosaka N, Hoshino S, Shi M, Ambrosini YM, Gershwin ME, Ikehara S.

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There is increasing evidence that both autoimmune and autoinflammatory mechanisms are involved in the development of not only type 1 diabetes mellitus (T1 DM), but also type 2 diabetes mellitus (T2 DM). Our laboratory has focused on this concept, and in earlier efforts replaced the bone marrow cells (BMCs) of leptin

receptor-deficient (db/db) mice, an animal model of T2DM, with those of normal C57BL/6 (B6) mice by IBM-BMT. However, the outcome was poor due to incomplete recovery of T cell function. Therefore, we hypothesized that intra-bone marrow-bone marrow transplantation plus thymus transplantation (IBM-BMT + TT) could be used to treat T2 DM by normalizing the T cell imbalance. Hence we addressed this issue by using such dual transplantation and demonstrate herein that seven weeks later, recipient db/db mice manifested improved body weight, reduced levels of blood glucose, and a reduction of plasma IL-6 and IL-1 $\beta$ . More importantly, this treatment regimen showed normal CD4/CD8 ratios, and increased plasma adiponectin levels, insulin sensitivity, and the number of insulin-producing cells. Furthermore, the expression of pancreatic pAKT, pLKB1, pAMPK and HO-1 was increased in the mice treated with IBM-BMT + TT. Our data show that IBM-BMT + TT treatment normalizes T cell subsets, cytokine imbalance and insulin sensitivity in the db/db mouse, suggesting that IBM-BMT + TT is a viable therapeutic option in the treatment of T2 DM.

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DOI: 10.1016/j.jaut.2010.09.001

PMCID: PMC5553687

PMID: 20884174 [Indexed for MEDLINE]

3187. Mult Scler. 2010 Dec;16(12):1517-20. doi: 10.1177/1352458510382933. Epub 2010 Sep 27.

Concurrent TNFRSF1A R92Q and pyrin E230K mutations in a child with multiple sclerosis.

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We report a 16-year-old female patient with a severe course of multiple sclerosis and concomitant symptoms suggestive of a hereditary autoinflammatory disease.

Genetic analyses revealed that she inherited a TNFRSF1A R92Q mutation from her mother and a pyrin E230K mutation from her father. To our knowledge, this is the first report of a patient with severe childhood multiple sclerosis and mutations in two genes which predispose to hereditary autoinflammatory disorders. We speculate that these mutations contribute to early multiple sclerosis manifestation and enhance the inflammatory damage inflicted by the autoimmune response.

DOI: 10.1177/1352458510382933

PMID: 20876156 [Indexed for MEDLINE]

3188. Postgrad Med. 2010 Sep;122(5):125-33. doi: 10.3810/pgm.2010.09.2209.

Inflammasome-mediated autoinflammatory disorders.

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The nucleotide-binding domain leucine-rich repeat containing (NLR) family of receptors are members of the innate immune system, and have a critical role in host defense. These molecules are key to driving inflammatory responses to abnormal cellular conditions. Many NLRs serve this role on activation by forming a multiprotein complex called an inflammasome. The inflammasome drives the processing and release of cytokines, such as the proinflammatory cytokines interleukin (IL)-1 $\beta$  and IL-18. Recently, the important function of NLR molecules in autoinflammatory disorders has been recognized, in part through the identification of the role of IL-1 $\beta$  in the pathogenesis of several autoinflammatory diseases. Cryopyrin-associated periodic syndromes were the first autoinflammatory disorders found to be directly mediated by dysfunctional inflammasome activation. This finding has subsequently led to studies in both murine models and humans that have revealed several other inflammatory conditions associated with activation of NLR-containing inflammasomes. Understanding the molecular pathophysiology of these autoinflammatory disorders has further guided the successful development of targeted therapy against IL-1. In this review, we

provide an overview of the inflammasomes and describe the important role they play in the development and manifestation of autoinflammatory diseases.

DOI: 10.3810/pgm.2010.09.2209

PMCID: PMC3648991

PMID: 20861596 [Indexed for MEDLINE]

3189. Hum Genet. 2010 Nov;128(5):473-9. doi: 10.1007/s00439-010-0890-8. Epub 2010 Sep 18.

The molecular basis of autosomal recessive diseases among the Arabs and Druze in Israel.

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The Israeli population mainly includes Jews, Muslim and Christian Arabs, and Druze. In the last decade, data on genetic diseases present in the population have been systematically collected and are available online in the Israeli national genetic database ( <http://www.goldenhelix.org/server/israeli> ). In the non-Jewish population, up to 1 July 2010, the database included molecular data on six diseases relatively frequent in the whole population: thalassemia, familial Mediterranean fever (FMF), cystic fibrosis, deafness, phenylketonuria and congenital adrenal hyperplasia, as well as data on 195 autosomal recessive diseases among Muslim Israeli Arabs, 11 among the Christian Arabs and 31 among Druze. A single mutation was characterized in 149 out of the 238 rare disorders for which the molecular basis was known. In many diseases, mutation had never been observed in any other population and was present in one family only suggesting that it occurred as a de novo event. In other diseases, the mutation was present in more than one community or even in other populations such as Bedouins from the Arab peninsula or Christians from Lebanon. In the 89 other disorders, more than one mutation was characterized either in the same gene or in more than one gene. While it is probable that most of these cases represent random events in some cases such as Bardet Biedl among the Bedouins, the reason

may be a selective advantage to the heterozygotes.

DOI: 10.1007/s00439-010-0890-8

PMID: 20852892 [Indexed for MEDLINE]

3190. Mol Biol Rep. 2011 Mar;38(3):2033-6. doi: 10.1007/s11033-010-0326-5. Epub 2010 Sep 16.

Arthritis patterns in familial Mediterranean fever patients and association with M694V mutation.

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Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent attacks of febrile peritonitis, pleuritis and synovitis. Arthritis is a common and important feature of FMF. The clinical spectrum of arthritis in 71 FMF patients was retrospectively investigated. Mutations in the familial Mediterranean (MEFV) gene were screened. Unlike the previous reports on arthritis of FMF, most of the FMF patients (59%) in this study had symmetric two-joint arthritis whereas monoarticular, oligoarticular and polyarticular arthritis was presented in 20, 8 and 10% of the patients, respectively. Knees were affected in 45 (63%) patients, ankles in 30 (42%), elbows in 11 (15%), wrists in 12 (17%), hips in 12 (17%), small joints of the hands 7 (10%), small joints of the feet 2 (3%) and sacroiliac in 1 (1%). Destruction of the hip was observed in 2 (3%) patients and required hip replacement. Amyloidosis developed in 2 (3%) of our patients. Mutations in the MEFV gene were identified in 50 (71%) patients and the most dominant mutation detected was M694V (64%). Since FMF can be diagnosed by a simple DNA mutation analysis, all arthritis patients of certain origins (Arabs, Turks, Armenians and Jews) should be tested for FMF in order to prevent the complications (amyloidosis and protracted arthritis) by introducing colchicine which is the treatment of choice for FMF.

DOI: 10.1007/s11033-010-0326-5

3191. Semin Arthritis Rheum. 2011 Apr;40(5):467-72. doi: 10.1016/j.semarthrit.2010.06.009. Epub 2010 Sep 9.

The familial Mediterranean fever gene as a modifier of periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome.

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**OBJECTIVE:** Periodic fever, aphthous stomatitis, pharyngitis, and adenopathy (PFAPA) syndrome is a sporadic disease, characterized by periodic attacks of inflammation. Mutations in the MEFV, the gene associated with familial Mediterranean fever (FMF), may lead to subclinical inflammation in asymptomatic carriers and modify the phenotype of some inflammatory diseases. We aimed at investigating the effect of MEFV gene mutations on disease phenotype in PFAPA.

**PATIENTS AND METHODS:** The cohort of this ongoing prospective study consisted of 124 children with PFAPA syndrome, followed in a single referral center, who were tested for MEFV mutations. Demographic data, clinical characteristics, and disease course of 65 PFAPA patients with and 59 without MEFV mutations (M+ and M-, respectively) were compared.

**RESULTS:** PFAPA attacks in carriers of MEFV mutations were shorter compared with patients without mutations ( $3.8 \pm 1.7$  versus  $4.8 \pm 1.9$  days,  $P < 0.01$ ). The difference was more pronounced in those carrying the M694V mutation. In M+ patients, the rates of patients with regularity of their attacks (49.2%) and oral aphthae (24.6%) were lower, compared with M- patients (74.5% and 43.9%, respectively,  $P < 0.05$  for each of the 2 comparisons). M+ patients needed a lower corticosteroid (beclomethasone) dose to abort the attacks ( $0.16 \pm 0.07$ mg/kg versus  $0.19 \pm 0.08$ ,  $P = 0.028$ ). No differences were observed in all other clinical and laboratory parameters, over a follow-up period of 4.3 years.

**CONCLUSION:** In PFAPA, MEFV is a modifier gene associated with an attenuated disease severity.

DOI: 10.1016/j.semarthrit.2010.06.009  
PMID: 20828792 [Indexed for MEDLINE]

3192. J Neurol Sci. 2010 Nov 15;298(1-2):163; author reply 163-4. doi: 10.1016/j.jns.2010.08.018. Epub 2010 Sep 9.

The role of MEFV gene mutations in Multiple Sclerosis susceptibility.

Zahednasab H, Saadatnia M, Jabalameli MR, Bahreini SA.

Comment on  
J Neurol Sci. 2010 Jul 15;294(1-2):38-42.

DOI: 10.1016/j.jns.2010.08.018  
PMID: 20828766 [Indexed for MEDLINE]

3193. BMC Pediatr. 2010 Sep 6;10:65. doi: 10.1186/1471-2431-10-65.

Profile of blood cells and inflammatory mediators in periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome.

Brown KL(1), Wekell P, Osla V, Sundqvist M, Sävman K, Fasth A, Karlsson A, Berg S.

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**BACKGROUND:** This study aimed to profile levels of blood cells and serum cytokines during afebrile and febrile phases of periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome to advance pathophysiological understanding of this pediatric disease.

**METHODS:** A cohort of patients with a median age of 4.9 years experiencing 'typical PFAPA' episodes participated in this study. Blood cells and serum cytokines were analyzed by CBC analysis and multiplex ELISA.

**RESULTS:** Oscillations in the concentration of blood cells during the afebrile and

febrile phases of typical PFAPA syndrome were observed; novel findings include increased monocytes and decreased eosinophils during a febrile episode and increased thrombocytes in the afebrile interval. Relatively modest levels of pro-inflammatory cytokines were present in sera. IFN $\gamma$ -induced cytokine IP10/CXCL10 was increased after the onset of fever while T cell-associated cytokines IL7 and IL17 were suppressed during afebrile and febrile periods. CONCLUSIONS: Identification of dysregulated blood cells and serum cytokines is an initial step towards the identification of biomarkers of PFAPA disease and/or players in disease pathogenesis. Future investigations are required to conclusively discern which mediators are associated specifically with PFAPA syndrome.

DOI: 10.1186/1471-2431-10-65

PMCID: PMC2944328

PMID: 20819226 [Indexed for MEDLINE]

#### 3194. RETRACTED ARTICLE

Nat Med. 2010 Sep;16(9):1018-23. doi: 10.1038/nm.2209. Epub 2010 Sep 5.

CXCR2 mediates NADPH oxidase-independent neutrophil extracellular trap formation in cystic fibrosis airway inflammation.

Marcos V(1), Zhou Z, Yildirim AO, Bohla A, Hector A, Vitkov L, Wiedenbauer EM, Krautgartner WD, Stoiber W, Belohradsky BH, Rieber N, Kormann M, Koller B, Roscher A, Roos D, Griesse M, Eickelberg O, Döring G, Mall MA, Hartl D.

#### Author information:

(1)Research Center, Children's Hospital, Ludwig-Maximilians-University, Munich, Germany.

#### Retraction in

Nat Med. 2011 Jul;17(7):899.

#### Comment in

Nat Med. 2010 Sep;16(9):967-9.

Upon activation, neutrophils release DNA fibers decorated with antimicrobial



proteins, forming neutrophil extracellular traps (NETs). Although NETs are bactericidal and contribute to innate host defense, excessive NET formation has been linked to the pathogenesis of autoinflammatory diseases. However, the mechanisms regulating NET formation, particularly during chronic inflammation, are poorly understood. Here we show that the G protein-coupled receptor (GPCR) CXCR2 mediates NET formation. Downstream analyses showed that CXCR2-mediated NET formation was independent of NADPH oxidase and involved Src family kinases. We show the pathophysiological relevance of this mechanism in cystic fibrosis lung disease, characterized by chronic neutrophilic inflammation. We found abundant NETs in airway fluids of individuals with cystic fibrosis and mouse cystic fibrosis lung disease, and NET amounts correlated with impaired obstructive lung function. Pulmonary blockade of CXCR2 by intra-airway delivery of small-molecule antagonists inhibited NET formation and improved lung function in vivo without affecting neutrophil recruitment, proteolytic activity or antibacterial host defense. These studies establish CXCR2 as a receptor mediating NADPH oxidase-independent NET formation and provide evidence that this GPCR pathway is operative and druggable in cystic fibrosis lung disease.

DOI: 10.1038/nm.2209

PMID: 20818377 [Indexed for MEDLINE]

3195. J Inherit Metab Dis. 2010 Oct;33(5):625-32. doi: 10.1007/s10545-010-9173-8. Epub 2010 Sep 3.

Compromized geranylgeranylation of RhoA and Rac1 in mevalonate kinase deficiency.

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Mevalonate kinase deficiency (MKD) is an autoinflammatory disorder caused by mutations in the MVK gene resulting in decreased activity of the enzyme mevalonate kinase (MK). Although MK is required for biosynthesis of all isoprenoids, in MKD, in particular, the timely synthesis of geranylgeranyl pyrophosphate appears to be compromised. Because small guanosine triphosphatases (GTPases) depend on geranylgeranylation for their proper signaling function, we

studied the effect of MK deficiency on geranylgeranylation and activation of the two small GTPases, RhoA and Rac1. We demonstrate that both geranylgeranylation and activation of the two GTPases are more easily disturbed in MKD cells than in control cells when the flux through the isoprenoid biosynthesis pathway is suppressed by low concentrations of simvastatin. The limited capacity of geranylgeranylation in MKD cells readily leads to markedly increased levels of nonisoprenylated and activated GTPases, which will affect proper signaling by these GTPases.

DOI: 10.1007/s10545-010-9173-8

PMCID: PMC2946549

PMID: 20814828 [Indexed for MEDLINE]

3196. Ital J Pediatr. 2010 Sep 3;36:57. doi: 10.1186/1824-7288-36-57.

Autoinflammatory syndromes: diagnosis and management.

De Sanctis S(1), Nozzi M, Del Torto M, Scardapane A, Gaspari S, de Michele G, Breda L, Chiarelli F.

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During the last decades the description of autoinflammatory syndromes induced great interest among the scientific community. Mainly rheumatologists, immunologists and pediatricians are involved in the discovery of etiopathogenesis of these syndromes and in the recognition of affected patients. In this paper we will discuss the most important clues of monogenic and non-genetic inflammatory syndromes to help pediatricians in the diagnosis and treatment of these diseases.

DOI: 10.1186/1824-7288-36-57

PMCID: PMC2941754

PMID: 20813071 [Indexed for MEDLINE]

3197. J Rheumatol. 2010 Sep;37(9):1971-2. doi: 10.3899/jrheum.100352.

Effectiveness of colchicine therapy in 4 cases of retroperitoneal fibrosis associated with autoinflammatory diseases.

de Socio G, Verrecchia E, Fonnesu C, Giovinale M, Gasbarrini GB, Manna R.

DOI: 10.3899/jrheum.100352

PMID: 20810528 [Indexed for MEDLINE]

3198. J Clin Rheumatol. 2010 Sep;16(6):290-2. doi: 10.1097/RHU.0b013e3181eedb15.

Familial Mediterranean fever presenting as anti-cyclic citrullinated peptide antibody negative palindromic rheumatism.

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A 64-year-old Egyptian man who resides in the United States presented to the rheumatology clinic with 6 months history of episodic recurrent pauci--arthritis along with constitutional symptoms. His Mediterranean ancestry, anti-cyclic citrullinated peptide negativity, and cyclical palindromic rheumatism prompted an investigation for familial Mediterranean fever gene mutation. He was found to have heterozygous 694I gene mutation during MEFV analysis. He also met Liveneh 1 major and 1 minor criteria for the diagnosis of familial Mediterranean fever.

DOI: 10.1097/RHU.0b013e3181eedb15

PMID: 20808171 [Indexed for MEDLINE]

3199. Iran J Pediatr. 2010 Sep;20(3):367-9.

A rare presentation of familial mediterranean Fever; acute scrotum and hydrocele amyloidosis.

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Author information:

(1)Department of Pediatrics, School of Medicine Gaziosmanpasa University Tokat, Turkey.

**BACKGROUND:** Familial Mediterranean Fever (FMF) is a genetic disease characterized by recurrent febrile attacks and inflammation of serous membranes. Amyloidosis is frequent in untreated FMF patients and is also the most important complication of FMF. It is generally seen with renal, hepatic, gastrointestinal, spleen, testicular and thyroidal involvement.

**CASE PRESENTATION:** Herein, we report a case with acute scrotum and hydrocele amyloidosis as a presenting finding in a child with FMF.

**CONCLUSION:** Although the acute scrotum and scrotal swelling are not characteristic clinical features of FMF, this genetic disease should not be forgotten in the differential diagnosis of acute scrotum in patients of Mediterranean origins.

PMCID: PMC3446044

PMID: 23056732

3200. Curr Allergy Asthma Rep. 2010 Nov;10(6):398-404. doi: 10.1007/s11882-010-0141-z.

Periodic Fever syndromes.

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The periodic syndromes represent a heterogeneous group of disorders that can be very difficult for practicing physicians to diagnosis and treat. This article presents an orderly approach to hyperimmunoglobulin D syndrome; tumor necrosis factor receptor-1 periodic syndrome; familial Mediterranean fever; periodic fever with aphthous stomatitis, pharyngitis, and adenitis syndrome; and cryopyrin-associated periodic syndromes by highlighting the disease presentation, diagnosis, pathogenesis, and treatment. Recent advances are also discussed.

DOI: 10.1007/s11882-010-0141-z  
PMID: 20734171 [Indexed for MEDLINE]

3201. *Pediatr Int.* 2010 Jun;52(3):e137-40. doi: 10.1111/j.1442-200X.2010.03058.x.

Protracted febrile myalgia in two children with familial Mediterranean fever.

Duru NS(1), Civilibal M, Karakoyun M, Payasli M, Eevli M.

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(1)Department of Pediatrics, Haseki Educational and Research Hospital, Istanbul, Turkey.

DOI: 10.1111/j.1442-200X.2010.03058.x  
PMID: 20723111 [Indexed for MEDLINE]

3202. *Arthritis Rheum.* 2010 Dec;62(12):3783-91. doi: 10.1002/art.27696.

Risk factors for severe Muckle-Wells syndrome.

Kümmerle-Deschner JB(1), Tyrrell PN, Reess F, Kötter I, Lohse P, Girschick H, Huemer C, Horneff G, Haas JP, Koitschev A, Deuter C, Benseler SM.

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**OBJECTIVE:** Muckle-Wells syndrome (MWS) is an inherited autoinflammatory disease resulting in excessive interleukin-1 release. It is unknown whether demographic, clinical, or laboratory characteristics at the time of diagnosis may identify patients who are at high risk for severe disease activity. This study was undertaken to analyze clinical and laboratory features of MWS, compare genetically defined subcohorts, and identify risk factors for severe MWS.

**METHODS:** A multicenter cohort study of consecutive MWS patients was performed. Parameters assessed included clinical features, MWS Disease Activity Score (MWS-DAS), inflammation markers, and cytokine levels. E311K mutation-positive patients were compared with E311K mutation-negative patients. Putative risk factors for severe MWS (defined as an MWS-DAS score of  $\geq 10$ ) were assessed in

univariate analyses, and significant predictors were entered into a multivariate model.

**RESULTS:** Thirty-two patients (15 male and 17 female) were studied. The most frequent organ manifestations were musculoskeletal symptoms and eye and skin disorders. Renal disease and hearing loss were seen in >50% of the patients.

Genetically defined subcohorts had distinct phenotypes. Severe disease activity was documented in 19 patients (59%). Predictors of severe MWS identified at the time of diagnosis were female sex, hearing loss, musculoskeletal disease, increased erythrocyte sedimentation rate, and low hemoglobin level. Female sex and hearing loss remained significant after adjustment for age in a multivariate model (relative risk 1.8 and 2.6, respectively).

**CONCLUSION:** MWS patients at high risk for severe disease can be identified at the time of diagnosis. Female patients presenting with hearing loss have the highest likelihood of manifesting severe MWS and should be considered a high-risk group.

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DOI: 10.1002/art.27696

PMID: 20722029 [Indexed for MEDLINE]

3203. Rheumatol Int. 2011 Nov;31(11):1531-3. doi: 10.1007/s00296-010-1604-1. Epub 2010 Aug 19.

Molecular evaluation of 458 patients referred with a clinical diagnosis of familial Mediterranean fever in Scandinavia.

Cornelius N, Duno M.

DOI: 10.1007/s00296-010-1604-1

PMID: 20721559 [Indexed for MEDLINE]

3204. Br J Dermatol. 2010 Dec;163(6):1351-3. doi: 10.1111/j.1365-2133.2010.09978.x. Epub 2010 Nov 4.

Interleukin-17 expression in the urticarial rash of familial cold autoinflammatory syndrome: a case report.

Yamauchi A, Iwata H, Ohnishi H, Teramoto T, Kondo N, Seishima M.

DOI: 10.1111/j.1365-2133.2010.09978.x

PMID: 20716212 [Indexed for MEDLINE]

3205. Inflammation. 2011 Oct;34(5):379-87. doi: 10.1007/s10753-010-9245-9.

TLR polymorphisms in FMF: association of TLR-2 (Arg753Gln) and TLR-4 (Asp299Gly, Thre399Ile) polymorphisms and myeloid cell TLR-2 and TLR-4 expression with the development of secondary amyloidosis in FMF.

Soylu A(1), Ateş H, Cingöz S, Türkmen M, Demir BK, Tunca M, Sakızlı M, Cirit M, Ersoy R, Ulgenalp A, Kavukçu S.

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Amyloidosis is the major complication of familial Mediterranean fever (FMF). Toll-like receptors (TLR) are involved in the activation of an innate immune system TLR-2 and TLR-4 recognize lipoteichoic acid and lipopolysaccharides (LPS), respectively. While TLR-2 Arg753Gln polymorphism upregulates, TLR-4 Asp299Gly and Thre399Ile polymorphisms downregulate inflammation. We investigated the effect of these polymorphisms on the development of amyloidosis in FMF patients. We also investigated myeloid cell TLR-2 and TLR-4 expressions in these patients. We studied 26 FMF patients and 13 FMF patients with amyloidosis. TLR-2 Arg753Gln and TLR-4 Asp299Gly and Thr399Ile polymorphisms were analyzed with the polymerase chain reaction-restriction fragment length polymorphism method. Myeloid cell baseline TLR-2 and TLR-4 and LPS-induced TLR-4 expressions were evaluated. The TLR-2 and TLR-4 polymorphism rate was compared with the results of 100 healthy subjects in our previous study. In addition, 13 healthy controls were enrolled for leukocyte TLR-2 and TLR-4 expressions. Serum amyloid A (SAA) levels were measured in these 13 control cases and in FMF patients during attack-free periods. The frequency of TLR-2 Arg753Gln, TLR-4 Asp299Gly, and Thr399Ile polymorphisms in healthy controls in our previous study were 1%, 3%, and 2%, respectively. The frequency of these polymorphisms were not different in FMF patients (with or without amyloidosis) compared to the control group. Likewise, myeloid cell TLR-2 and TLR-4 expressions were not different among the controls

and FMF patients. However, LPS-induced TLR-4 expression in granulocytes was more prominent in FMF patients. There was no correlation between TLR-2 and TLR-4 expressions and SAA levels. Neither myeloid cell TLR-2 and TLR-4 expressions nor TLR-2 Arg753Gln, TLR-4 Asp299Gly, and Thr399Ile polymorphisms seem to affect the development of secondary amyloidosis in FMF patients in our study population.

DOI: 10.1007/s10753-010-9245-9

PMID: 20714796 [Indexed for MEDLINE]

3206. Acta Paediatr. 2011 Jan;100(1):21-5. doi: 10.1111/j.1651-2227.2010.01974.x. Epub 2010 Aug 26.

Hyperimmunoglobulinemia D and periodic fever syndrome in children. Review on therapy with biological drugs and case report.

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Hyperimmunoglobulinemia D syndrome (HIDS) is a rare, autosomal recessively inherited autoinflammatory disease caused by mutations in the mevalonate kinase gene. HIDS usually starts in infancy with recurrent fever episodes lasting 3-7 days and recurring every 4-6 weeks, with only partial symptom decrease in adulthood. Fever is typically accompanied by abdominal pain, vomiting, diarrhoea and cervical lymphadenopathy, and sometimes by skin and joint symptoms. Blood leukocytes and serum C-reactive protein are elevated during the episode, and in addition, high levels of interleukine-1 (IL-1), IL-6 and tumour necrosis factor (TNF) and respective soluble receptors have been measured. Instead, serum immunoglobulin D (IgD) is usually normal until 3 years of age. Currently, there is no established treatment for HIDS. Thus far, four children have been successfully treated with etanercept, TNF-alpha inhibitor, and three children with anakinra, IL-1 receptor antagonist. CONCLUSION: This review summarizes currently available data on the use biological medicines for HIDS in children. A Finnish 1.5-year-old patient with disease onset at 6 months of age, treated successfully with anakinra, is presented.



DOI: 10.1111/j.1651-2227.2010.01974.x

PMID: 20712835 [Indexed for MEDLINE]

3207. Acta Reumatol Port. 2010 Apr-Jun;35(2):146-54.

[Autoinflammatory syndromes].

[Article in Portuguese]

Gomes JM(1), Gomes SM, Conde M.

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Autoinflammatory syndromes (AIS) are a heterogeneous group of congenital diseases characterized by the presence of recurrent episodes of fever and local or generalized inflammation, in the absence of infectious agents, detectable auto-antibodies or antigen-specific autoreactive T-cells. These diseases have been much better understood during the past 15 years, mainly due to the marked advances of the Human Genoma Project and its implications in the identification and characterization of genetic mutations. In this paper we make a revision of the classification of AIS and focus our attention specially on the cryopyrin-associated periodic syndromes (CAPS), in particular the CINCA syndrome that shares many clinical characteristics with juvenile idiopathic arthritis.

PMID: 20711090 [Indexed for MEDLINE]

3208. Z Rheumatol. 2010 Sep;69(7):581-93. doi: 10.1007/s00393-009-0530-7.

[IL-1 antagonists].

[Article in German]

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Interleukin (IL)-1 plays an important role not only in the mediation of inflammation but also in the destruction of cartilage and bone. Together with TNF-alpha it is one of the most important cytokines in the pathogenesis of rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA). The first IL-1 antagonist to be approved for RA was Anakinra, an IL-1 receptor antagonist. Anakinra appears to be less effective for RA than TNF blockers. Hence, Anakinra is rarely used for the treatment of RA, but more for the treatment of IL-1-mediated diseases such as autoinflammatory syndromes, adult-onset Still's disease and systemic onset JIA. Two newer IL-1 antagonists have recently been approved for the treatment of CAPS (cryopyrin-associated periodic syndromes): Canakinumab, a fully human IL-1beta antibody, and rilonacept, a fusion protein consisting of the ligand-binding domain of the IL-1 receptor and the IL-1-receptor accessory protein, bound to human IgG1. For RA, there is only one proof-of-concept study to date with canakinumab. There are no prospective data for the treatment of patients with RA who did not respond to or tolerate TNF antagonists; in a retrospective analysis, only 8% of anti-TNF pretreated patients achieved an ACR 20 response.

DOI: 10.1007/s00393-009-0530-7

PMID: 20703489 [Indexed for MEDLINE]

3209. Rheumatology (Oxford). 2010 Nov;49(11):2200-3. doi: 10.1093/rheumatology/keq252. Epub 2010 Aug 5.

Validation of the new paediatric criteria for the diagnosis of familial Mediterranean fever: data from a mixed population of 100 children from the French reference centre for auto-inflammatory disorders.

Kondi A(1), Hentgen V, Piram M, Letierce A, Guillaume-Czitrom S, Koné-Paut I.

Author information:

(1)Department of Pediatrics and Pediatric Rheumatology, National Reference Center for Auto-inflammatory Disorders, Bicêtre University Paris Sud Hospital, Le Kremlin-Bicêtre, France.

**OBJECTIVE:** We aimed to validate the new paediatric criteria for diagnosis of FMF in a mixed population of 100 French patients.

**METHODS:** The study group included 100 FMF children from the French reference centre for auto-inflammatory disorders. A control group of 40 patients with unexplained recurrent fever was reviewed in parallel. Both groups of patients were assessed for both the Tel Hashomer and the new paediatric criteria published by Yalcinkaya et al.

**RESULTS:** Comparison of Tel Hashomer vs Yalcinkaya's criteria in both groups gave a sensitivity of 99 vs 100%, a specificity of 45 vs 50%, a positive predictive value (PPV) of 81.8 vs 83.3% and a negative predictive value (NPV) of 94.7 vs 100%. However, when we used at least three Yalcinkaya's criteria we obtained a sensitivity of 77% and a specificity of 95% with a PPV of 97.3% and an NPV of 62.3%. The number of mutations in the MEFV gene did not modify results for both sets of criteria.

**CONCLUSION:** The new paediatric Turkish criteria did not make a better contribution to FMF diagnosis than the Tel Hashomer criteria in our mixed population of French children while using an appropriate control group. However, if needed, they can be applied using at least three criteria, which slightly decreases their sensitivity but markedly increases their specificity.

DOI: 10.1093/rheumatology/keq252

PMID: 20688806 [Indexed for MEDLINE]

3210. Nippon Ganka Gakkai Zasshi. 2010 Jul;114(7):621-8.

[A case of frosted branch angiitis associated with retinal vein occlusion as a complication of familial Mediterranean fever].

[Article in Japanese]

Satoh S(1), Itoh C, Nakamura N.

Author information:

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**BACKGROUND:** Familial Mediterranean fever (FMF) is characterized by recurrent episodes of fever and serositis caused by autosomal recessive inheritance MEFV gene mutations. It is reported that the onset of angiitis is high among patients with this disease, but no reports were found in the field of ophthalmology in Japan. In this paper, we report one case that developed from optic disc vasculitis to frosted branch angiitis associated with retinal vein occlusion.

**CASE:** A 39 year old male. Fever, abdominal pain and chest pain were continued from childhood. In 2006, an idiopathic fever was reported with a renal disorder. Based on the results of laboratory examinations, he was diagnosed with FMF and started oral colchicines to stabilize the symptoms. In October 2007, he complained of blurry vision in his left eye that lasted for about one week prior to his visit and decided to visit our department for an examination. Visual acuity was right 1.5 and left 1.2. Although no abnormalities were found in the anterior chamber or optic media of either eye, the left eye papilla was reddish and swollen, and varicose enlargement of the retinal veins and a small retinal hemorrhage were found. Four days later, a white vascular infiltration spread to all branches of the retinal veins at the upper-half of the left eye papilla, the hemorrhage increased in the entire retina and the visual acuity decreased to 0.1. He was hospitalized and systemic administration of an antiviral agent, an antibacterial agent and a steroidal agent (prednisolone 60 mg/day) was started. Subsequently, the left eye ocular fundus findings slowly improved and he was cured 7 months later with a visual acuity of 1.0.

**CONCLUSION:** Frosted branch angiitis may occur with systemic gene abnormalities as an underlying condition and it is important in the future to consider FMF as a causative disease.

PMID: 20681258 [Indexed for MEDLINE]

3211. J Rheumatol. 2010 Aug 1;37(8):1780-2. doi: 10.3899/jrheum.091094.

Successful treatment with infliximab of a patient with tumor necrosis factor-associated periodic syndrome (TRAPS) who failed to respond to etanercept.

Krelenbaum M, Chaiton A.

DOI: 10.3899/jrheum.091094

PMID: 20675856 [Indexed for MEDLINE]

3212. Curr Opin Rheumatol. 2010 Sep;22(5):567-78. doi: 10.1097/BOR.0b013e32833ceff4.

Monogenic autoinflammatory diseases: new insights into clinical aspects and pathogenesis.

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**PURPOSE OF REVIEW:** The genetic and clinical characterizations of monogenic autoinflammatory syndromes have led to ground breaking insights into the regulation of inflammatory responses to endogenous and exogenous inducers or triggers of inflammation and continue to uncover key inflammatory pathways of the innate immune system. This article summarizes recent progress in the clinical aspects and understanding of the pathogenesis of this growing spectrum of diseases.

**RECENT FINDINGS:** The understanding of the spectrum of organ manifestations in autoinflammation was expanded by the discovery of two novel monogenic diseases both caused by the absence of an anti-inflammatory signal and added evidence that increased IL-1 signaling can cause aseptic osteolytic bone lesions and that the absence of IL-10 signaling causes inflammatory enterocolitis in neonates. New knock in animal models for TNF-receptor-associated periodic syndrome, and familial Mediterranean fever and cryopyrin-associated periodic syndromes allow insights into the complexity of the dysregulated immune pathways. Exploring 'triggers' of the NLRP3 inflammasome spurred studies of tissue inflammation in diseases including gout and those that previously have not been considered inflammatory in nature such as diabetes, fibrosing lung disease and possibly coronary artery disease.

**SUMMARY:** The genetic characterization of a growing number of monogenic autoinflammatory diseases has provided important insights into the phenotypic

expression of single gene disorders and the complexity of the dysregulated inflammatory pathways leading to clinical disease. Knowledge obtained from these disorders is pertinent to a number of common disorders and provides new targets for drug development.

DOI: 10.1097/BOR.0b013e32833ceff4

PMCID: PMC3020910

PMID: 20671522 [Indexed for MEDLINE]

3213. Bull Acad Natl Med. 2009 Nov;193(8):1873-83; discussion 1883-4.

[From hereditary recurrent fevers to autoinflammatory syndromes: the contribution of genetics].

[Article in French]

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Hereditary recurrent fevers are rare genetic diseases characterized by febrile periods of variable duration. Classically, four such diseases were recognized, namely familial Mediterranean fever (previously called periodic disease in France), the Muckle-Wells syndrome, Hibernian fever, and hyper IgD with recurrent fever. The discovery of culprit genes has led to an overhaul of this classification. Molecular diagnosis of these diseases, that are difficult to identify on clinical grounds alone, is now possible. Timely diagnosis is particularly important as, in the absence of treatment, there is a risk of secondary AA amyloidosis, which is fatal within 5 to 10 years. The discovery of underlying genetic mechanisms has also led to the development of new therapeutic approaches, which are currently being tested in clinical trials.

PMID: 20669551 [Indexed for MEDLINE]

3214. Arthritis Rheum. 2010 Nov;62(11):3232-6. doi: 10.1002/art.27683.

Association of familial Mediterranean fever-related MEFV variations with ankylosing spondylitis.

Cosan F(1), Ustek D, Oku B, Duymaz-Tozkiir J, Cakiris A, Abaci N, Ocal L, Aral O, Gül A.

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**OBJECTIVE:** The pathogenesis of ankylosing spondylitis (AS) has a strong genetic contribution. Familial Mediterranean fever (FMF) is an autosomal recessively inherited autoinflammatory disorder caused by MEFV gene missense variations, and a clinical association between FMF and AS has been reported previously. The aim of this study was to analyze the association of common MEFV variations (M694V, M680I, V726A, and E148Q) with AS in a group of Turkish patients.

**METHODS:** The study group comprised 193 patients with AS and 103 matched healthy control subjects. All individuals were genotyped for 4 MEFV variations and HLA-B27 using genomic DNA, and association of the variations with the clinical and laboratory features of the patients was analyzed.

**RESULTS:** The MEFV missense variations were significantly more frequent in patients with AS (22.3%) compared with healthy control subjects (9.7%; odds ratio [OR] 2.67, 95% confidence interval [95% CI] 1.28-5.56). This difference was more prominent for exon 10 variations (M694V, V726A, M680I) (OR 3.75, 95% CI 1.41-9.97), especially for the most-penetrant variation M694V (OR 4.73, 95% CI 1.39-16.12). MEFV variations were more frequent in HLA-B27-negative patients with AS, and the difference was statistically significant in patients carrying exon 10 variants.

**CONCLUSION:** FMF-related MEFV variations are associated with AS, and these variations may contribute to the pathogenesis of AS, especially in populations in which the prevalence of FMF is high.

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DOI: 10.1002/art.27683

PMID: 20669279 [Indexed for MEDLINE]

3215. *Dermatol Ther.* 2010 Jul-Aug;23(4):389-402. doi: 10.1111/j.1529-8019.2010.01339.x.

Cytophagic histiocytic panniculitis and hemophagocytic lymphohistiocytosis: an overview.

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Cytophagic histiocytic panniculitis (CHP) is a rare panniculitis that is associated with systemic features including fevers, hepatosplenomegaly, lymphadenopathy, pancytopenia, hepatic abnormalities, hypertriglyceridemia, and coagulopathy without an elevated erythrocyte sedimentation rate. The panniculitis lesions show adipose tissue lymphocytic and histiocytic infiltration along with hemophagocytosis, which may also appear in bone marrow, spleen, lymph nodes, and liver. Patients may have a rapidly fatal disease course, a longer disease course with intermittent remissions and exacerbations for many years prior to death, or a nonfatal acute or intermittent course responsive to treatment. The cytophagocytic disorder in these patients is a hemophagocytic lymphohistiocytosis (HLH), similar to the infection-activated reaction associated with perforin mutations found in familial hemophagocytic lymphohistiocytosis. HLH is a group of autoinflammatory disorders, which include macrophage activation syndrome and infection-associated hemophagocytic syndrome, which if not treated rapidly, can be fatal. The relationship of CHP and HLH is discussed. CHP associated diseases include: subcutaneous panniculitis-like T cell lymphomas; infections, connective tissue diseases, other malignancies, and the molecular disorders that cause HLH. Treatment of CHP includes: glucocorticoids in combination with cyclosporine, combined chemotherapeutic medications and most recently, anakinra, an Interleukin-1 receptor antagonist; along with supportive care, search for underlying malignancies and treatment thereof, and control of associated infections.

DOI: 10.1111/j.1529-8019.2010.01339.x

PMID: 20666826 [Indexed for MEDLINE]

3216. *Z Rheumatol.* 2010 Aug;69(6):488-95. doi: 10.1007/s00393-010-0632-2.



[Genetic background of juvenile idiopathic arthritis].

[Article in German]

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Several genetic factors have recently been observed as having an influence on susceptibility, course and prognosis of juvenile idiopathic arthritis (JIA): 1. Affected sib pairs were observed to have a low concordance in terms of disease incidence, but significant concordance in terms of subtype and course of disease. 2. Each subtype of JIA was observed to have a distinct genetic background. 3. Some JIA patients do not carry any of the defined risk genes. 4. Most subtypes of JIA have a distinct different genetic background to rheumatoid arthritis in adults. 5. Multiple factors have been observed to be involved in pathogenesis implying genetic and environmental factors. 6. Systemic JIA differs from all other subtypes in terms of genetic background and treatment options. It is currently assumed to be an autoinflammatory disease. 7. Genetic factors not only affect the course of the disease, but also response and complication rate. Increasing knowledge on the factors involved in the pathogenesis of JIA as well as analysis of large patient cohorts in consortiums cooperating on an international level have helped define many important polymorphisms; these are currently the subject of further investigation.

DOI: 10.1007/s00393-010-0632-2

PMID: 20665039 [Indexed for MEDLINE]

3217. J Clin Rheumatol. 2010 Aug;16(5):229-32. doi: 10.1097/RHU.0b013e3181e96342.

Colchicine myopathy and neuromyopathy: two cases with different characteristics.

Cantarini L(1), Volpi N, Galeazzi M, Giani T, Fanti F, Lucherini OM, Aglianò M, Alessandrini C, Giannini F, Magi S, Greco G, Baldari CT, Cimaz R.

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Comment in

J Clin Rheumatol. 2013 Mar;19(2):108-9.

J Clin Rheumatol. 2012 Dec;18(8):453-4.

Colchicine, a long established anti-inflammatory agent now used in several rheumatologic conditions, acts by inhibiting microtubular polymerization, as it binds equimolarly to tubulin molecules. Cytoskeletal microtubules are crucial in processes of cell viability, such as mitosis and intracellular vesicle motility. Gastrointestinal side effects are quite common and often minor in nature or duration, whereas neuromuscular toxicity is rare. We report 2 cases of colchicine myopathy in the context of very different clinical settings.

DOI: 10.1097/RHU.0b013e3181e96342

PMID: 20661070 [Indexed for MEDLINE]

3218. Arch Pediatr. 2010 Sep;17(9):1313-6. doi: 10.1016/j.arcped.2010.06.007. Epub 2010 Jul 23.

[Periodic fever with increased IgD].

[Article in French]

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Periodic fever or hereditary inflammatory fevers are characterized by intermittent inflammatory attacks. Many entities are well recognized today such as familial mediterranean fever (FMF) and hyperimmunoglobulinemia D syndrome (HIDS). We report on the case of a 6-year-old boy referred for evaluation of a recurrent fever associated with chest pain, pneumonitis, or pleuritis since the

age of 5 years. Laboratory data showed leukocytosis, a high erythrocyte sedimentation rate, and C-reactive protein; however, a permanent high serum level IgD was noted. Stereotypical episodes of fever appeared every 4-6 weeks, while infectious, malignant, and auto-immune causes were eliminated. A search for the most common mutations of the FMF gene in Tunisian patients (M694V, M680I, V726A, E148Q, M694I, and A744S) were negative. Likewise, urinary leukotriene E(4), which may be increased in HIDS, was normal in this patient. Mevalonate kinase activity in lymphocytes was not assayed. Ethnic origin and clinical presentation suggest FMF with an increased IgD rather than authentic HIDS, in spite of the lack of improvement under colchicine treatment and the negativity of the main mutations involved in FMF.

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DOI: 10.1016/j.arcped.2010.06.007

PMID: 20655711 [Indexed for MEDLINE]

3219. Arch Pediatr. 2010 Jun;17(6):609-10. doi: 10.1016/S0929-693X(10)70021-X.

[Treatment of autoinflammatory diseases: which projections?].

[Article in French]

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DOI: 10.1016/S0929-693X(10)70021-X

PMID: 20654803 [Indexed for MEDLINE]

3220. Arch Pediatr. 2010 Jun;17(6):604-6. doi: 10.1016/S0929-693X(10)70019-1.

[Practical step in recurrent fever in children: from symptoms to etiology].

[Article in French]

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DOI: 10.1016/S0929-693X(10)70019-1

PMID: 20654801 [Indexed for MEDLINE]

3221. Rheumatol Int. 2011 Jan;31(1):121-5. doi: 10.1007/s00296-010-1550-y. Epub 2010 Jul 22.

Assessment of heart rate recovery index in patients with familial Mediterranean fever.

Ardic I(1), Kaya MG, Yarlioglues M, Dogdu O, Celikbilek M, Akpek M, Akyol L, Torun E.

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Heart rate recovery after exercise is a function of vagal reactivation, and its impairment is an independent prognostic indicator for cardiovascular and all-cause mortality. The aim of our study was to evaluate heart rate recovery in patients with familial Mediterranean fever (FMF). The study population included 38 patients with FMF (14 men; mean age,  $36.2 \pm 12.1$  years, and mean disease duration =  $11.3 \pm 6.5$  years) and 35 healthy control subjects (12 men; mean age =  $34.1 \pm 9.9$  years). Basal electrocardiography, echocardiography, and treadmill exercise testing were performed in all patients and control participants. The heart rate recovery index was defined as the reduction in the heart rate from the rate at peak exercise to the rate 1st-minute (HRR(1)), 2nd-minute (HRR(2)), 3rd-minute (HRR(3)), and 5th-minute (HRR(5)) after the cessation of exercise stress testing. There are significant differences in HRR(1) and HRR(2) indices between patients with FMF and control group ( $26.4 \pm 7.4$  vs.  $35.0 \pm 8.0$ ;  $P = 0.001$  and  $47.3 \pm 11.8$  vs.  $54.8 \pm 10.3$ ;  $P = 0.002$ , respectively). Similarly, HRR(3) and

HRR(5) indices of the recovery period were lower in patients with FMF, when compared with indices in the control group ( $56.0 \pm 14.0$  vs.  $63.7 \pm 11.2$ ;  $P = 0.01$  and  $64.1 \pm 14.7$  vs.  $71.5 \pm 12.7$ ;  $P = 0.02$ , respectively). There were also remarkably positive correlations between the disease duration and HRR(1) ( $r = 0.31$ ,  $P = 0.02$ ), and HRR(2) ( $r = 0.26$ ,  $P = 0.04$ ). The heart rate recovery index impaired in patients with FMF compared to control subjects. When the prognostic significance of the heart rate recovery index is considered, a useful, simple, and noninvasive test may be clinically helpful in the recognition of high-risk patients with FMF.

DOI: 10.1007/s00296-010-1550-y

PMID: 20652273 [Indexed for MEDLINE]

3222. Nephrology (Carlton). 2010 Aug;15(5):513-21. doi: 10.1111/j.1440-1797.2010.01343.x.

Review: T helper 17 cells: their role in glomerulonephritis.

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T helper (Th) cells are an integral part of the host's immune response to eliminate invading pathogens. However, autoimmune or 'autoinflammatory' diseases can develop if Th cell responses are not effectively regulated. Several subsets of Th cells exist, including the Th17 subset that produces interleukin-17A, important in experimental models of organ-specific autoimmune inflammation. Its discovery has explained paradoxical observations in model systems thought to be Th1 mediated but were exacerbated in the absence of interferon-gamma, the prototypic Th1 effector cytokine. Th17 cells express unique transcription factors and secrete a unique pattern of cytokines. Interleukin-17A induces pro-inflammatory cytokines and chemokines and mediates neutrophil recruitment. Th17 cells have a reciprocal relationship with T regulatory cells and can also mediate suppression of Th1 responses. Recent studies also suggest that Th17 cells are not terminally differentiated but can switch into Th1 cells. Th17 cells have themselves been recently shown to induce antigen-specific cell-mediated

proliferative glomerulonephritis. There is increasing evidence implicating Th17 cells in anti-glomerular basement membrane disease, lupus nephritis and pauci-immune glomerulonephritis. This review will review the discovery of the Th17 subset, its properties, its relationship with other Th subsets and assess the current evidence implicating Th17 cells in glomerulonephritis.

DOI: 10.1111/j.1440-1797.2010.01343.x

PMID: 20649870 [Indexed for MEDLINE]

3223. Clin Rheumatol. 2011 Apr;30(4):491-5. doi: 10.1007/s10067-010-1537-9. Epub 2010 Jul 20.

Mediterranean fever (MEFV) gene mutation frequency is not increased in adults with rheumatic heart disease.

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It is well established that there are people with higher risk of developing acute rheumatic fever (ARF) and rheumatic heart disease (RHD). Mediterranean fever (MEFV) gene mutations might be one of the genetic predisposition factors in the development of ARF/RHD since defect in familial Mediterranean fever (FMF) patients is proposed to be heightened inflammatory response to certain stimuli. Previous clinical observations suggested a relationship between FMF and ARF/RHD. The aim of this study was to investigate the role of the MEFV gene mutations in the susceptibility to RHD in Turkish patients. A total of 100 patients with RHD and 100 healthy controls were included in the study. Diagnosis of RHD was based on echocardiographic findings in which a predominant mitral stenosis was used as an inclusion criterion. Genetic analysis was carried out by sequence analysis investigating two hot spots (exons 2 and 10) for MEFV mutations. Mutation analysis showed that 22 RHD patients (22%) and 24 healthy controls (24%) carried at least one mutated allele. MEFV mutations were identified in 22 of 200 (11%) chromosomes in RHD patients while 26 of the 200 (13%) chromosomes of healthy controls were found to carry a mutated allele. No difference was found in allele frequencies and their distribution between the patients and healthy controls

( $p = 0.54$ ). MEFV mutations are not associated with a predisposition to develop RHD in adult Turkish patients.

DOI: 10.1007/s10067-010-1537-9

PMID: 20645115 [Indexed for MEDLINE]

3224. J Manag Care Pharm. 2010 Jul-Aug;16(6):402-16.

Formulary review of 2 new biologic agents: tocilizumab for rheumatoid arthritis and ustekinumab for plaque psoriasis.

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**BACKGROUND:** Two autoimmune biologics were recently approved by the FDA: ustekinumab in September 2009 for the treatment of moderate to severe plaque psoriasis in adults who are candidates for phototherapy or systemic therapy and tocilizumab in January 2010 for adult patients with moderate to severe rheumatoid arthritis (RA) who have not responded adequately to 1 or more tumor necrosis factor (TNF) antagonist therapies. Both agents use new mechanisms of action and add to the growing group of autoimmune biologics.

**OBJECTIVE:** To critically review the phase 3 trials for ustekinumab and tocilizumab and provide managed care considerations in the context of the 9 other biologic agents on the market in the United States that are used to treat moderate to severe RA or psoriasis.

**METHODS:** A MEDLINE review was performed for articles published and available through January 2010 using keywords "ustekinumab" and "tocilizumab" with an emphasis on phase 3 trials. The literature search was limited to articles in English, clinical trials, randomized controlled trials, and research conducted in humans. Search results for ustekinumab included 8 articles of which 4 were excluded for not being psoriasis or psoriatic arthritis trials. Search results for tocilizumab included 16 articles of which 8 were excluded for not being RA trials or using biomarkers as primary endpoints. Additional information was obtained from the FDA website.

**RESULTS:** Three phase 3 trials are available for ustekinumab. Ustekinumab

demonstrated superior efficacy to placebo in 2 trials for the treatment of psoriasis. In a 12-week trial, ustekinumab 45 milligrams (mg) and 90 mg demonstrated significantly higher rates of 75% improvement in the psoriasis area and severity index (PASI 75) (67.5% and 73.8%, respectively) compared with etanercept (56.8%) in the first phase 3 comparative psoriasis trial between autoimmune biologics ( $P < 0.05$  for both comparisons). In a phase 3 trial of RA patients who had failed prior TNF antagonist therapy, a 20% improvement in signs or symptoms according to the American College of Rheumatology criteria (ACR 20) at week 24 was achieved by significantly more study participants in the tocilizumab 8 mg per kilogram (kg) (50.0%) and 4 mg per kg (30.4%) groups than the placebo group (10.1%,  $P < 0.001$  for both tocilizumab groups compared with placebo). Safety data for ustekinumab are limited to use for less than 2 years, and the prescribing information contains warnings regarding infection and malignancy. Tocilizumab is associated with neutropenia, thrombocytopenia, and elevations in lipids and liver function tests. Tocilizumab has unique adverse events when compared with other autoimmune biologics and requires laboratory testing and careful monitoring.

**CONCLUSIONS:** Ustekinumab and tocilizumab are new additions to the treatment of autoinflammatory disease. The majority of safety data for both agents are from trials lasting 3 to 6 months. Published long-term safety data for tocilizumab are limited to less than 143 patients treated longer than 5 years, and safety data for ustekinumab are scant beyond 2 years of use; therefore, clinicians should exercise caution prior to widespread adoption. The comparative efficacy and safety trial of etanercept and ustekinumab brings important clinical information to decision makers. Tocilizumab is indicated after failure or intolerance to a TNF antagonist and has unique safety concerns. Managed care plans will consider the experience and long-term data of these agents along with efficacy data and cost when establishing management programs such as prior authorization or step therapy.

DOI: 10.18553/jmcp.2010.16.6.402

PMID: 20635831 [Indexed for MEDLINE]

3225. Rheumatology (Oxford). 2010 Dec;49(12):2454-5. doi: 10.1093/rheumatology/keq227. Epub 2010 Jul 15.

Tumor necrosis factor receptor-associated periodic syndrome P46L and bilateral amputation in diabetes.



Quimby KR, Greenidge AR, Hennis AJ, Harrison DK, Landis RC.

DOI: 10.1093/rheumatology/keq227

PMID: 20634234 [Indexed for MEDLINE]

3226. J Biol Chem. 2010 Sep 10;285(37):28806-11. doi: 10.1074/jbc.M110.125948. Epub 2010 Jul 14.

Mammalian telomeric DNA suppresses endotoxin-induced uveitis.

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Telomeric regions of mammalian chromosomes contain suppressive TTAGGG motifs that inhibit several proinflammatory and Th1-biased immune responses. Synthetic oligodeoxynucleotides (ODN) expressing suppressive motifs can reproduce the down-regulatory activity of mammalian telomeric repeats and have proven effective in the prevention and treatment of several autoimmune and autoinflammatory diseases. Endotoxin-induced uveitis (EIU) is an established animal model of acute ocular inflammation induced by LPS administration. Augmented expression of proinflammatory cytokines/chemokines such as TNF $\alpha$ , IL-6, and MCP1 and bactericidal nitric oxide production mediated by LPS contribute to the development of EIU. Suppressing these mediators using agents that are devoid of undesirable systemic side effects may help prevent the development of EIU. This study demonstrates the selective down-regulatory role of suppressive ODN after (i) local or (ii) systemic treatment in EIU-induced rabbits and mice. Our results indicate that suppressive ODN down-regulate at both the transcript and protein levels of several proinflammatory cytokines and chemokines as well as nitric oxide and co-stimulatory surface marker molecules when administered prior to, simultaneously with, or even after LPS challenge, thereby significantly reducing ocular inflammation in both rabbit and mouse eyes. These findings strongly suggest that suppressive ODN is a potent candidate for the prevention of uveitis and could be applied as a novel DNA-based immunoregulatory agent to control other

autoimmune or autoinflammatory diseases.

DOI: 10.1074/jbc.M110.125948

PMCID: PMC2937908

PMID: 20630869 [Indexed for MEDLINE]

3227. Internist (Berl). 2010 Aug;51(8):1013-26; quiz 1027-8. doi: 10.1007/s00108-010-2682-6.

[Systemic lupus erythematosus. A problem based approach].

[Article in German]

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Comment in

Internist (Berl). 2011 Jun;52(6):768-70.

Systemic lupus erythematosus (SLE) is a chronic autoinflammatory disease of unknown etiology with predominance of the female sex. Clinical criteria as well as immunological characteristics, e. g. autoantibodies, are necessary for diagnosis. The clinical course of SLE is variable and may be characterized by periods of remissions and chronic or acute relapses. New symptoms are often challenging regarding differential diagnosis. This review will discuss symptoms with a problem based approach. Parameters of activity are helpful to differentiate between disease activity and associated problems, e. g. infections. Lupus patients have a 5 times increased mortality compared to the normal population. The main reasons for mortality are infections and cardiovascular events, rather than disease manifestations. Therefore, besides the fast and precise use of immunosuppressants the consequent therapy of co-morbidities is a major issue in dealing with these patients. Cardiovascular risk factors need to be controlled, life style modifications should be started early, and diagnosis and therapy of osteoporosis should not be neglected.

DOI: 10.1007/s00108-010-2682-6

PMID: 20628717 [Indexed for MEDLINE]

3228. J Immunol. 2010 Aug 1;185(3):1711-9. doi: 10.4049/jimmunol.1000105. Epub 2010 Jul 7.

Inflammasome activation by adenylate cyclase toxin directs Th17 responses and protection against *Bordetella pertussis*.

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Inflammasome-mediated IL-1 $\beta$  production is central to the innate immune defects that give rise to certain autoinflammatory diseases and may also be associated with the generation of IL-17-producing CD4(+) T (Th17) cells that mediate autoimmunity. However, the role of the inflammasome in driving adaptive immunity to infection has not been addressed. In this article, we demonstrate that inflammasome-mediated IL-1 $\beta$  plays a critical role in promoting Ag-specific Th17 cells and in generating protective immunity against *Bordetella pertussis* infection. Using a murine respiratory challenge model, we demonstrated that the course of *B. pertussis* infection was significantly exacerbated in IL-1R type I-defective (IL-1RI(-/-)) mice. We found that adenylate cyclase toxin (CyaA), a key virulence factor secreted by *B. pertussis*, induced robust IL-1 $\beta$  production by dendritic cells through activation of caspase-1 and the NALP3-containing inflammasome complex. Using mutant toxins, we demonstrate that CyaA-mediated activation of caspase-1 was not dependent on adenylate cyclase enzyme activity but was dependent on the pore-forming capacity of CyaA. In addition, CyaA promoted the induction of Ag-specific Th17 cells in wild-type but not IL-1RI(-/-) mice. Furthermore, the bacterial load was enhanced in IL-17-defective mice. Our findings demonstrate that CyaA, a virulence factor from *B. pertussis*, promotes innate IL-1 $\beta$  production via activation of the NALP3 inflammasome and, thereby, polarizes T cell responses toward the Th17 subtype. In addition to its known role in subverting host immunity, our findings suggest that CyaA can promote

IL-1beta-mediated Th17 cells, which promote clearance of the bacteria from the respiratory tract.

DOI: 10.4049/jimmunol.1000105

PMID: 20610650 [Indexed for MEDLINE]

3229. Transplantation. 2010 Jul 15;90(1):102-3. doi: 10.1097/TP.0b013e3181d84cc3.

Transmission of familial Mediterranean fever mutation after bone marrow transplantation and successful treatment with anakinra.

Petropoulou AD, Robin M, Socié G, Galicier L.

DOI: 10.1097/TP.0b013e3181d84cc3

PMID: 20606570 [Indexed for MEDLINE]

3230. Expert Rev Clin Immunol. 2010 Jul;6(4):633-41. doi: 10.1586/eci.10.29.

Mycobacteria in Crohn's disease: how innate immune deficiency may result in chronic inflammation.

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Crohn's disease (CD) is often considered to be an autoimmune condition or, alternatively, an autoinflammatory condition, based on the observation of host-directed inflammatory processes. However, the underlying basis of this deleterious inflammatory response remains elusive. Recent findings from genetic and genomic studies have altered the perspective on the pathogenesis of CD, hinting at defects in innate immune sensing of intracellular bacteria and the handling of these organisms through autophagy. These findings are consistent with emerging data from immunological studies that point to a systemic immune deficiency in CD patients. Both sets of data (genetic predisposition and immunodeficiency) are consistent with the longstanding hypothesis that

mycobacteria might be involved in the etiology of CD. In this article, we discuss the convergence of these three lines of investigation and highlight important knowledge gaps required in order to address the mycobacterial hypothesis with greater clarity. In the coming years, clinical immunological investigations should focus on defining the specificity of functional immune defects with regards to microbes and their associated ligands. Should CD result from a dysfunctional host-pathogen interaction, elucidation of the microbes that can exploit such defects to induce a chronic inflammatory disease is critical for the development of subsequent diagnostic assays and clinical interventions.

DOI: 10.1586/eci.10.29

PMID: 20594136 [Indexed for MEDLINE]

3231. Curr Opin Endocrinol Diabetes Obes. 2010 Aug;17(4):314-21. doi: 10.1097/MED.0b013e32833bf6dc.

Role of IL-1beta in type 2 diabetes.

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**PURPOSE OF REVIEW:** To understand the role of inflammation as the fundamental cause of type 2 diabetes and specifically to examine the contribution of IL-1beta.

**RECENT FINDINGS:** Recent studies from animals, in-vitro cultures and clinical trials provide evidence that support a causative role for IL-1beta as the primary agonist in the loss of beta-cell mass in type 2 diabetes. In vitro, IL-1beta-mediated autoinflammatory process results in beta-cell death. The autoinflammation is driven by glucose, free fatty acids, leptin, and IL-1beta itself. Caspase-1 is required for IL-1beta activity and the release of free fatty acids from the adipocyte. An emerging hypothesis gains support from patients with type 2 diabetes in which an imbalance in the amount of IL-1beta agonist activity versus the specific countering by the naturally occurring IL-1 receptor antagonist (IL-1Ra) determines the outcome of islet inflammation. An important confirmation comes from clinical trials. Blockade of IL-1 receptor with anakinra,

the recombinant form of IL-1Ra, or neutralizing anti-IL-1beta antibodies, provides proof-of-principle data that reducing IL-1beta activity is sufficient for correcting dysfunctional beta-cell production of insulin in type 2 diabetes, including a possibility that suppression of IL-1beta-mediated inflammation in the microenvironment of the islet allows for regeneration.

SUMMARY: Monotherapy or add-on therapy targeting IL-1beta in type 2 diabetes holds promise for long-term benefits in glycemic control and possibly reducing cardiovascular events.

DOI: 10.1097/MED.0b013e32833bf6dc

PMID: 20588114 [Indexed for MEDLINE]

3232. Clin Toxicol (Phila). 2010 Jun;48(5):407-14. doi: 10.3109/15563650.2010.495348.

Colchicine poisoning: the dark side of an ancient drug.

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INTRODUCTION: Colchicine is used mainly for the treatment and prevention of gout and for familial Mediterranean fever (FMF). It has a narrow therapeutic index, with no clear-cut distinction between nontoxic, toxic, and lethal doses, causing substantial confusion among clinicians. Although colchicine poisoning is sometimes intentional, unintentional toxicity is common and often associated with a poor outcome.

METHODS: We performed a systematic review by searching OVID MEDLINE between 1966 and January 2010. The search strategy included "colchicine" and "poisoning" or "overdose" or "toxicity" or "intoxication."

TOXICOKINETICS: Colchicine is readily absorbed after oral administration, but undergoes extensive first-pass metabolism. It is widely distributed and binds to intracellular elements. Colchicine is primarily metabolized by the liver, undergoes significant enterohepatic re-circulation, and is also excreted by the kidneys. THERAPEUTIC AND TOXIC DOSES: The usual adult oral doses for FMF is

1.2-2.4 mg/day; in acute gout 1.2 mg/day and for gout prophylaxis 0.5-0.6 mg/day three to four times a week. High fatality rate was reported after acute ingestions exceeding 0.5 mg/kg. The lowest reported lethal doses of oral colchicine are 7-26 mg.

**DRUG INTERACTIONS:** CYP 3A4 and P-glycoprotein inhibitors, such as clarithromycin, erythromycin, ketoconazole, ciclosporin, and natural grapefruit juice can increase colchicine concentrations. Co-administration with statins may increase the risk of myopathy.

**MECHANISMS OF TOXICITY:** Colchicine's toxicity is an extension of its mechanism of action - binding to tubulin and disrupting the microtubular network. As a result, affected cells experience impaired protein assembly, decreased endocytosis and exocytosis, altered cell morphology, decreased cellular motility, arrest of mitosis, and interrupted cardiac myocyte conduction and contractility. The culmination of these mechanisms leads to multi-organ dysfunction and failure.

**REPRODUCTIVE TOXICOLOGY AND LACTATION:** Colchicine was not shown to adversely affect reproductive potential in males or females. It crosses the placenta but there is no evidence of fetal toxicity. Colchicine is excreted into breast milk and considered compatible with lactation.

**CLINICAL FEATURES:** Colchicine poisoning presents in three sequential and usually overlapping phases: 1) 10-24 h after ingestion - gastrointestinal phase mimicking gastroenteritis may be absent after intravenous administration; 2) 24 h to 7 days after ingestion - multi-organ dysfunction. Death results from rapidly progressive multi-organ failure and sepsis. Delayed presentation, pre-existing renal or liver impairment are associated with poor prognosis. 3) Recovery typically occurs within a few weeks of ingestion, and is generally a complete recovery barring complications of the acute illness.

**DIAGNOSIS:** History of ingestion of tablets, parenteral administration, or consumption of colchicine-containing plants suggest the diagnosis. Colchicine poisoning should be suspected in patients with access to the drug and the typical toxidrome (gastroenteritis, hypotension, lactic acidosis, and prerenal azotemia).

**MANAGEMENT:** Timely gastrointestinal decontamination should be considered with activated charcoal, and very large, recent (<60 min) ingestions may warrant gastric lavage. Supportive treatments including administration of granulocyte colony-stimulating factor are the mainstay of treatment. Although a specific experimental treatment (Fab fragment antibodies) for colchicine poisoning has been used, it is not commercially available.

**CONCLUSION:** Although colchicine poisoning is relatively uncommon, it is imperative to recognize its features as it is associated with a high mortality rate when missed.

DOI: 10.3109/15563650.2010.495348  
PMID: 20586571 [Indexed for MEDLINE]

3233. Bol Asoc Med P R. 2010 Jul-Sep;102(3):69-71.

Late presentation of familial mediterranean fever: a case report.

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Familial Mediterranean Fever (FMF) is an autosomal recessive disorder predominantly affecting people of Mediterranean origin. It is characterized by recurrent episodes of fever and polyserositis of unexplained origin. Most patients with FMF experience their first attack in early childhood with 90% suffering their first bout of pain by the age of 20. We present a case of a 68 years old woman who presented with fevers of 9 months of evolution which culminated with a diagnosis of Familial Mediterranean Fever after successful treatment with Colchicine.

PMID: 23875524 [Indexed for MEDLINE]

3234. Arch Dis Child. 2011 Jul;96(7):688-93. doi: 10.1136/adc.2009.176610. Epub 2010 Jun 28.

Review of haemophagocytic lymphohistiocytosis.

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Haemophagocytic lymphohistiocytosis (HLH) describes a clinical syndrome of hyperinflammation resulting in an uncontrolled and ineffective immune response. It may develop subsequent to a number of recognised genetic mutations or in association with infection, malignancy, autoinflammatory or metabolic conditions. Even with the published diagnostic criteria it can be difficult to make the diagnosis of HLH. Patients presenting acutely to the general paediatrician or paediatric intensivist with a clinical picture of likely sepsis, ie fever, laboratory evidence of inflammatory response, coagulopathy and thrombocytopenia should be appropriately investigated and managed for sepsis, but the possible diagnosis of HLH should be borne in mind, particularly in the child who deteriorates despite maximal therapy. This review discusses current knowledge on the classification, diagnosis and management of primary and secondary HLH, and suggests a pathway of investigation for the paediatrician faced with a potential case.

DOI: 10.1136/adc.2009.176610

PMID: 20584844 [Indexed for MEDLINE]

3235. Arthritis Rheum. 2010 Oct;62(10):3123-4; author reply 3124-5. doi: 10.1002/art.27619.

Enhanced NF- $\kappa$ B activation with an inflammasome activator correlates with activity of autoinflammatory disease associated with NLRP3 mutations outside of exon 3: comment on the article by J  ru et al.

Kambe N, Satoh T, Tanizaki H, Fujisawa A, Saito MK, Nishikomori R.

Comment on

Arthritis Rheum. 2010 Apr;62(4):1176-85.

DOI: 10.1002/art.27619

PMID: 20583107 [Indexed for MEDLINE]

3236. Am J Obstet Gynecol. 2010 Aug;203(2):144.e1-6. doi: 10.1016/j.ajog.2010.02.063. Epub 2010 Jul 1.

Pregnancy outcome after in utero exposure to colchicine.

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OBJECTIVE: We sought to examine the fetal safety of colchicine.

STUDY DESIGN: This was a prospective observational comparative cohort study regarding colchicine exposure during pregnancy including contacts to 2 Teratology Information Services in Israel from 1994 through 2006.

RESULTS: In all, 238 colchicine-exposed pregnancies (97.0% first trimester) and 964 pregnancies with nonteratogenic exposure were followed up. Treatment indications were: familial Mediterranean fever (87.3%), Behçet disease (7.5%), or other (5.2%). The rate of major congenital anomalies was comparable between the groups (10/221 [4.5%] vs 35/908 [3.9%];  $P = .648$ ). There were no cytogenetic anomalies in the colchicine group. The median gestational age at delivery was earlier (39 [38-40] vs 40 [38-41] weeks;  $P < .001$ ), the rate of preterm deliveries was higher (32/214 [15.0%] vs 51/867 [5.9%];  $P < .001$ ), and the median birthweight was lower (3000 [2688-3300] vs 3300 [2900-3600] g;  $P < .001$ ) in the colchicine group.

CONCLUSION: The present study suggests that colchicine does not appear to be a major human teratogen, and, probably, has no cytogenetic effect.

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DOI: 10.1016/j.ajog.2010.02.063

PMID: 20579964 [Indexed for MEDLINE]

3237. Rev Med Interne. 2010 Sep;31(9):637-9. doi: 10.1016/j.revmed.2009.12.021. Epub 2010 Jun 23.

[TRAPS: clinical significance of genotype. A report of two cases].

[Article in French]

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**INTRODUCTION:** Tumor necrosis factor receptor associated periodic fever syndrome (TRAPS) is defined as recurrent attacks of generalized inflammation for which no infectious or auto-immune cause can be identified; it is caused by dominantly inherited mutations in the gene encoding the first TNF receptor. We report two additional cases of patients with TRAPS, suggesting that mutation pattern of TNFRSF 1A gene may influence the TRAPS phenotype.

**CASE REPORTS:** The first patient, with a C30S mutation, exhibited severe digestive clinical manifestations; because the patient required high-dose corticosteroids regimen to improve TRAPS manifestations, he was further given successfully etanercept. The second patient, with a R92Q mutation of TNFRSF 1A gene, presented with moderate symptoms; TRAPS outcome was favourable after corticosteroid therapy initiation.

**CONCLUSION:** Therefore, R92Q may be associated with a mild disease phenotype. On the other hand, C30S mutation appears to be associated with a severe phenotype, leading to an increased risk of amyloidosis. These findings suggest that these latter patients may require a closer follow-up.

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DOI: 10.1016/j.revmed.2009.12.021

PMID: 20576331 [Indexed for MEDLINE]

3238. Dtsch Med Wochenschr. 2010 Jun;135(25-26):1312-4. doi: 10.1055/s-0030-1255161. Epub 2010 Jun 16.

[Immunology 2010].

[Article in German]

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DOI: 10.1055/s-0030-1255161

PMID: 20556689 [Indexed for MEDLINE]

3239. Echocardiography. 2010 Oct;27(9):1056-60. doi: 10.1111/j.1540-8175.2010.01217.x.

Evaluation of left ventricle function by strain imaging in patients with familial Mediterranean fever.

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AIM: Familial Mediterranean Fever (FMF) is a hereditary inflammatory disease characterized by recurrent fever and serositis. We aimed to evaluate cardiac involvement in FMF patients by using strain and strain rate echocardiographic imaging method in this study.

MATERIALS AND METHODS: Echocardiographic evaluation was performed in 23 FMF patients and 22 healthy controls. FMF diagnosis was based on Tell-Hashomer diagnostic criteria. Conventional echocardiography, tissue Doppler echocardiography and longitudinal two-dimensional (2D) strain and strain rate imaging were performed in patient and control groups.

RESULTS: There were no significant differences between patient and control groups in terms of 2D, M-mode, conventional Doppler and tissue Doppler velocities. Left ventricle strain value was significantly lower in five out of eight segments in FMF patients than controls and left ventricle strain rate value was significantly lower in three out of eight segments in FMF patients than controls. Mean left ventricle strain value was significantly lower in FMF patients than controls ( $-21.1 \pm 2.2\%$  vs.  $-23.8 \pm 2.2\%$ ;  $P < 0.001$ ). No significant difference was noted between FMF patients and controls in mean left ventricle strain rate value ( $-1.61 \pm 0.23$  vs.  $-1.58 \pm 0.21$ ;  $P = 0.48$ ).

CONCLUSION: We have shown that although conventional echocardiography and tissue Doppler velocity data were similar, strain, strain rate values were significantly lower in FMF patients than controls. We know that strain and strain rate imaging

method might be useful for evaluating subclinical cardiac involvement in case of normal conventional and tissue Doppler velocity data in patients with FMF.

© 2010, Wiley Periodicals, Inc.

DOI: 10.1111/j.1540-8175.2010.01217.x

PMID: 20553317 [Indexed for MEDLINE]

3240. *Mod Rheumatol*. 2010 Dec;20(6):566-72. doi: 10.1007/s10165-010-0317-3. Epub 2010 Jun 15.

Common MEFV mutation analysis in 36 Iranian patients with familial Mediterranean fever: clinical and demographic significance.

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The aim of our study was to determine the spectrum of the 12 most common familial Mediterranean fever gene (MEFV) mutations in Iranian patients with heterogeneous ethnicity, using the familial Mediterranean fever (FMF) strip assay test. A total of 36 patients were diagnosed according to established clinical criteria. Genomic DNA from all patients was tested for 12 common mutations located in exon 2 (E148Q), 3 (P369S), 5 (F479L), 10 [M680I (G>C), M680I (G>A), I692del, M694V, M694I, K695R, V726A, A744S, R761H], respectively, using the FMF strip assay test. Of the 35 patients with mutations, ten were homozygote, 20 were compound heterozygote, and five were heterozygote. The most frequent genotype was M680I/M680I (6 patients, 16.7%). The most frequent mutation was M680I, followed by M694V, and V726A. The FMF strip assay test for common these 12 mutations was positive in 90.6% of alleles in this study, indicating that it appears to be an effective method for FMF mutation screening in Iranian patients.

DOI: 10.1007/s10165-010-0317-3

PMID: 20549290 [Indexed for MEDLINE]

3241. Rev Med Interne. 2011 Apr;32(4):218-24. doi: 10.1016/j.revmed.2010.02.013. Epub 2010 Jun 11.

[Inflammasome and interleukin 1].

[Article in French]

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The innate immune system, which corresponds to the first line of defense against microorganisms, brings into play cell surface and intracellular sensors that detect pathogen ligands and danger signals. Among them, NOD-like receptors (NLRs) are intracellular proteins involved in inflammatory signaling pathways. NLRs are part of multiprotein complexes, called inflammasomes, which usually bring into play a NLR, an adaptor protein called ASC, and the pro-inflammatory caspase 1 protein. The activation of inflammasome by different stimuli triggers the proteolytic cleavage of pro-caspase 1 into active caspase 1, which, in turn, converts pro-interleukin 1 $\beta$  (pro-IL1 $\beta$ ) into the mature IL1 $\beta$ . IL1 $\beta$  plays a crucial role in systemic inflammation due to its ability to induce the expression of a large panel of pro-inflammatory genes and to act on various target organs. Mutations in NLR genes are responsible for several autoinflammatory and/or autoimmune disorders. For example, mutations in NLRP3, which are responsible for three Mendelian autoinflammatory disorders called cryopyrinopathies, lead to inflammasome autoactivation. Peripheral blood mononuclear cells from patients carrying NLRP3 mutations secrete high levels of IL1 $\beta$ ; in many patients presenting with autoinflammatory disorders, blocking IL1 activity by anti-IL1 therapy significantly improves their manifestations. The mechanisms leading to IL1 $\beta$  hypersecretion in other autoinflammatory disorders remain to be identified, as is the case for the role of each inflammasome in vivo. Better knowledge in this field should also contribute to the development of new anti-inflammatory treatments.

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DOI: 10.1016/j.revmed.2010.02.013  
PMID: 20541850 [Indexed for MEDLINE]

3242. FEBS Lett. 2010 Jul 16;584(14):3193-7. doi: 10.1016/j.febslet.2010.06.006. Epub 2010 Jun 10.

Activated endothelial cells induce neutrophil extracellular traps and are susceptible to NETosis-mediated cell death.

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Neutrophil interaction with activated endothelial cells (EC) is required for transmigration. We examined consequences of this interaction on NETosis. Co-culture of activated EC with neutrophils induced neutrophil extracellular trap (NET) formation, which was partially dependent on production of IL-8 by activated EC. Extended neutrophil/EC co-culture resulted in EC damage, which could be abrogated by inclusion of either diphenyleneiodonium to inhibit the NADPH oxidase pathway required for NETosis, or DNase to disrupt NETs. These findings offer new insight into mechanisms whereby NETs trigger damage to the endothelium in sepsis, small vessel vasculitis and possibly the villous trophoblast in preeclampsia.

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DOI: 10.1016/j.febslet.2010.06.006  
PMID: 20541553 [Indexed for MEDLINE]

3243. Presse Med. 2010 Jul-Aug;39(7-8):853-4. doi: 10.1016/j.lpm.2010.04.008. Epub 2010 May 27.

[Recurrent erysipelas].

[Article in French]

Grasland A(1), Groza M, Affo L, Mahé I.

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DOI: 10.1016/j.lpm.2010.04.008

PMID: 20537854 [Indexed for MEDLINE]

3244. J Clin Endocrinol Metab. 2010 Sep;95(9):E58-63. doi: 10.1210/jc.2010-0488. Epub 2010 Jun 9.

An autosomal recessive syndrome of joint contractures, muscular atrophy, microcytic anemia, and panniculitis-associated lipodystrophy.

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**CONTEXT:** Genetic lipodystrophies are rare disorders characterized by partial or complete loss of adipose tissue and predisposition to insulin resistance and its complications such as diabetes mellitus, hypertriglyceridemia, hepatic steatosis, acanthosis nigricans, and polycystic ovarian syndrome.

**OBJECTIVE:** The objective of the study was to report a novel autosomal recessive lipodystrophy syndrome.

**RESULTS:** We report the detailed phenotype of two males and one female patient, 26-34 yr old, belonging to two pedigrees with an autosomal recessive syndrome presenting with childhood-onset lipodystrophy, muscle atrophy, severe joint contractures, erythematous skin lesions, and microcytic anemia. Other variable clinical features include hypergammaglobulinemia, hepatosplenomegaly, generalized seizures, and basal ganglia calcification. None of the patients had diabetes mellitus or acanthosis nigricans. Two had mild hypertriglyceridemia and all had low levels of high-density lipoprotein cholesterol. Skin biopsy of an



erythematous nodular skin lesion from one of the patients revealed evidence of panniculitis. The lipodystrophy initially affected the upper body but later became generalized involving abdomen and lower extremities as well.

CONCLUSIONS: We conclude that these patients represent a novel autoinflammatory syndrome resulting in joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy. The molecular genetic basis of this disorder remains to be elucidated.

DOI: 10.1210/jc.2010-0488

PMCID: PMC2936059

PMID: 20534754 [Indexed for MEDLINE]

3245. Best Pract Res Clin Rheumatol. 2010 Jun;24(3):401-11. doi: 10.1016/j.berh.2009.12.009.

Autoinflammatory conditions: when to suspect? How to treat?

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The term 'autoinflammatory disease' encompasses an enlarging group of inflammatory disorders defined as Mendelian genetic diseases of the innate immune system. This group is growing considering the fact that diseases sharing strong similarities with this core group can be defined as autoinflammatory. The core group consists now of six disorders also known as hereditary recurrent fever syndromes. The most common is familial Mediterranean fever, an autosomal recessive disease affecting mainly populations of Mediterranean ancestry. All these six diseases are characterised by inflammatory attacks both at the clinical and at the biological level. The diagnosis of each of these diseases relies first on clinical features and second on genetic testing, which is guided by the clinical results. Deciphering the role of interleukin-1 in the regulation of the inflammatory response through the inflammasome represents a major advance in the knowledge of the mechanisms of these diseases with, as a main consequence,

treatment with interleukin-1 inhibitors.

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DOI: 10.1016/j.berh.2009.12.009

PMID: 20534373 [Indexed for MEDLINE]

3246. BMC Med Genet. 2010 Jun 9;11:87. doi: 10.1186/1471-2350-11-87.

1Novel MEFV transcripts in Familial Mediterranean fever patients and controls.

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**BACKGROUND:** Familial Mediterranean fever is a recessive autoinflammatory disease frequently encountered in Armenians, Jews, Arabs and Turks. The MEFV gene is responsible for the disease. It encodes a protein called pyrin/marenostrin involved in the innate immune system. A large number of clinically diagnosed FMF patients carry only one MEFV mutation. This study aims at studying the MEFV gene splicing pattern in heterozygous FMF patients and healthy individuals, in an attempt to understand the mechanism underlying the disease in these patients.

**METHODS:** RNA was extracted from peripheral blood leucocytes of 41 FMF patients and 34 healthy individuals. RT-PCR was then performed, and the amplified products were migrated on a polyacrylamide electrophoresis gel, characterized by gel extraction of the corresponding bands followed by sequencing.

**RESULTS:** Five novel splicing events were observed in both patients and controls deleting either exons 3, 4 (del34), or exons 2, 3, 4 (del234), or exons 2, 3, 4, 5 (del2345) or exon7 (del7) or exons 7 and 8 (del78).

**CONCLUSIONS:** The observation of such qualitative variability in the expression of the MEFV gene suggests a complex transcriptional regulation. However, the expression of these novel transcripts in both patients and controls is not in favour of a severe pathogenic effect.

DOI: 10.1186/1471-2350-11-87

PMCID: PMC2894788

3247. Arthritis Rheum. 2010 Oct;62(10):3059-63. doi: 10.1002/art.27598.

Increased prevalence of M694V in patients with ankylosing spondylitis: additional evidence for a link with familial mediterranean fever.

Akkoc N(1), Sari I, Akar S, Binicier O, Thomas MG, Weale ME, Birlik M, Savran Y, Onen F, Bradman N, Plaster CA.

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**OBJECTIVE:** To assess whether there is a statistically significant difference in the frequency of common MEFV allele variants in patients with ankylosing spondylitis (AS) as compared with control patients with rheumatoid arthritis (RA) and with healthy control subjects.

**METHODS:** Sixty-two patients with AS, 50 healthy control subjects, and 46 patients with RA were assessed for the presence of MEFV variants. Exon 10 was analyzed by direct sequencing. E148Q was analyzed by restriction endonuclease enzyme digestion (REED) or by direct sequencing when REED analysis failed.

**RESULTS:** The allele frequency of all MEFV variants in the AS group was significantly higher than that in the pooled control group of healthy subjects plus RA patients (15.3% versus 6.8%;  $P = 0.021$ ). M694V was the only variant that was significantly more common in the AS group than in the combined or individual control groups ( $P = 0.026$  for AS patients versus healthy controls,  $P = 0.046$  for AS patients versus RA patient controls, and  $P = 0.008$  for AS patients versus healthy and RA patient control groups). The carriage rate of M694V was also significantly higher in the AS patient group than in the combined control group (odds ratio 7.0,  $P = 0.014$ ). Neither M694V nor any other MEFV variant showed a correlation with most of the disease-related measures examined.

**CONCLUSION:** We found an increased frequency of MEFV variants in AS patients as compared with healthy controls and with RA patient controls. This was primarily due to the presence of M694V. The roles of other exon 10 variants, as well as the relationship between the variant status and the severity and clinical course of the disease, need to be explored in further studies that include sufficiently large sample sizes.

DOI: 10.1002/art.27598

PMID: 20533539 [Indexed for MEDLINE]

3248. Clin Rheumatol. 2013 Mar;32 Suppl 1:S83-5. doi: 10.1007/s10067-010-1507-2. Epub 2010 Jun 10.

A novel TNFRSF1 gene mutation in a Turkish family: a report of three cases.

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Tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is an autosomal dominantly inherited rare autoinflammatory disease. It is caused by mutations in exons 2-3 and 4-5 of the tumor necrosing factor receptor superfamily 1A (TNFRSF1A) gene on chromosome 12p13.2. TNFRSF1A gene encodes the 55-kDa receptor for tumor necrosis factor. Attacks are associated with abdominal pain, myalgia, erythematous skin rash, conjunctivitis, and periorbital edema. Until now, more than 80 mutations have been identified. We herein report three patients with TRAPS of Turkish origin. The patients were followed up in our outpatient clinic in Kocaeli University Division of Rheumatology. Because of their TRAPS associated clinical features, we isolated genomic DNA from whole blood and sequenced the exon 2-3 and 4-5 third exon of TNFRSF1A gene after amplification with appropriate primers. One of the patients with TRAPS was 47-year-old female, who described recurrent attacks of fever, urticarial rash, conjunctivitis, arthralgia, myalgia, abdominal pain, thoracic pain, headache, fatigue, and elevated acute phase response since her childhood. With the sequencing of the TNFRSF1A gene, we identified heterozygous C29R mutation, which has not been reported before in any TRAPS patient. The other patients are her sons with similar findings and age 29 and 26. They were heterozygous for C29R mutation in TNFRSF1A gene too. We report novel C29R mutation in three TRAPS patients of Turkish origin, in which the main clinical features are recurrent fever attacks, erythematous skin rash, conjunctivitis, myalgia, and arthralgia. Treatment with steroids resolved the symptoms and lesions.

DOI: 10.1007/s10067-010-1507-2  
PMID: 20532935 [Indexed for MEDLINE]

3249. *Biologics*. 2010 May 25;4:131-8.

Critical appraisal of canakinumab in the treatment of adults and children with cryopyrin-associated periodic syndrome (CAPS).

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The cryopyrin-associated syndromes (CAPS) include three autosomal-dominant syndromes, that are caused by a mutation in the NLRP3 gene on chromosome 1, encoding the cryopyrin protein. These syndromes, familial cold autoinflammatory syndrome, Muckle-Wells syndrome and neonatal-onset multisystem inflammatory disease, are characterized by urticaria-like rash, fever, central nervous system inflammation, an arthropathy and a risk of the development of amyloidosis in a respectively escalating degree of severity between the various syndromes. Recently the role of cryopyrin in the regulation of interleukin (IL)-1 production and activation was described and anti IL-1 therapies were found to be very effective in treating these syndromes. There are several types of anti IL-1 medications based on different mechanisms of antagonizing IL-1. This paper focuses on the efficacy and safety of canakinumab, a long-acting humanized anti IL-1 antibody, in treating these syndromes.

PMCID: PMC2880341  
PMID: 20531965

3250. *Rheumatology (Oxford)*. 2010 Nov;49(11):2221-3. doi: 10.1093/rheumatology/keq157. Epub 2010 Jun 4.

Colchicine-responsive chronic recurrent multifocal osteomyelitis with MEFV mutations: a variant of familial Mediterranean fever?

Shimizu M, Tone Y, Toga A, Yokoyama T, Wada T, Toma T, Yachie A.

DOI: 10.1093/rheumatology/keq157

PMID: 20525738 [Indexed for MEDLINE]

3251. Int J Immunogenet. 2010 Oct;37(5):387-91. doi: 10.1111/j.1744-313X.2010.00938.x. Epub 2010 May 27.

The rate of MEFV gene mutations in hematolymphoid neoplasms.

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The aim of this study was to determine the rate of MEFV gene mutations, the gene responsible for familial Mediterranean fever (FMF), in patients with hematolymphoid neoplasm. The rate of the five most common MEFV gene mutations (M694V, M680I, V726A, M694I and E148Q) was determined in 46 patients with hematolymphoid neoplasm. We found a high frequency of carriers in patients with multiple myeloma (60%) and acute lymphocytic leukaemia (33.3%), whereas patients with chronic lymphocytic leukaemia (9%) and non-Hodgkin lymphoma (5%) had a low mutation carrier rate. There is no MEFV gene mutation in patients with Hodgkin lymphoma. Furthermore, the statistically significant predominance of strong heterozygous mutations such as M694V and M680I in patients with hematolymphoid neoplasm; none had own and/or family history compatible with FMF, is interesting. In conclusion, we found a high frequency of carriers for MEFV gene in patients with multiple myeloma and acute lymphocytic leukaemia. The data of our study may provide some new insights in understanding of individual genetic differences in susceptibility to these neoplasms.

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DOI: 10.1111/j.1744-313X.2010.00938.x

PMID: 20518828 [Indexed for MEDLINE]

3252. Protein Pept Lett. 2010 Oct;17(10):1258-62.

Serum adiponectin levels in patients with familial Mediterranean fever.

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Familial mediterranean fever (FMF) is a systemic disorder characterized by recurrent attacks of fever and polyserositis. In FMF, several pro-inflammatory cytokines have been found to be elevated during the attacks. In recent years, it is shown that some proteins originated from adipose tissue play important role in inflammatory process. One of them, adiponectin decreases the expression of adhesion molecules and inhibits the attachment of active macrophages to the endothelial surface, so that it acts antiinflammatory effect. In this study, we analyzed the possible role of serum adiponectin in the pathogenesis of FMF. Thirty five patients with FMF and 13 healthy controls (5 female,8 male; mean age  $22.3 \pm 4.2$  years) were enrolled in this study. Fifteen patients were in active stage (6 female, 9 male, mean age;  $22.4 \pm 4.1$  years, mean disease duration  $6.1 \pm 2.3$  years) and 20 patients were in inactive stage (6 female,14 male, mean age; $22.6 \pm 4.2$  years, mean disease duration;  $5.7 \pm 1.6$  years). Serum adiponectin and IL-6 levels were determined by ELISA. The mean serum adiponectin levels were  $5.3 \pm 1.6$  ng/ml in healthy controls,  $55.3 \pm 21.8$  ng/ml in active FMF patients and  $17.1 \pm 4.7$  ng/ml in inactive FMF patients. The mean serum IL-6 levels were  $1.9 \pm 0.4$  ng/ml in healthy controls,  $4.7 \pm 1.1$  ng/ml in active FMF patients and  $2.9 \pm 1.3$  ng/ml in inactive FMF patients. Serum adiponectin levels in patients with FMF were significantly higher than in healthy controls ( $p < 0.001$ ). Serum adiponectin levels were significantly high both in active FMF patients and in inactive FMF patients compared with healthy control ( $p < 0.001$ ,  $p < 0.001$  respectively). Serum IL-6 levels were significantly higher both in patients with active and inactive disease as compared with healthy controls ( $p < 0.01$  and  $p < 0.05$  respectively). In serum adiponectin levels were correlated with high levels of serum IL-6 in the active and inactive patients. Serum adiponectin and IL-6 levels were during both active and inactive stages in patents with FMF.

PMID: 20518740 [Indexed for MEDLINE]

3253. Medicine (Baltimore). 2010 Mar;89(2):75-84. doi: 10.1097/MD.0b013e3181d5dca7.

Familial Mediterranean fever and central nervous system involvement: a case series.

Kalyoncu U(1), Eker A, Oguz KK, Kurne A, Kalan I, Topcuoglu AM, Anlar B, Bilginer Y, Arici M, Yilmaz E, Kiraz S, Calguneri M, Karabudak R.

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We conducted this study to determine familial Mediterranean fever (FMF)-associated central nervous system involvement including demyelinating lesions, stroke, and posterior reversible leukoencephalopathy syndrome (PRES). Patients with MEFV mutations were systematically reviewed through the Medical Biology Unit database. All samples sent for mutation analysis were screened for 10 common MEFV mutations. Patients with FMF and neurologic disorders according to the clinical records were invited for reevaluation. Lumbar puncture, electroencephalography, and evoked potentials were used to determine the type of neurologic involvement in selected cases. Electrocardiography, transthoracic and/or transesophageal echocardiography, and magnetic resonance imaging and/or angiography were performed to clarify the etiology of cerebrovascular disease. Of 8864 patients in the genetic testing database, 18 with neurologic signs were assessed. The mean age of patients was 31.0 +/- 11.8 years, mean age at first FMF symptom was 12.6 +/- 5.6 years, and mean age at neurologic involvement was 25.8 +/- 12.2 years. Fifty-five percent of patients were women. A homozygote MEFV mutation was detected in 16 of 18 patients (88.8%), and a homozygote M694V mutation was found in 72.2% of patients. We found 7 FMF patients with demyelinating lesions, 7 with cerebrovascular disease, and 4 with PRES. The mean interval between first FMF sign and neurologic involvement was 13.7 +/- 8.9 years in the demyelinating group, and 23.4 +/- 10.3 years in the group with cerebrovascular disease. Mean stroke age was 28.5 +/- 16.4 years. All patients in the PRES group had hypertension. Three different neurologic conditions in FMF patients were noticeable. Demyelinating lesions and cerebrovascular disease were



the most common clinical presentations. Approximately 70% of patients had the homozygote M694V mutation. Neurologic involvement is rare but serious in FMF.

DOI: 10.1097/MD.0b013e3181d5dca7

PMID: 20517179 [Indexed for MEDLINE]

3254. J Radiol. 2010 Apr;91(4):501-3.

[Imaging features of joint involvement in Familial Mediterranean Fever: A case report and value of diffusion weighted MR imaging].

[Article in French]

Gabaudan C, Cerdan F, La Folie T, Le Bougeant D, Richez P.

PMID: 20514007 [Indexed for MEDLINE]

3255. Arthritis Care Res (Hoboken). 2010 Sep;62(9):1294-8. doi: 10.1002/acr.20213.

Role of the R92Q TNFRSF1A mutation in patients with familial Mediterranean fever.

Marek-Yagel D(1), Berkun Y, Padeh S, Lidar M, Shinar Y, Bar-Joseph I, Reznik-Wolf H, Langevitz P, Livneh A, Pras E.

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**OBJECTIVE:** To define the frequency of the R92Q tumor necrosis factor receptor-associated periodic syndrome (TRAPS) mutation in patients with familial Mediterranean fever (FMF) and to study the role of this mutation in FMF.

**METHODS:** Ninety-two FMF patients and 250 controls were genotyped for the R92Q mutation. The frequency of R92Q was assessed among 5 groups of FMF patients.

**RESULTS:** R92Q was found in 6% of the controls, with an especially high carrier rate among Moroccan Jews (8%). R92Q was found in 3 (3.2%) of the 92 FMF patients, 1 homozygous for the MEFV M694V mutation and 2 heterozygous for M694V. All 3 patients showed partial response to colchicine. R92Q was not found in patients

unresponsive to colchicine, nor was it found in patients with amyloidosis or in patients with FMF-like disease without MEFV mutations.

CONCLUSION: The frequency of the R92Q mutation in FMF patients is comparable with that of controls. Despite the fact that TRAPS and FMF share common biochemical pathways, we found no evidence for an interaction between these two genes.

DOI: 10.1002/acr.20213

PMID: 20506103 [Indexed for MEDLINE]

3256. Cancer Sci. 2010 Aug;101(8):1822-7. doi: 10.1111/j.1349-7006.2010.01610.x. Epub 2010 May 3.

Activation of ASC induces apoptosis or necrosis, depending on the cell type, and causes tumor eradication.

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The adaptor protein ASC (also called TMS1) links certain NLR proteins (e.g., NLRC4, NLRP3) and caspases. It is involved in the chemosensitivity of tumor cells and inflammation. Here, we found that ASC activation using NLRC4 mimicry or an autoinflammatory disease-associated NLRP3 mutant induced necrosis in COLO205 colon adenocarcinoma cells, but induced caspase-8-dependent apoptosis in NUGC-4 stomach cancer cells. As the Fas ligand induced caspase-8-dependent apoptosis in COLO205 cells, caspase-8 was intact in this cell line. ASC-mediated necrosis was preceded by lysosomal leakage, and diminished by inhibitors for vacuolar H(+)-ATPase, cathepsins, and calpains but not by inhibitors for caspase-8, or aspartic proteases, suggesting that lysosomes and certain proteases were involved in this process. Finally, growing tumors of transplanted human cancer cells in nude mice were eradicated by the activation of endogenous ASC in the tumor cells, irrespective of the form of cell death. Thus, ASC mediates distinct forms of cell death in different cell types, and is a promising target for cancer therapy.

DOI: 10.1111/j.1349-7006.2010.01610.x

PMID: 20500518 [Indexed for MEDLINE]

3257. J Immunol. 2010 Jul 1;185(1):134-43. doi: 10.4049/jimmunol.0803474. Epub 2010 May 24.

High expression of the ectonucleotidase CD39 on T cells from the inflamed site identifies two distinct populations, one regulatory and one memory T cell population.

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The ectonucleotidase CD39 has recently been described as being highly expressed on regulatory Foxp3(+) CD4 T cells. Through hydrolysis of proinflammatory extracellular ATP, CD39 activity represents a newly described mechanism of regulatory T cell action. We report a novel population of human CD4 T cells that express CD39 yet are Foxp3 negative. These cells produce the proinflammatory cytokines IFN-gamma and IL-17 and fail to suppress proliferation; however, they still have high ATP hydrolysis activity. In the inflammatory site in human juvenile idiopathic arthritis, the CD39(+)Foxp3(-) population is greatly increased compared with peripheral blood of patients or healthy controls. We also show that cells expressing the AMPase CD73 are less frequent in the joint than in blood. To our knowledge, this is the first study to describe and characterize CD39 function on CD4 T cells from the target site in a human autoinflammatory condition. Our data suggest that in human CD4(+) T cells from the inflamed site, CD39 can be highly expressed on two populations, one regulatory and the other of a memory phenotype.

DOI: 10.4049/jimmunol.0803474

PMCID: PMC2890024

PMID: 20498355 [Indexed for MEDLINE]

3258. Clin Exp Rheumatol. 2010 May-Jun;28(3):405-7. Epub 2010 Jun 23.

Familial clustering of recurrent pericarditis may disclose tumour necrosis factor receptor-associated periodic syndrome.

Cantarini L(1), Lucherini OM, Baldari CT, Laghi Pasini F, Galeazzi M.

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**OBJECTIVES:** Although several causes of recurrent pericarditis have been identified, the etiology remains obscure in most cases. The tumour necrosis factor receptor-1 associated periodic syndrome (TRAPS) is the most common autosomal dominant autoinflammatory disorder and is caused by mutations in the TNFRSF1A gene encoding the 55-kD receptor for tumour necrosis factor-(TNF)-alpha. Serosal membrane inflammation is a common feature of TRAPS, usually in the form of polyserositis. In addition, patients affected with recurrent pericarditis as the only clinical manifestation of TRAPS have been recently described. Our aim was to investigate the possible involvement of mutations in the TNFRSF1A gene in a cohort of patients affected with idiopathic recurrent pericarditis.

**METHODS:** Twenty consecutive patients diagnosed with idiopathic recurrent pericarditis were enrolled. Each patient underwent detailed examinations in order to rule out underlying diseases such as infections, connective tissue disorders and malignancies, and mutations of the TNFRSF1A gene were searched for by amplifying, using polymerase chain reaction (PCR), genomic DNA, and direct sequencing.

**RESULTS:** TNFRSF1A mutations were found in 2 of the 20 patients. They were siblings, and they both carried a heterozygous low-penetrance R92Q mutation in the TNFRSF1A gene.

**CONCLUSIONS:** Familial clustering has been recently reported in up to 10% of patients with recurrent pericarditis, thus suggesting in some cases a possible genetic predisposition. Our study suggests that familial clustering may represent a clue for investigating mutations in the TNFRSF1A gene in these patients and eventually disclose TRAPS.

PMID: 20497634 [Indexed for MEDLINE]

3259. Rheumatol Int. 2011 Dec;31(12):1591-4. doi: 10.1007/s00296-010-1508-0. Epub 2010 May 23.

P wave dispersion in familial Mediterranean fever.

Nussinovitch N(1), Livneh A, Katz K, Nussinovitch M, Volovitz B, Lidar M, Nussinovitch U.

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Familial Mediterranean fever (FMF) is a hereditary disease characterized by recurrent and self-terminated attacks of fever and polyserositis. A recent study found that FMF patients had an abnormally high P wave duration and P wave dispersion, markers for supraventricular arrhythmogenicity. The aim of our study was to further evaluate atrial dispersion in FMF patients. The study group consisted of 26 patients with uncomplicated FMF and age- and sex-matched control subjects. All participants underwent 12-lead electrocardiography under strict standards. P wave length and P wave dispersion were computed from a randomly selected beat and from an averaged beat constructed from 7 to 12 beats, included in a 10-s ECG. No statistically significant differences were found between the groups in minimal, maximal, and average P wave duration and P wave dispersion calculated either from a random beat or averaged beats. During 6 months of follow-up, no supraventricular arrhythmias were documented in either group. FMF patients who are continuously treated with colchicine and do not develop amyloidosis have normal atrial conduction parameters and therefore seemingly do not have an increased electrocardiographic risk of atrial fibrillation.

DOI: 10.1007/s00296-010-1508-0

PMID: 20496067 [Indexed for MEDLINE]

3260. Rheumatol Int. 2011 Jul;31(7):979-80. doi: 10.1007/s00296-010-1530-2. Epub 2010 May 22.

Autoinflammatory disorders and patients with isolated serosal involvement.

Cantarini L, Lucherini OM, Cimaz R, Brizi MG, Galeazzi M.

Comment on

Rheumatol Int. 2010 Feb;30(4):531-4.

DOI: 10.1007/s00296-010-1530-2

PMID: 20495922 [Indexed for MEDLINE]

3261. Clin Neurol Neurosurg. 2010 Oct;112(8):713-6. doi: 10.1016/j.clineuro.2010.04.017. Epub 2010 May 20.

Transverse myelitis and polymyositis associated with antiphospholipid antibody syndrome.

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(1)Department of Neurology, Tokushima University, Tokushima, Japan.

Antiphospholipid antibody syndrome (APS) has been widely recognized to be associated with various neurological complications. In addition to the classical notion of APS as a thrombotic disorder, APS has been suggested to be an autoinflammatory disease as well. We present a previously healthy 46-year-old man who concurrently developed transverse myelitis and polymyositis whose laboratory studies were significant for the elevated antiphospholipid antibodies such as anti-cardiolipin (CL)/beta2-glycoprotein I (beta 2GPI) antibody. This report further enhances the recognized clinical phenotypes of the neurological complications of APS and the understanding of its pathomechanism.

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DOI: 10.1016/j.clineuro.2010.04.017

PMID: 20493629 [Indexed for MEDLINE]

3262. Eur J Intern Med. 2010 Jun;21(3):157-63. doi: 10.1016/j.ejim.2010.03.005. Epub 2010 Mar 30.

Targeting IL-1beta in disease; the expanding role of NLRP3 inflammasome.

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NLRP3 inflammasome activation and IL-1 $\beta$  secretion have recently emerged as a central mechanism in the pathogenesis of disease. Genetically defined syndromes like cryopyrin-associated periodic syndromes (CAPS, cryopyrinopathies) and familial Mediterranean fever (FMF) or diseases associated with NLRP3 activation by danger signals like gout, pseudogout, Alzheimer's disease or type 2 diabetes are included in this group of diseases. The contribution of anakinra, a recombinant, nonglycosylated human IL-1 receptor antagonist, in both the identification and treatment of such syndromes was considerable. Recently, rilonacept, a long-acting IL-1 receptor fusion protein, and canakinumab, a fully humanized anti-IL-1 $\beta$  monoclonal antibody, have been developed, with the intention to further extend IL-1 $\beta$  inhibition treatment strategies to a broader spectrum of disorders beyond the characterized autoinflammatory syndromes, offering a more favorable administration profile. On the other hand, the developed caspase-1 inhibitors, even though effective in experimental models, were not proven efficient in the treatment of inflammatory diseases.

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DOI: 10.1016/j.ejim.2010.03.005

PMID: 20493414 [Indexed for MEDLINE]

3263. Immunol Allergy Clin North Am. 2010 May;30(2):261-2. doi: 10.1016/j.iac.2010.03.004.

Indications for hemopoietic stem cell transplantation.

Roifman CM(1), Fischer A, Notarangelo LD, de la Morena MT, Seger RA.

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Immunodeficiency, The Jeffrey Modell Research Laboratory for the Diagnosis of Primary Immunodeficiency, The Hospital for Sick Children, University of Toronto, 555 University Avenue, Toronto, ON M5G 1X8, Canada. [chaim.roifman@sickkids.ca](mailto:chaim.roifman@sickkids.ca)

A complete list of definite, as well as possible, indications for hemopoietic stem cell transplantation in primary immunodeficiency is provided. Included are: severe combined immunodeficiency, profound T cell defects, autoimmune and autoinflammatory syndromes, innate immune defects, hemophagocytic disorders, and other conditions. Some causes and limitations are included.

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DOI: 10.1016/j.iac.2010.03.004

PMID: 20493401 [Indexed for MEDLINE]

3264. Mediators Inflamm. 2010;2010:986596. doi: 10.1155/2010/986596. Epub 2010 May 18.

Classification, mechanisms of action, and therapeutic applications of inhibitory oligonucleotides for Toll-like receptors (TLR) 7 and 9.

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Our immune defense depends on two specialized armed forces. The innate force acts as an alarm mechanism that senses changes in the microenvironment through the recognition of common microbial patterns by Toll-like receptors (TLR) and NOD proteins. It rapidly generates an inflammatory response aimed at neutralizing the intruder at the mucosal checkpoint. The innate arm also communicates this message with more specialized adaptive forces represented by pathogen-specific B cells and T cells. Interestingly, B cells also express some innate sensors, like TLR7 and TLR9, and may respond to bacterial hypomethylated CpG motifs and single-stranded RNA viruses. Intracellular nucleic acid sensing TLRs play an important role in the pathogenesis of Systemic Lupus Erythematosus (SLE). In this review, we describe recent achievements in the development of



oligonucleotide-(ODN)-based inhibitors of TLR9 and/or TLR7 signaling. We categorize these novel therapeutics into Classes G, R, and B based on their cellular and molecular targets. Several short ODNs have already shown promise as pathway-specific therapeutics for animal lupus. We envision their future use in human SLE, microbial DNA-dependent sepsis, and in other autoinflammatory diseases.

DOI: 10.1155/2010/986596

PMCID: PMC2873634

PMID: 20490286 [Indexed for MEDLINE]

3265. J Hum Genet. 2010 Jun;55(6):389-93. doi: 10.1038/jhg.2010.52. Epub 2010 May 20.

Genotype-phenotype studies in a large cohort of Armenian patients with familial Mediterranean fever suggest clinical disease with heterozygous MEFV mutations.

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Familial Mediterranean fever (FMF) is an autoinflammatory disorder generally caused by recessively inherited mutations in the MEFV gene. FMF is quite prevalent in Armenian population in which majority of patients have two mutated alleles, yet in 18% of symptomatic patients just one mutation has been detected. To explain this finding, we analyzed the symptoms and genotypes of 1,299 patients, including 236 affected heterozygous patients with definite diagnosis of FMF. We selected a subset of 63 heterozygous, homozygous and asymptomatic normal individuals and completely sequenced their MEFV genes (exons) to discover any other mutations potentially missed by currently used screening method. Besides four synonymous polymorphisms in exon two and five, we found a T267I mutation in one heterozygous patient with a severe case of FMF who should have been designated as compound heterozygous, yet the other genotypes were all accurate. We used binomial probability distribution of symptoms in homozygous FMF patients to estimate the likelihood of their occurrences in heterozygous patients and demonstrated the assemblage of patients into groups with similar clinical criteria using statistical clustering. We found extremely high probabilities for

the presence of FMF symptoms in heterozygous individuals and determined that symptoms were equally likely to occur in both analyzed genotypes. Therefore, our study supports the rising evidence that a single MEFV mutation could be associated with mild FMF symptoms. However, heterozygous patients presenting with severe phenotype should be further analyzed for less common second MEFV mutation using gene sequencing.

DOI: 10.1038/jhg.2010.52

PMID: 20485448 [Indexed for MEDLINE]

3266. Respiration. 2010;80(3):260-1; author reply 262. doi: 10.1159/000314981. Epub 2010 May 20.

Serosal involvement in adult-onset autoinflammatory disorders.

Cantarini L, Lucherini OM, Cimaz R, Brizi MG, Galeazzi M.

Comment on

Respiration. 2010;79(6):508-10.

DOI: 10.1159/000314981

PMID: 20484886 [Indexed for MEDLINE]

3267. J Neurol Sci. 2010 Jul 15;294(1-2):38-42. doi: 10.1016/j.jns.2010.04.008. Epub 2010 May 18.

Evaluation of common mutations in the Mediterranean fever gene in Multiple Sclerosis patients: is it a susceptibility gene?

Unal A(1), Dursun A, Emre U, Tascilar NF, Ankarali H.

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Comment in

J Neurol Sci. 2010 Nov 15;298(1-2):163; author reply 163-4.

**PURPOSE:** Multiple Sclerosis (MS) is a disease of the central nervous system characterized by multiple areas of inflammation and demyelination in the white matter of the brain and spinal cord. MEFV gene, which is the main factor in familial Mediterranean fever, is an intracellular regulator of inflammation. This study was designed to determine if known mutations in pyrin domain of MEFV gene are involved in MS and associated with MS morbidity.

**METHODS:** Fifty-three patients with MS and 66 healthy subjects, who were all Turkish, were included in this study. Five pyrin gene mutations (E148Q, M680I, M694V, M694I and V726A) were detected in the patients and controls by using the PRONTO FMF Basic Kit according to the manufacturer's instructions.

**RESULTS:** Pyrin gene mutations were found in 20 of the 53 MS patients (38%) and in seven of the 66 healthy subjects (11%). The frequency of total pyrin domain mutations was significantly higher in the MS patients than in the healthy subjects ( $p < 0.0001$ ). The frequencies of M694V, E148Q and V726A mutations were significantly higher in the patients than in the healthy subjects ( $p = 0.02$ ,  $p = 0.013$ ,  $p = 0.004$  respectively). The mean time to reach EDSS score 3.0 was earlier in the patients with MEFV gene mutation ( $p = 0.02$ ) and the relapse rate was slightly higher among the MS patients carrying MEFV gene mutation ( $p = 0.04$ ).

**CONCLUSION:** The results of this study supported the hypothesis that MS patients with MEFV mutation seem to have the susceptibility to develop a more progressive disease. Moreover, these data suggest that MEFV mutations may increase the risk of MS development.

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DOI: 10.1016/j.jns.2010.04.008

PMID: 20483145 [Indexed for MEDLINE]

3268. Clin Exp Rheumatol. 2010 Mar-Apr;28(2):290-1. Epub 2010 May 14.

Sacroileitis and pericarditis: atypical presentation of tumor necrosis factor receptor-associated periodic syndrome and response to etanercept therapy.

Cantarini L, Lucherini OM, Cimaz R, Baldari CT, Laghi Pasini F, Galeazzi M.

PMID: 20483057 [Indexed for MEDLINE]

3269. Clin Exp Rheumatol. 2010 Mar-Apr;28(2):287. Epub 2010 May 14.

Familial Mediterranean fever in Iranian children. First report from Iran.

Salehzadeh F, Jahangiri S, Emami D, Emami D, Shiari R.

PMID: 20483055 [Indexed for MEDLINE]

3270. Rheumatol Int. 2012 Dec;32(12):4015-8. doi: 10.1007/s00296-010-1512-4. Epub 2010 May 15.

Typical and severe tumor necrosis factor receptor-associated periodic syndrome in the absence of mutations in the TNFRSF1A gene: a case series.

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Tumor necrosis factor receptor-1-associated periodic syndrome (TRAPS) is the most common autosomal dominant autoinflammatory disorder and is caused by mutations in the TNFRSF1A gene encoding the 55-kDa receptor for tumor necrosis factor (TNF)- $\alpha$ . TRAPS is characterized by recurrent attacks of fever, typically lasting from 1 to 3 weeks. In addition to fever, common clinical features include periorbital edema, a migratory erythematous plaque simulating erysipela with underlying myalgia, and arthralgia or arthritis. Serosal membrane inflammation is also a common feature, usually in the form of polyserositis. To date, at least 40 different TNFRSF1A mutations have been identified, but few patients with symptoms highly suggestive of TRAPS with no mutations in the TNFRSF1A gene have recently been described, thus suggesting that not all mutations are yet known or that alternative mechanisms might be involved in the pathogenesis of the disease. We

report on three such patients here.

DOI: 10.1007/s00296-010-1512-4

PMID: 20473499 [Indexed for MEDLINE]

3271. Open Cardiovasc Med J. 2010 Feb 23;4:83-8. doi: 10.2174/1874192401004020083.

Arterial distensibility in chronic inflammatory rheumatic disorders.

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The pulse wave velocity (PWV), as an indicator of arterial distensibility, may play an important role in the stratification of patients based on the cardiovascular risk. PWV inversely correlates with arterial distensibility and relative arterial compliance. Decreased arterial distensibility alters arterial blood pressure and flow dynamics, and disturbs coronary perfusion. Systemic immune and inflammatory diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are associated with increased morbidity and mortality, predominantly due to adverse cardiovascular events. Systemic inflammation in these disorders may alter arterial compliance and arterial distensibility and, through this effect, lead to accelerated atherosclerosis. We have demonstrated an increase in the carotid-femoral (aortic) PWV that is a technique in which large artery elasticity is assessed from analysis of the peripheral arterial waveform, in patients with chronic inflammatory conditions such as RA, SLE, familial Mediterranean fever (FMF), Wegener's granulomatosis (WG), sarcoidosis, psoriasis and psoriatic arthritis except Behçet's disease (BD). In this review, the issue of arterial stiffness in RA, SLE, as well as WG, psoriasis, FMF, BD, sarcoidosis, systemic sclerosis (SS) and Takayasu's arteritis (TA) is overviewed.

DOI: 10.2174/1874192401004020083

PMCID: PMC2847817

PMID: 20461114

3272. Proc Natl Acad Sci U S A. 2010 May 25;107(21):9801-6. doi: 10.1073/pnas.0914118107. Epub 2010 May 10.

Concerted action of wild-type and mutant TNF receptors enhances inflammation in TNF receptor 1-associated periodic fever syndrome.

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Comment in

Nat Rev Rheumatol. 2010 Jul;6(7):384.

TNF, acting through p55 tumor necrosis factor receptor 1 (TNFR1), contributes to the pathogenesis of many inflammatory diseases. TNFR-associated periodic syndrome (TRAPS, OMIM 142680) is an autosomal dominant autoinflammatory disorder characterized by prolonged attacks of fevers, peritonitis, and soft tissue inflammation. TRAPS is caused by missense mutations in the extracellular domain of TNFR1 that affect receptor folding and trafficking. These mutations lead to loss of normal function rather than gain of function, and thus the pathogenesis of TRAPS is an enigma. Here we show that mutant TNFR1 accumulates intracellularly in peripheral blood mononuclear cells of TRAPS patients and in multiple cell types from two independent lines of knockin mice harboring TRAPS-associated TNFR1 mutations. Mutant TNFR1 did not function as a surface receptor for TNF but rather enhanced activation of MAPKs and secretion of proinflammatory cytokines upon stimulation with LPS. Enhanced inflammation depended on autocrine TNF secretion and WT TNFR1 in mouse and human myeloid cells but not in fibroblasts. Heterozygous TNFR1-mutant mice were hypersensitive to LPS-induced septic shock, whereas homozygous TNFR1-mutant mice resembled TNFR1-deficient mice and were resistant to septic shock. Thus WT and mutant TNFR1 act in concert from distinct cellular locations to potentiate inflammation in TRAPS. These findings establish a mechanism of pathogenesis in autosomal dominant diseases where full expression of the disease phenotype depends on functional cooperation between WT and mutant proteins and also may explain partial responses of TRAPS patients to TNF

blockade.

DOI: 10.1073/pnas.0914118107

PMCID: PMC2906866

PMID: 20457915 [Indexed for MEDLINE]

3273. Proc Natl Acad Sci U S A. 2010 May 25;107(21):9789-94. doi: 10.1073/pnas.1000779107. Epub 2010 May 5.

Altered redox state of monocytes from cryopyrin-associated periodic syndromes causes accelerated IL-1beta secretion.

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In healthy monocytes, Toll-like receptor (TLR) engagement induces production of reactive oxygen species (ROS), followed by an antioxidant response involved in IL-1beta processing and secretion. Markers of the antioxidant response include intracellular thioredoxin and extracellular release of reduced cysteine.

Cryopyrin-associated periodic syndromes (CAPS) are autoinflammatory diseases in which Nod-like receptor family pyrin domain-containing 3 (NLRP3) gene mutations lead to increased IL-1beta secretion. We show in a large cohort of patients that IL-1beta secretion by CAPS monocytes is much faster than that by healthy monocytes. This accelerated kinetics is caused by alterations in the basal redox state, as well as in the redox response to TLR triggering displayed by CAPS monocytes. Indeed, unstimulated CAPS monocytes are under a mild oxidative stress, with elevated levels of both ROS and antioxidants. The redox response to LPS is quickened, with early generation of the reducing conditions favoring IL-1beta processing and secretion, and then rapidly exhausted. Therefore, secretion of IL-1beta is accelerated, but reaches a plateau much earlier than in healthy controls. Pharmacologic inhibition of the redox response hinders IL-1beta release, confirming the functional link between redox impairment and altered kinetics of secretion. Monocytes from patients with juvenile idiopathic arthritis display normal kinetics of redox response and IL-1beta secretion, excluding a role of chronic inflammation in the alterations observed in CAPS. We conclude that preexisting redox alterations distinct from CAPS monocytes anticipate the

pathogen-associated molecular pattern molecule-induced generation of the reducing environment favorable to inflammasome activation and IL-1 $\beta$  secretion.

DOI: 10.1073/pnas.1000779107

PMCID: PMC2906851

PMID: 20445104 [Indexed for MEDLINE]

3274. Neurol Res. 2010 Dec;32(10):1117-20. doi: 10.1179/016164110X12681290831487. Epub 2010 May 4.

Topical use of colchicine to prevent spinal epidural fibrosis in rats.

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**OBJECTIVES:** Epidural fibrosis after spinal surgery may be the cause in most cases of recurrent pain. Numerous pharmacological agents and anti-adhesive barriers have been used to prevent epidural fibrosis, but the success rates are variable. Colchicine is an historical drug extracted from the flowers of *Colchium autumnale* widely used in arthritic conditions in the past. Currently, it is used in acute gout attacks, familial mediterranean fever for its anti-inflammatory and antifibrotic effects. Also, colchicine is used locally in the cutaneous diseases (e.g. actinic keratoses, psoriasis) for its similar effects. In present study, we investigated the effect of topical colchicine on spinal epidural fibrosis in the rats.

**METHODS:** The rats were randomly divided to three groups of six animals each. Total L4-5 laminectomy was performed, and ligamentum flavum and epidural fat were removed gently. Meticulous hemostasis was achieved by using cotton pad when necessary, and no bone wax and cauterization were used. Dura was left clean with no hemorrhages. In treatment group cotton pads (5 × 5 mm) soaked with 0.005 mg/ml colchicine and applied on laminectomy sites for 10 minutes and removed, in sham group only saline irrigation was done. In control group no medication or irrigation was applied. The wound was closed in layers using the same material in each group. Four weeks later, the rats were killed, and the spinal column, including surrounding muscle tissue, was removed en bloc, decalcified, and fixed



in formaldehyde. Epidural fibrosis was evaluated histologically.

RESULTS: In colchicine-treated group, epidural fibrosis was significantly reduced compared with control and sham groups.

CONCLUSIONS: Epidural fibrosis is a well-known complication following lumbar disc surgery. Topical application of colchicine is very effective in preventing epidural fibrosis.

DOI: 10.1179/016164110X12681290831487

PMID: 20444324 [Indexed for MEDLINE]

3275. Int J Hematol. 2010 Jun;91(5):758-61. doi: 10.1007/s12185-010-0577-x. Epub 2010 May 1.

High frequency of MEFV gene mutations in patients with myeloid neoplasm.

Oktenli C(1), Sayan O, Celik S, Erikci AA, Tunca Y, Terekeci HM, Umur EE, Sanisoglu YS, Torun D, Tangi F, Sahan B, Nalbant S.

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We aimed to investigate the rate of MEFV, the gene mutated in familial Mediterranean fever, mutations in patients with myeloid neoplasm and to determine if known mutations of MEFV cause a tendency for myeloid neoplasms. The frequency of the five most common MEFV gene mutations (M694V, M680I, V726A, E148Q and M694I) was determined in 26 patients with myeloid neoplasm. We identified 1 homozygous (E148Q/E148Q), 1 compound heterozygous (M694V/E148Q) and 5 heterozygous MEFV gene mutations; none had their own and/or family history compatible with familial Mediterranean fever. The mean overall mutation rate was 0.269. We found a high frequency of carriers in patients with myelodysplastic syndrome (66.6%), polycythemia vera (33.3%) and acute myeloid leukemia (28.6%). However, there was no MEFV gene mutation in patients with chronic myeloid leukemia. In conclusion, this study reports for the first time a possibly high prevalence of MEFV gene mutations in patients with myeloid neoplasm, especially myelodysplastic syndrome, polycythemia vera and acute myeloid leukemia. Our findings could open new perspectives for MEFV gene mutations in myeloid neoplasms and its association with tumor promotion. Further research is needed to determine

the actual role of MEFV gene mutations in these malignancies.

DOI: 10.1007/s12185-010-0577-x

PMID: 20437121 [Indexed for MEDLINE]

3276. Gastroenterol Hepatol. 2010 Oct;33(8):615. doi: 10.1016/j.gastrohep.2010.02.013.

[Fever and recurrent abdominal pain].

[Article in Spanish]

Reguera García A, León Martínez MD, Aguayo Jiménez C, Sánchez Serrano A.

DOI: 10.1016/j.gastrohep.2010.02.013

PMID: 20435385 [Indexed for MEDLINE]

3277. Saudi J Kidney Dis Transpl. 2010 May;21(3):546-7.

Renal artery embolization in a patient with severe nephrotic syndrome.

Solak Y, Atalay H, Polat I, Turkmen K, Koc O, Turk S.

PMID: 20427891 [Indexed for MEDLINE]

3278. Curr Rheumatol Rep. 2010 Apr;12(2):101-7. doi: 10.1007/s11926-010-0086-1.

Hyperimmunoglobulin D syndrome in childhood.

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Hyperimmunoglobulinemia D and periodic fever syndrome, an autoinflammatory

syndrome, is caused by mutations in the gene coding for mevalonate kinase. The disease is clinically characterized by recurrent attacks of fever accompanied by an array of inflammatory symptoms including lymphadenopathy, rash, arthritis, and gastrointestinal complaints. Most patients have their first attack in the first year of life, typically after a childhood vaccination. The frequency of attacks is highest during childhood, with a gradual decrease after adolescence. Frequent fever attacks impair quality of life and the achievement of educational milestones. Recent reports show promising results with anakinra and etanercept to treat the attacks.

DOI: 10.1007/s11926-010-0086-1

PMID: 20425018 [Indexed for MEDLINE]

3279. Intern Med. 2010;49(8):767-9. Epub 2010 Apr 15.

Coexistence of systemic lupus erythematosus and familial Mediterranean fever.

Yildiz G(1), Kayatas M, Uygun Y, Timuçin M, Candan F.

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Clinical symptoms and findings of familial Mediterranean fever (FMF), occur as a result of autoimmune inflammation of the serous membrane which is also seen in systemic lupus erythematosus (SLE). Difficulties are sometimes encountered in the differential diagnosis of FMF because of similar clinical features with other autoimmune inflammatory diseases, and very rarely it can be seen with SLE. The association of FMF and SLE has been reported in one childhood case in Turkey. As far as we know, there is no report in the adult age group. Here, we present the first FMF and SLE association in an adult and discuss the pertinent literature in Turkey.

PMID: 20424368 [Indexed for MEDLINE]

3280. Neurology. 2010 Apr 20;74(16):1267-70. doi: 10.1212/WNL.0b013e3181d9ed69.

## Neurologic manifestations of the cryopyrin-associated periodic syndrome.

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**BACKGROUND:** The cryopyrin-associated periodic syndrome (CAPS) is a rare but treatable hereditary autoinflammatory condition. Without treatment, one third of patients develop amyloidosis with consequent renal failure and death. CAPS encompasses 3 conditions: familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and chronic infantile, neurologic, cutaneous, and articular syndrome. Neurologic complications are common in children with the chronic infantile, neurologic, cutaneous, and articular phenotype, but there are no previous published reports of neurologic features in adults with milder phenotypes.

**METHODS:** In this case series, we report in detail an adult case of CAPS and summarize the neurologic features seen in 12 other adults with genetically proven CAPS. These patients participated in a recent randomized study of canakinumab in CAPS and we used pretreatment data collected in this study.

**RESULTS:** Twelve of the 13 patients (92%) had headache, of whom 10 (77%) had features of migraine. Seven patients (54%) had sensorineural deafness. Nine patients (69%) reported myalgia. Six patients (46%) had papilledema and a further 2 (15%) had optic disc pallor. MRI brain scan was normal in all patients.

**CONCLUSION:** CAPS is a rare but treatable condition that may be encountered by neurologists in adult clinical practice since it can present with headache, myalgia, papilledema, sensorineural deafness, and aseptic meningitis.

Unrecognized and untreated, it can lead to significant morbidity and mortality from renal failure. Treatment with anti-interleukin-1 therapy leads to complete resolution of symptoms and should also prevent progression to amyloidosis and subsequent renal failure.

DOI: 10.1212/WNL.0b013e3181d9ed69

PMID: 20404307 [Indexed for MEDLINE]

A novel missense mutation in tumour necrosis factor receptor superfamily 1A (TNFRSF1A) gene found in tumour necrosis factor receptor-associated periodic syndrome (TRAPS) with high serum interleukin (IL)-22.

Nakamura M, Tokura Y.

DOI: 10.1684/ejd.2010.0951

PMID: 20400394 [Indexed for MEDLINE]

3282. N Engl J Med. 2010 Jun 3;362(22):2045-7. doi: 10.1056/NEJMp1003126. Epub 2010 Apr 14.

Incentives for drug development--the curious case of colchicine.

Kesselheim AS(1), Solomon DH.

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(1)Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, and Harvard Medical School, Boston, USA.

Comment in

N Engl J Med. 2010 Dec 2;363(23):2267-8.

N Engl J Med. 2010 Oct 7;363(15):1484; author reply 1484-5.

DOI: 10.1056/NEJMp1003126

PMID: 20393164 [Indexed for MEDLINE]

3283. Genet Mol Res. 2010 Apr 6;9(2):611-9. doi: 10.4238/vol9-2gmr743.

Mediterranean fever gene mutation analysis in infertile Turkish males.

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Male infertility is a common barrier that prevents successful conception. There have been reports of azoospermia in men with familial Mediterranean fever, some of whom had not been treated with colchicine. Variation in this disorder could be a risk factor for amyloidosis associated with azoospermia. We determined the frequency of 6 of the most common Mediterranean fever gene mutations, M680I, M694V, M694I, V726A, P369S, and A744S, in 74 infertile men, 155 men diagnosed with familial Mediterranean fever and 55 healthy fertile men in eastern Turkey. All three groups were screened for the 6 mutations using an amplification refractory mutation system and restriction fragment length polymorphism methods. Allelic frequencies were 2.7% for M694V and 1.35% for V726A in the infertile patient group and 1.8% for M694V and 1.8% for V726A in healthy subjects. Other mutations were not detected in patients or controls. The mutation frequency was not found to be significantly higher in infertile patients when compared with healthy fertile male controls. To our knowledge, this is the first study to determine the frequency of Mediterranean fever gene mutations in infertile male and the infertility rate of male patients with familial Mediterranean fever.

DOI: 10.4238/vol9-2gmr743

PMID: 20391345 [Indexed for MEDLINE]

3284. J Cardiovasc Med (Hagerstown). 2010 Aug;11(8):557-62. doi: 10.2459/JCM.0b013e3283352356.

Management of pericardial diseases during pregnancy.

Imazio M(1), Brucato A, Rampello S, Armellino F, Trincherò R, Spodick DH, Adler Y.

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Relatively few data have been published on the management of pericardial diseases during pregnancy. Pericardial involvement is sporadic during pregnancy, and pregnant women do not show any specific predisposition to pericardial diseases. The more common form of pericardial involvement is hydropericardium, usually as a benign mild effusion recorded in about 40% of pregnant women by the third trimester, followed by pericarditis as the more common disease requiring medical

therapy. The general management of these conditions is not different from those of nonpregnant women, although specific precautions should be followed for specific diagnostic and therapeutic issues during pregnancy. If possible, pregnancy should be planned in a phase of disease quiescence. Nonselective cyclooxygenase inhibitors and aspirin can be used safely during the first and second trimester, but should be withdrawn later and in any case at gestational week 32, because of the possible effects on ductus arteriosus and renal function. Low-medium doses of prednisone are allowed during all pregnancy and breastfeeding. Colchicine is generally contraindicated during pregnancy, except in women with familial Mediterranean fever. These pregnancies should be followed by a dedicated multidisciplinary teams.

DOI: 10.2459/JCM.0b013e3283352356

PMID: 20389257 [Indexed for MEDLINE]

3285. Rheumatol Int. 2012 Oct;32(10):3277-9. Epub 2010 Apr 13.

Efficacy of anakinra treatment in a patient with colchicine-resistant familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by self-limited recurrent attacks of fever and serositis. The serious complication of FMF is AA-type amyloidosis, which can result in end-stage renal disease. Although colchicine is effective in the majority of patients, there is no established treatment for those who are resistant or intolerant to colchicine. We herein report the efficacy of anakinra in a 52-year-old Turkish patient with FMF, secondary amyloidosis and renal transplant, who was resistant to colchicine treatment.

DOI: 10.1007/s00296-010-1474-6

PMID: 20386914 [Indexed for MEDLINE]

3286. Clin Rheumatol. 2010 Dec;29(12):1353-6. doi: 10.1007/s10067-010-1434-2. Epub 2010 Apr 11.

QT dispersion in uncomplicated familial Mediterranean fever.

Nussinovitch N(1), Livneh A, Katz K, Langevitz P, Feld O, Nussinovitch M, Volovitz B, Lidar M, Nussinovitch U.

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The aim of the study was to further evaluate repolarization dispersion in familial Mediterranean fever (FMF). Findings on 12-lead electrocardiography were compared with 32 patients with uncomplicated FMF and age- and sex-matched control subjects. All procedures followed stringent standards. Repolarization and dispersion parameters were computed with designated computer software, and results of the five beats were subsequently averaged. There were no statistically significant differences between the groups in average QT and average corrected QT interval length, average QT interval dispersion, average QT corrected dispersion, or QT dispersion ratio. During 6 months of follow-up, no cases of sudden death or arrhythmia were documented in either group. Patients with FMF who are continuously treated with low-dose colchicine and have not developed amyloidosis seem to have QT dispersion parameters similar to those of healthy subjects and therefore apparently have no increased risk of adverse cardiac events associated with abnormal repolarization.

DOI: 10.1007/s10067-010-1434-2

PMID: 20383732 [Indexed for MEDLINE]

3287. Rheumatol Int. 2011 Jul;31(7):971-2. doi: 10.1007/s00296-010-1498-y. Epub 2010 Apr 10.

An unusual effect of colchicine treatment in familial Mediterranean fever-associated glomerulonephritis.

Ceri M, Unverdi S, Altay M, Yilmaz R, Duranay M.



3288. Genet Test Mol Biomarkers. 2010 Jun;14(3):325-8. doi: 10.1089/gtmb.2009.0189.

Genotype-phenotype correlation in patients with familial Mediterranean fever in East Anatolia (Turkey).

Albayrak F(1), Selcuk NY, Odabas AR, Cetinkaya R, Pirim I.

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**AIMS:** Familial Mediterranean fever (FMF) is an autosomal recessive hereditary disease. Clinical symptoms and findings (phenotypes) seen in this disease are generally fever, abdominal pain, and arthritis. Amyloidosis is also a significant complication. Phenotype-genotype correlations in FMF have not been conclusively resolved. The aims of this study were to find the most frequent mutation/genotype of FMF, as well as to investigate the role of genetic factors on the phenotype and on the development of amyloidosis in a population living in East Anatolia (Turkey). This study included 105 adult patients with FMF. DNA samples were obtained from peripheral blood lymphocytes of the patients. Mutations of the Mediterranean fever (MEFV) gene were analyzed with an FMF Strip Assay test kit (ViennaLab Labordiagnostika GmbH, Vienna, Austria). Patients were separated according to genotypes, and phenotypes were compared statistically by the chi-square test.

**RESULTS:** The most frequent mutation was M694V (53%) and the most frequent genotype was M694V/M694V (26%). In total, 81% of the patients experienced abdominal pain, 76% had fever, and 22% had arthritis. Fever and arthritis were determined in similar ratios to other genotypes (76% and 19%, respectively) in the M694V/M694V genotype (74% and 29%, respectively) ( $p > 0.50$  and  $p > 0.20$ , respectively). However, the patients without the M694V/M694V genotype (86%) had a higher abdominal pain ratio than did the patients with the M694V/M694V genotype (67%) ( $p < 0.05$ ). Renal amyloidosis was determined in 33% of both M694V/M694V and M680I(G/C)/M680I(G/C) homozygous groups and in 12% of the heterozygous groups ( $p < 0.02$  and  $p < 0.00002$ , respectively). In other words, homozygous groups had

higher ratios of renal amyloidosis.

CONCLUSIONS: The most frequent mutation in FMF was M694V and the most frequent genotype was M694V/M694V. Fever, abdominal pain, arthritis, and renal amyloidosis were determined not only in patients with M694V/M694V genotype but also in other genotypes. Therefore, genotypes may not predict phenotypes in FMF. Renal amyloidosis was seen more frequently in homozygous genotypes.

DOI: 10.1089/gtmb.2009.0189

PMID: 20373849 [Indexed for MEDLINE]

3289. Ren Fail. 2010 Jan;32(3):401-3. doi: 10.3109/08860221003640090.

Familial Mediterranean fever and membranous glomerulonephritis: report of a case.

Ceri M(1), Unverdi S, Altay M, Unverdi H, Ensari A, Duranay M.

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Familial Mediterranean fever (FMF) is an autosomal recessive genetic disease characterized by recurrent attacks of fever and painful episodes of sterile polyserositis. Kidney involvement may occur as a result of secondary amyloidosis during the course of FMF. Previously, different types of glomerulopathies such as IgM and IgA nephropathy, crescentic glomerulonephritis, diffuse proliferative glomerulonephritis, minimal change disease, and membranoproliferative glomerulonephritis were rarely reported. We herein represent a first case of membranous glomerulonephritis who had complete remission with colchicine treatment in the course of familial Mediterranean fever.

DOI: 10.3109/08860221003640090

PMID: 20370460 [Indexed for MEDLINE]

3290. Arch Pathol Lab Med. 2010 Apr;134(4):532-44. doi: 10.1043/1543-2165-134.4.532.

A proposed histopathologic classification, scoring, and grading system for renal amyloidosis: standardization of renal amyloid biopsy report.

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Comment in

Arch Pathol Lab Med. 2011 Feb;135(2):168; author reply 168-9.

**CONTEXT:** A disease associated with amyloid deposits, called amyloidosis, is associated with characteristic electron microscopic appearance, typical x-ray pattern, and specific staining. Renal involvement mainly occurs in AA amyloidosis and AL amyloidosis and usually progresses to renal failure.

**OBJECTIVE:** The renal histopathologic changes with amyloidosis comprise a spectrum. Clear relationships between the extent of amyloid deposition and the severity of clinical manifestations have not been demonstrated. Whether there is a lack of clinicopathologic correlation is not clear, but studies have revealed the need for standardization of the renal amyloid biopsy report. With these objectives in mind, we proposed a histopathologic classification, scoring, and grading system. Renal amyloidosis was divided into 6 classes, similar to the classification of systemic lupus erythematosus. Amyloid depositions and other histopathologic lesions were scored. The sum of these scores was termed the renal amyloid prognostic score and was divided into 3 grades.

**DATA SOURCES:** AA amyloidosis was detected in 90% of cases, mostly related to familial Mediterranean fever. Positive correlations between class I and grade I, class VI and grade III, and class III and grade II were observed. Also, a positive correlation was identified between severity of glomerular amyloid depositions, interstitial fibrosis, and inflammation. Because of the inadequacy of the patients' records and outcomes, different therapy regimes, and etiologies, clinical validation of this study has not been completed.

**CONCLUSIONS:** Standardization of the renal amyloid pathology report might be critical for patients' medication and comparison of outcome and therapeutic trials between different clinics. Because of our AA to AL amyloidosis ratio and the predisposition of familial Mediterranean fever-related AA amyloidosis, there is a need for further international collaborative studies.

DOI: 10.1043/1543-2165-134.4.532

PMID: 20367305 [Indexed for MEDLINE]

3291. Open Cardiovasc Med J. 2010 Feb 23;4:51-6. doi: 10.2174/1874192401004020051.

Familial mediterranean Fever as an emerging clinical model of atherogenesis associated with low-grade inflammation.

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Numerous inflammatory and innate immune pathways are involved in atherogenesis. Elaboration of clinical models of inflammation-induced atherogenesis may further advance our knowledge of multiple inflammatory pathways implicated in atherogenesis and provide a useful tool for cardiovascular prevention. Familial Mediterranean fever (FMF) is a chronic inflammatory disorder with profiles of inflammatory markers close to that seen in the general population. In a few recent studies, it has been shown that endothelial dysfunction, increased atherosclerotic burden and activation of platelets accompany attack-free periods of FMF. Colchicine is proved to be useful in suppression of inflammation in FMF. Preliminary basic and clinical studies suggest that this relatively safe drug may be useful for cardiovascular protection in patients with FMF and in the general population. Multinational prospective studies are warranted to further elaborate clinical model of inflammation-induced atherosclerosis associated with FMF.

DOI: 10.2174/1874192401004020051

PMCID: PMC2847313

PMID: 20360981

3292. Am J Med Genet A. 2010 Apr;152A(4):938-42. doi: 10.1002/ajmg.a.33359.

Familial Aicardi-Goutières syndrome due to SAMHD1 mutations is associated with chronic arthropathy and contractures.

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We report on two siblings doubly heterozygous for null mutations in the recently identified AGS5 gene SAMHD1. The older female child showed mild intellectual disability with microcephaly. Her brother demonstrated a significant spastic paraparesis with normal intellect and head size. Both children had an unclassified chronic inflammatory skin condition with chilblains, and recurrent mouth ulcers. One child had a chronic progressive deforming arthropathy of the small and large joints, with secondary contractures. This family illustrate the remarkable phenotypic diversity accruing from mutations in genes associated with Aicardi-Goutières syndrome (AGS). The association of arthropathy with SAMHD1 mutations highlights a phenotypic overlap of AGS with familial autoinflammatory disorders such as chronic infantile neurological cutaneous and articular syndrome (CINCA). This family therefore illustrate the need to consider mutation analysis of SAMHD1 in non-specific inflammatory phenotypes of childhood. We propose that arthropathy with progressive contractures should now be considered part of the spectrum of Aicardi-Goutières syndrome because of SAMHD1 mutations.

(c) 2010 Wiley-Liss, Inc.

DOI: 10.1002/ajmg.a.33359

PMID: 20358604 [Indexed for MEDLINE]

3293. J Clin Immunol. 2010 Jul;30(4):485-90. doi: 10.1007/s10875-010-9383-8. Epub 2010 Apr 1.

Modulation of inflammasome activity for the treatment of auto-inflammatory disorders.

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INTRODUCTION: The innate immune system orchestrates inflammatory responses to microorganisms or danger-associated molecular patterns generated, for example, by

the deposition of uric acid in the joints of gout patients. The innate immune system comprises multiple germ-line encoded receptors, of which the nucleotide-binding domain and leucine-rich repeat containing receptors (NLRs) are crucial for the maturation of pro-inflammatory cytokines. NLRs oligomerize to form large multi-protein complexes termed inflammasomes that generate active caspase-1 fragments leading to the cleavage and secretion of mature cytokines such as IL-1 $\beta$  and IL-18. THE REGULATION OF MULTIPLE INFLAMMASOMES: At least four independent inflammasomes have been identified, NLRP1, NLRP3, IPAF, and AIM2. These inflammasomes assemble in response to different stimuli to confer specificity and are also subject to negative regulatory mechanisms to ensure that once a productive inflammatory response has been mounted, inflammatory cytokine production is restrained. TREATMENT OF AUTO-INFLAMMATORY DISORDERS: A number of human conditions are characterized by unrestrained inflammasome activation. As much is now known about how inflammasomes are regulated, it is hoped that this can be channeled into the development of novel therapeutics, for example, those that may block the upstream activation and assembly of inflammasomes.

DOI: 10.1007/s10875-010-9383-8

PMCID: PMC2900592

PMID: 20358394 [Indexed for MEDLINE]

3294. Rheumatol Int. 2011 Jun;31(6):837-8. doi: 10.1007/s00296-010-1405-6. Epub 2010 Apr 1.

Psychological correlates of child and adolescents with familial Mediterranean fever.

Fidan T, Ertekin V, Sürücü I.

DOI: 10.1007/s00296-010-1405-6

PMID: 20358207 [Indexed for MEDLINE]

3295. Clin Immunol. 2010 May;135(2):210-22. doi: 10.1016/j.clim.2010.02.013. Epub 2010 Mar 30.

Monogenic IL-1 mediated autoinflammatory and immunodeficiency syndromes: finding the right balance in response to danger signals.

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**INTRODUCTION:** Interleukin-1 was the first cytokine identified and is a powerful inducer of fever and inflammation. The biologically active receptor for IL-1, shares signaling pathways with some pathogen recognition receptors, the Toll-like receptors (TLRs) which early on suggested an important role in innate immune function.

**DISCUSSION:** The discovery that some intracellular "danger receptors", the NOD like receptors (NLRs) can assemble to form multimolecular platforms, the inflammasomes, that not only sense intracellular danger but also activate IL-1 $\beta$ , has provided the molecular basis for the integration of IL-1 as an early response mediator in danger recognition. The critical role of balancing IL-1 production and signaling in human disease has recently been demonstrated in rare human monogenic diseases with mutations that affect the meticulous control of IL-1 production, release and signaling by leading to decreased or increased TLR/IL-1 signaling. In diseases of decreased TLR/IL-1 signaling (IRAK-4 and MyD88 deficiencies) patients are at risk for infections with gram positive organisms; and in diseases of increased signaling, patients develop systemic autoinflammatory diseases (cryopyrin-associated periodic syndromes (CAPS), and deficiency of the IL-1 receptor antagonist (DIRA)).

**CONCLUSION:** Monogenic defects in a number of rare diseases that affect the balance of TLR/IL-1 signaling have provided us with opportunities to study the systemic effects of IL-1 in human diseases. The molecular defects in CAPS and DIRA provided a therapeutic rationale for targeting IL-1 and the impressive clinical results from IL-1 blocking therapies have undoubtedly confirmed the pivotal role of IL-1 in human disease and spurred the exploration of modifying IL-1 signaling in a number of genetically complex common human diseases.

Published by Elsevier Inc.

DOI: 10.1016/j.clim.2010.02.013

PMCID: PMC2856775

PMID: 20353899 [Indexed for MEDLINE]

3296. Eurasian J Med. 2010 Apr;42(1):19-20. doi: 10.5152/eajm.2010.06.

The frequency of familial mediterranean Fever related amyloidosis in renal waiting list for transplantation.

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**OBJECTIVE:** Our goal is to investigate the distribution of MEFV mutations in patients with renal amyloidosis who are in renal transplant waiting list which is prepared for transplantation.

**MATERIALS AND METHODS:** FMF was diagnosed in 25 of the 297 patients between the years 2004 and 2008, who were involved in the study (15 male, 10 female; age  $34 \pm 7.8$ ). 5 out of 25 patients were transplanted, remaining were waiting for Tx. Biopsy results were amyloidosis and taken from renal (n:16), rectal (n:8) and duodenal (1). All of them were carrier of mutations in both pyrin alleles. The primer cause of chronic renal failure in our group was secondary AA amyloidosis. DNA was isolated from 25 whole blood samples. The NanoChip Molecular Biology Workstation (Nanogen) uses electronic microarrays for mutation detection. Exon 2,3,5 and 10 of pyrin gene genotypes were identified in the NanoChip.

**RESULTS:** Genetic analysis of the patients demonstrated that each subject carries either homozygote or compound heterozygote mutations of the gene. The most common mutations were M694V, V726A, E148Q and M680I.

**CONCLUSIONS:** The clinic manifestation and complain of our patients were febrile and painful attacks such as in the abdomen, chest and joints due to inflammation of the peritoneum, pleura and synovial membrane. The major problem in FMF is the occurrence of amyloidosis that primarily affects the kidneys causing proteinuria and renal failure. Dialysis and renal transplantation can be treatment, but it is important to diagnose FMF at earliest stages. The percentage of FMF patients in our waiting list was 8.4%. Moreover, in our region FMF incidence is highly frequent, so FMF should be chased by genetically so as to prevent chronic renal



failure due to amyloidosis.

Publisher: Çalışmamızın amacı, böbrek nakli bekleme listemizdeki ailesel Akdeniz ateşi'ne (AAA) bağlı amiloidoz gelişmiş son dönem böbrek yetmezlikli hastaların sıklığı ve MEFV genindeki mutasyon dağılımını araştırmaktır. 2004–2008 yılları arasında bekleme listesinde olan toplam 297 hastadan AAA tanısı almış olan ve biyopsi ile amiloidoz tespit edilmiş olan 25 (15 erkek, 10 kadın) hasta çalışmamıza dahil edildi. AAA olan hastaların 5'ine böbrek nakli yapıldı. Hastaların 16'sına renal, 8'ine rektal ve 1'ine duodenal biyopsi yapılarak amiloidoz geliştiği belirlenmiş. Yirmibeş hastanın periferik kanından DNA izole edildi. Vakalarımızın tümünde pyrin geninin her iki allelinde de mutasyon bulundu. Çalışmada pyrin geninin exon 2, 3, 5 ve 10 bölgelerindeki mutasyonların belirlenmesi için DNA analizörü NanoChip kullanıldı. Yirmi beş hastanın herbiri için mutasyon analizi yapıldı. Her bir hastanın ya homozigot veya heterozigot MFEV gen mutasyonu taşıdığı bulundu. En sık görülen mutasyonların sırasıyla M694V, V726A, E148Q ve M680I olduğu tespit edildi. AAA'nin yaygın olduğu bir bölgede bulunduğumuz dikkate alındığında, diyaliz ve böbrek nakli tedavi seçenekleri olmasına rağmen AAA'nin erken teşhisi ve tedavisi önem arz etmektedir. Pyrin genindeki mutasyonlar ile amiloidoz güçlü bir ilişki göstermektedir.

DOI: 10.5152/eajm.2010.06

PMCID: PMC4261305

PMID: 25610112

3297. Mod Rheumatol. 2010 Aug;20(4):410-2. doi: 10.1007/s10165-010-0288-4. Epub 2010 Mar 30.

Protracted febrile myalgia syndrome in familial Mediterranean fever.

Senel K(1), Melikoglu MA, Baykal T, Melikoglu M, Erdal A, Ugur M.

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Familial Mediterranean fever (FMF) is an autosomal, recessively inherited multisystem disease that affects various groups of people originating from the Mediterranean Sea region, most specifically those of Jewish, Turkish, Armenian,

and Arabic ethnicity. Recurrent attacks of fever and sterile polyserositis of the peritoneum, synovial membranes, and pleura are the main clinical features, although the clinical features of FMF have been expanded in recent years to also include severe myalgia, scrotal swelling, cardiac involvement, and protracted febrile myalgia syndrome (PFMS). PFMS is seen in only a small percentage of FMF patients and is characterized by severe debilitating myalgia of the upper and lower extremities and high fever, occasionally accompanied by abdominal pain, diarrhea, arthritis/arthralgia, and transient vasculitic purpura mimicking Henoch-Schönlein purpura (HSP). Here, we report on a patient with FMF who also presents with PFMS, which is an uncommon and severe manifestation of the disease.

DOI: 10.1007/s10165-010-0288-4

PMID: 20352466 [Indexed for MEDLINE]

3298. Rheumatol Int. 2012 Jun;32(6):1801-4. doi: 10.1007/s00296-010-1429-y. Epub 2010 Mar 30.

Pneumonia in a patient with familial Mediterranean fever successfully treated with anakinra--case report and review.

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We report the case of a 35-years-old renal transplant patient known to have familial Mediterranean fever with serum amyloid A (SAA)-amyloidosis, who presented with his second episode of bilateral pneumonia. As antimicrobials failed to control the first episode of pneumonia and all studies done were non-contributory, we attributed the condition to the highly active Mediterranean fever presumably resistant to colchicine and treated the patient with the interleukin-1 receptor antagonist anakinra: the patient substantially improved by clinical symptoms, chemistry and radiological evidence within no more than 2 days and was discharged in good health after 4 days.

DOI: 10.1007/s00296-010-1429-y

3299. J Infect. 2010 Jun;60(6):409-16. doi: 10.1016/j.jinf.2010.03.016. Epub 2010 Mar 27.

The diagnostic role of procalcitonin and other biomarkers in discriminating infectious from non-infectious fever.

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Comment in

J Infect. 2011 Jul;63(1):93-5.

J Infect. 2010 Oct;61(4):355-8.

J Infect. 2010 Dec;61(6):512-5.

J Infect. 2011 Mar;62(3):237-40.

J Infect. 2012 Jan;64(1):122-4.

J Infect. 2012 May;64(5):540-2.

J Infect. 2012 Aug;65(2):187-9.

Fever is not only observed in the course of a bacterial or viral infection, but can be a symptom of, for instance, auto-immune, malignant or thromboembolic disease. Determining the etiology of fever in a fast and reliable way is of pivotal importance, as different causes of fever may ask for different therapies. Neither clinical signs and symptoms, nor traditional biomarkers, such as CRP, leukocytes and ESR have sufficient sensitivity and specificity to guide treatment decisions. In this review we focus on the value of traditional and newer biomarkers in non-infectious febrile diseases. Procalcitonin (PCT) seems to be the most helpful laboratory marker for the differentiation of causes of fever, particularly in autoimmune, autoinflammatory and malignant diseases.

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PMID: 20347867 [Indexed for MEDLINE]

3300. Clin Exp Rheumatol. 2010 Jan-Feb;28(1):94-6.

A novel mutation in TNFRSF1A associated with overlapping features of tumor necrosis factor receptor-associated periodic syndrome and hyper-IgD syndrome.

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We describe a 10-year-old child with a novel mutation, c.352A>G/p.Thr118Ala (T89A) in the tumour necrosis factor receptor superfamily 1A (TNFRSF1A) gene. The patient presented with periodic fevers beginning at 2 years of age. He had overlapping clinical and laboratory features of tumour necrosis factor receptor-associated periodic syndrome (TRAPS) and hyper-IgD syndrome (HIDS). This patient expands the clinical and genetic spectrum of TRAPS.

PMID: 20346247 [Indexed for MEDLINE]

3301. Clin Exp Rheumatol. 2010 Jan-Feb;28(1):30-4.

Possible association between NOD2 variants and joint surgery in psoriatic arthritis.

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BACKGROUND: Psoriatic arthritis (PsA) has been inconsistently associated with

common NOD2 gene variants, although some of these studies did not include patient stratification by clinical phenotype.

**OBJECTIVES:** To analyse the association between the three common NOD2 variants (R702W, G908R and L1007fs) and clinical phenotypes of PsA, particularly with surrogate markers of severe joint destruction.

**PATIENTS AND METHODS:** A total of 183 unrelated PsA patients and 187 controls were included. Demographic, clinical, biological and immunological characteristics were collected. Genotypes for the three common NOD2 gene variants were obtained by PCR and direct sequencing.

**RESULTS:** NOD2 variants in PsA patients (7.6%) are just as prevalent as in healthy controls (7.5%). 18.5% of PsA patients carrying at least one NOD2 variant underwent joint surgery compared with 4.5% of those without these variants ( $p=0.019$ ). Multivariate analysis confirmed this finding (OR 8.82, CI 1.7-46.3). There was no requirement for early surgery in patients carrying the NOD2 variants but there was an increased possibility of requiring surgery at similar times of disease duration. No other association with clinical features and NOD2 status carrier was found.

**CONCLUSIONS:** Common NOD2 gene variants are not associated with PsA, but might increase the risk of undergoing joint replacement surgery, suggesting that this autoinflammatory-associated gene could act as a phenotypic modifier gene in PsA patients by increasing the risk of joint destruction. Given the small number of PsA patients with joint surgery included, we consider our findings a new hypothesis that will need further testing.

PMID: 20346235 [Indexed for MEDLINE]

3302. Dig Dis Sci. 2010 Dec;55(12):3488-94. doi: 10.1007/s10620-010-1178-5. Epub 2010 Mar 21.

The association of inflammatory bowel disease and Mediterranean fever gene (MEFV) mutations in Turkish children.

Uslu N(1), Yüce A, Demir H, Saltik-Temizel IN, Usta Y, Yilmaz E, Beşbaş N, Gürakan F, Ozen H, Ozen S.

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**BACKGROUND AND AIMS:** Familial Mediterranean fever (FMF) and inflammatory bowel disease (IBD) concordance has been investigated in a few studies. We investigated MEFV mutations and prevalence of FMF disease in Turkish children with IBD and their relationship with the disease severity.

**METHODS:** Sixteen patients with ulcerative colitis (UC), 14 with Crohn's disease (CD) and three with indeterminate colitis (IC) were enrolled in the study (median age 13 years, range 0.6-16 years, n = 19 boys). Demographic, clinical and laboratory characteristics of the patients were evaluated as well as the parameters of disease severity. All patients were screened for 12 common MEFV mutations.

**RESULTS:** MEFV mutations were detected in 17 of 66 (25.7%) alleles. Seven patients (four patients with CD, two with IC, and one with UC) were also diagnosed as FMF. FMF disease was found in seven of all IBD patients (21.2%) and four of them had CD. M694V was the leading mutation, and as a disease-causing mutation, it was found to be significantly more frequent in CD patients than UC patients (Fisher's exact test  $P = 0.03$ ). Demographics, laboratory evaluations, growth parameters, extraintestinal manifestations, and treatment with immunosuppressive agents other than steroids were comparable between the patients with and without FMF in most aspects.

**CONCLUSIONS:** Although this is a small cohort, disease-causing MEFV mutations and FMF disease rate were increased among our patients with IBD. The increase was prominent among CD patients, whereas in UC the rate was similar to the Turkish healthy control population.

DOI: 10.1007/s10620-010-1178-5

PMID: 20306331 [Indexed for MEDLINE]

3303. Rheumatol Int. 2012 Jun;32(6):1779-81. doi: 10.1007/s00296-010-1388-3. Epub 2010 Mar 20.

Posterior reversible encephalopathy during an attack of familial Mediterranean fever.

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Reported here is a 19-year-old female patient with familial Mediterranean fever who was seen for altered mental status and seizures. She was eventually diagnosed to have posterior reversible leukoencephalopathy syndrome. Although a variety of conditions have been reported in association with this syndrome, to our best notice, this is the second case in whom familial Mediterranean fever and posterior reversible leukoencephalopathy coexists.

DOI: 10.1007/s00296-010-1388-3

PMID: 20306050 [Indexed for MEDLINE]

3304. Cell. 2010 Mar 19;140(6):935-50. doi: 10.1016/j.cell.2010.02.043.

Anti-inflammatory Agents: Present and Future.

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Inflammation involving the innate and adaptive immune systems is a normal response to infection. However, when allowed to continue unchecked, inflammation may result in autoimmune or autoinflammatory disorders, neurodegenerative disease, or cancer. A variety of safe and effective anti-inflammatory agents are available, including aspirin and other nonsteroidal anti-inflammatories, with many more drugs under development. In particular, the new era of anti-inflammatory agents includes "biologicals" such as anticytokine therapies and small molecules that block the activity of kinases. Other anti-inflammatories currently in use or under development include statins, histone deacetylase inhibitors, PPAR agonists, and small RNAs. This Review discusses the current status of anti-inflammatory drug research and the development of new anti-inflammatory therapeutics.

DOI: 10.1016/j.cell.2010.02.043  
PMCID: PMC3752337  
PMID: 20303881 [Indexed for MEDLINE]

3305. Cell. 2010 Mar 19;140(6):784-90. doi: 10.1016/j.cell.2010.03.002.

Autoinflammatory disease reloaded: a clinical perspective.

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Our understanding of the etiology of autoinflammatory disease is growing rapidly. Recent advances offer new opportunities for therapeutic intervention and suggest that the definition of what constitutes an autoinflammatory disease should be reassessed.

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DOI: 10.1016/j.cell.2010.03.002  
PMCID: PMC3541025  
PMID: 20303869 [Indexed for MEDLINE]

3306. Cytokine. 2010 May;50(2):146-51. doi: 10.1016/j.cyto.2010.02.014. Epub 2010 Mar 16.

Comparative analysis of cytokine profiles in autoinflammatory and autoimmune conditions.

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**BACKGROUND:** Many disease states are characterized by a biased cytokine profile and determining the level of certain cytokines becomes an important diagnostic and research tool in clinical medicine. We hypothesized that, despite the highly dynamic nature, the profile of cytokines may be characteristic of disease.

**METHODS:** The level of systemic cytokines was studied in an autoinflammatory condition, familial Mediterranean fever; in an autoimmune disease, systemic lupus erythematosus (SLE), and in healthy controls.

**RESULTS:** Multivariate statistics with the use of seven variables clustered the patients and control subjects into the four well separated and distinct groups, corresponding to the SLE, FMF attack, FMF remission, and healthy states.

**CONCLUSIONS:** The model suggested the existence of specific patterns in cytokine levels reflecting the healthy and specific disease states. These findings warrant further investigations to establish whether this approach may serve as a potential meta-biomarker for other inflammatory disorders.

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DOI: 10.1016/j.cyto.2010.02.014

PMID: 20236834 [Indexed for MEDLINE]

3307. J Back Musculoskelet Rehabil. 2010;23(1):21-3. doi: 10.3233/BMR-2010-0243.

Anti-cyclic citrullinated peptide antibodies are not associated with familial Mediterranean fever.

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**OBJECTIVE:** This study investigated the presence of anti-cyclic citrullinated peptide (anti-CCP) antibodies in familial Mediterranean fever (FMF) patients and controls.

**MATERIAL AND METHODS:** Forty-nine patients with FMF were enrolled (23 had a history of arthritis during attacks and 26 had no such history). Two control groups were enrolled: 20 patients with rheumatoid arthritis (RA) and 30 healthy individuals. Clinical and laboratory assessments of the FMF patients were performed during attack-free periods. Erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP), rheumatoid factor (RF), and anti-CCP antibody levels were measured.

**RESULTS:** In RA patients' ESR and CRP levels, frequency of RF, and anti-CCP antibody levels were significantly higher than in both FMF patients and healthy controls ( $p < 0.001$ ). Moreover, anti-CCP was negative in all healthy controls as well as in all FMF patients.

**CONCLUSION:** Our results show that anti-CCP antibodies are not associated with FMF.

DOI: 10.3233/BMR-2010-0243

PMID: 20231785 [Indexed for MEDLINE]

3308. *Pediatr Rheumatol Online J.* 2010 Mar 16;8:9. doi: 10.1186/1546-0096-8-9.

Effect of anakinra on arthropathy in CINCA/NOMID syndrome.

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CINCA/NOMID is an autoinflammatory disorder characterized by the triad of neonatal onset of cutaneous symptoms, chronic meningitis, and recurrent fever and it presents with distinctive osteoarthropathy, synovitis mainly of the large joints and overgrowth of epimetaphyseal cartilage, particularly of the long bones. The cartilage overgrowth eventually causes osseous overgrowth and deformity that persists beyond skeletal maturity and leads to limb length discrepancy, joint contracture, and early degenerative arthropathy.

Autoinflammation in CAPS/NOMID has been proven to derive from excessive release of interleukin-1 (IL-1). It has been well documented that the IL-1 receptor antagonist anakinra (Kineret(R)) helps mitigate systemic inflammation in the

disorder. However, a general consensus has not been reached on its beneficial effect on osteoarthropathy. The case of a girl with CINCA/NOMID syndrome who showed dramatic improvement of osteoarthropathy after anakinra treatment is reported. A 4-year-old girl suffered at the age of 10 months from a generalized urticarial skin lesion with recurrent episodes of fever and growth disorder. Blood examination revealed persistent massive neutrophilia, anemia and intense acute phase response. She manifested knee joint swelling with limited ROM when she was 20 months old and was diagnosed as being CINCA/NOMID based on characteristic findings of radiograph despite negative CIAS1 mutation. Radiological examination demonstrated metaphyseal fraying and cupping and widening of the growth plate in the distal femur. MR imaging showed mottled gadolinium enhancement at the chondrosesous junction. Neither significant joint effusion nor synovitis was identified. At 2 years and 7 months of age, anakinra, 2 mg/kg/day given by regular daily subcutaneous injections, was started. A few days after the initiation of the treatment, her clinical symptoms and laboratory findings of active inflammation were promptly alleviated. She was not able to walk unaided prior to the treatment, but she walked independently 1 month after the treatment. Follow-up radiographs and MR imaging showed that growth plate widening and gadolinium enhancement at the chondrosesous junction were less conspicuous. Furthermore, longitudinal growth of the femur and tibia was identified during 20 months of observation.

DOI: 10.1186/1546-0096-8-9

PMCID: PMC2842264

PMID: 20230645

3309. Intern Med. 2010;49(6):619-22. Epub 2010 Mar 15.

Coexistence of familial Mediterranean fever and juvenile idiopathic arthritis with osteoporosis successfully treated with etanercept.

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Familial Mediterranean fever (FMF) is an autoinflammatory disorder characterized

by recurrent febrile polyserositis and arthritis attacks. Accompanying seronegative spondyloarthropathy has been reported in FMF in addition to its own joint involvement. However, the coexistence of FMF with juvenile idiopathic arthritis (JIA) is very rare, only three cases with severe joint involvement and mortal outcome have been reported in the literature. Here, we present another case with FMF and JIA with osteoporosis, successfully treated with etanercept with a four-year follow-up.

PMID: 20228604 [Indexed for MEDLINE]

3310. J Pediatr. 2010 Jun;156(6):985-989. doi: 10.1016/j.jpeds.2009.12.010. Epub 2010 Mar 15.

Familial Mediterranean Fever in the first two years of life: a unique phenotype of disease in evolution.

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**OBJECTIVE:** To characterize the clinical and genetic features of familial Mediterranean fever (FMF).

**STUDY DESIGN:** Clinical presentation and Mediterranean Fever mutation type of all patients with FMF, who first manifested the disease at < or =2 years of age were analyzed and compared with patients who first presented with FMF between 2 and 16 years.

RESULTS: Of 814 patients with FMF, in 254 patients (31.2%) the first FMF attack was at  $< \text{ or } = 2$  years of age, with a mean age at onset of  $1.1 \pm 0.8$  years. They were compared with 242 patients who presented with their first manifestation of FMF at 2 to 16 years. The clinical manifestations of FMF were comparable in the 2 patient groups, but the delay of diagnosis was longer in patients with early presentation ( $3.2 \pm 3.2$  years vs.  $1.9 \pm 2.7$  years in the group with onset at 2-16 years,  $P < .001$ ). A subgroup of patients (60/254), who were diagnosed at  $< \text{ or } = 2$  years had the highest rate of attacks of fever alone as their sole manifestation (40.0% vs 8.4%,  $P < .05$ ), and less peritonitis (45% vs 86.1%,  $P < .05$ ) and pleuritis (3.4% vs 32.9%,  $P < .05$ ). Most of these patients were homozygous for the M694V mutation and were of North African (Sephardic Jewish) extraction.

CONCLUSION: In early life, FMF often begins with an atypical presentation, characterized by attacks of fever alone, and its diagnosis and initiation of treatment is therefore significantly delayed.

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DOI: 10.1016/j.jpeds.2009.12.010

PMID: 20227729 [Indexed for MEDLINE]

3311. J Am Acad Dermatol. 2010 Apr;62(4):557-70; quiz 571-2. doi: 10.1016/j.jaad.2009.11.687.

Urticarial lesions: if not urticaria, what else? The differential diagnosis of urticaria: part II. Systemic diseases.

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There are a number of systemic disorders that can manifest with urticarial skin lesions, including urticarial vasculitis, connective tissue diseases, hematologic diseases, and autoinflammatory syndromes. All of these conditions may enter into the differential diagnosis of ordinary urticaria. In contrast to urticaria, urticarial syndromes may manifest with skin lesions other than wheals, such as

papules, necrosis, vesicles, and hemorrhages. Lesions may have a bilateral and symmetrical distribution; individual lesions have a long duration, and their resolution frequently leaves marks, such as hyperpigmentation or bruising. Moreover, systemic symptoms, such as fever, asthenia, and arthralgia, may be present. The most important differential diagnosis in this group is urticarial vasculitis, which is a small-vessel vasculitis with predominant cutaneous involvement. Systemic involvement in urticarial vasculitis affects multiple organs (mainly joints, the lungs, and the kidneys) and is more frequent and more severe in patients with hypocomplementemia. Clinicopathologic correlation is essential to establishing a correct diagnosis. LEARNING OBJECTIVES: After completing the learning activity, participants should be able to distinguish urticarial lesions suggesting diagnoses other than common urticaria; assess patients with urticarial lesions, and suspect systemic diseases presenting with urticarial skin lesions.

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DOI: 10.1016/j.jaad.2009.11.687

PMID: 20227577 [Indexed for MEDLINE]

3312. Tidsskr Nor Laegeforen. 2010 Mar 11;130(5):496. doi: 10.4045/tidsskr.09.1457.

[Children with frequent fever episodes].

[Article in Norwegian]

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DOI: 10.4045/tidsskr.09.1457

PMID: 20224618 [Indexed for MEDLINE]

3313. Tidsskr Nor Laegeforen. 2010 Mar 11;130(5):494-5. doi: 10.4045/tidsskr.09.0692.

[A three-year-old girl with abdominal pain and fever].

[Article in Norwegian]

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**MATERIAL AND METHODS:** A patient with both familial Mediterranean fever and coeliac disease is discussed. We present our case and then discuss symptoms and treatment of familial Mediterranean fever.

**CASE REPORT:** A 3 1/2 year-old girl from the Middle East, parents related, was admitted to the Paediatric Department with recurrent episodes of abdominal pain and fever. During each episode the inflammatory markers ESR and CRP were significantly raised, but with no apparent focus of infection. Each episode lasted 1-4 days and subsequently became more frequent. Laboratory evaluation revealed a high titer for IgA anti-tissue transglutaminase suggestive of coeliac disease. Coeliac disease was confirmed by small-bowel biopsy. A gluten-free diet was started, but she continued to have recurrent episodes of abdominal pain and fever. Because of her genetic origin the diagnosis familial Mediterranean fever was suspected. Genetic testing was performed, and she was found to be homozygote for the most common gene encoding for the disease. Colchicine therapy was initiated and her episodes with abdominal pain and fever became less frequent.

**CONCLUSION:** Familial Mediterranean fever is a rare disorder in Norway but frequent in many Mediterranean countries. Common symptoms are recurrent episodes of abdominal pain, chest pain, joint pain and fever. Treatment with colchicine reduces inflammation and the risk of developing amyloidosis.

DOI: 10.4045/tidsskr.09.0692

PMID: 20224617 [Indexed for MEDLINE]

3314. Rheumatol Int. 2011 Jun;31(6):779-84. doi: 10.1007/s00296-010-1383-8. Epub 2010 Mar 9.

Familial Mediterranean fever gene mutation frequencies and genotype-phenotype correlations in the Aegean region of Turkey.

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Comment in

Rheumatol Int. 2012 Nov;32(11):3705-6.

Familial Mediterranean fever (FMF) is a disease characterized by recurrent, self-limiting fever and serositis and caused by altered pyrin due to mutated MEFV gene. The aim of this study was to investigate clinical manifestations and MEFV mutations among patients with FMF and healthy controls in the Aegean region of Turkey. This study included 308 patients and 164 healthy controls. Patients were divided into three groups according to Tel-Hashomer criteria; definitive, probable, and suspicious. Among the patients, 146 were women (47.4%) and 162 were men (52.6%). The mean age ( $\pm$ SD) of the patients at the diagnosis was  $9.6\pm3.95$  (range 0.5-18). The mean age ( $\pm$ SD) at onset of the symptom was  $6.2\pm3.95$  (range 1-18). Symptoms were seen earlier onset in definitive group than the suspicious group in our cohort ( $4.7\pm3.9$  years,  $6.6\pm3.9$  years, respectively;  $P=0.001$ ). Clinical features were abdominal pain (83.1%), fever (55%), arthritis (17.1%), myalgia (4.5%), pleuritis (10%), and erysipelas-like erythema (7.7%). Fever, arthralgia, arthritis, chest pain, and amyloidosis were found statistically significant more in definitive group than suspicious group ( $P<0.001$ ,  $P<0.001$ ,  $P<0.001$ ,  $P<0.05$ , and  $P<0.001$ , respectively). MEFV gene mutations were identified in 199 patients (64.6%). The most commonly encountered MEFV mutation among the patients was M694V homozygote (25%). M694V homozygous mutation was found most frequently in definitive FMF group than other groups (49, 9, 8.9%, respectively). To our knowledge that FMF should be suspected in the case of non-specific but recurrent attacks of serositis and high fever, and molecular analysis should be performed in order to make diagnosis of FMF.

DOI: 10.1007/s00296-010-1383-8

PMID: 20217092 [Indexed for MEDLINE]

3315. Nihon Shokakibyo Gakkai Zasshi. 2010 Mar;107(3):427-31.



[A Japanese family with adult-onset familial Mediterranean fever and periodic episodes of high fever and abdominal pain].

[Article in Japanese]

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Familial Mediterranean fever (FMF) is an autoinflammatory disease. The patient was a 28-year-old Japanese man with attacks of fever and abdominal pain, which recurred at 1-to 3-month intervals. These symptoms usually improved spontaneously 1 week later. Physical examination showed tenderness in the right lateral abdomen. Routine laboratory tests demonstrated an increase in inflammatory reactions in the serum with leukocytosis. No abnormal findings were found on either chest, or abdominal CT scans, or endoscopic examinations of the upper or lower gastrointestinal tracts. Renal and hepatic function were within the normal limits, and no positive results were obtained for an anti-nuclear antibody. DNA analysis demonstrated a heterozygous mutation in the MEFV gene, the compound pyrin variant E148Q/M694I, leading to a diagnosis of FMF. His father had also had the same symptoms for 30 years, and was also heterozygous for the pyrin variant E148Q/M694I. They both responded dramatically to colchicine treatment and have remained in full remission until the time of writing.

PMID: 20203446 [Indexed for MEDLINE]

3316. Eur J Immunol. 2010 Mar;40(3):649-53. doi: 10.1002/eji.200940191.

New insights into the nature of autoinflammatory diseases from mice with Nlrp3 mutations.

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Mutations in the Nlrp3 (CIAS1, cryopyrin) gene are associated with cryopyrin-associated periodic syndrome, autoinflammatory diseases characterized by excessive IL-1 production and neutrophilia in blood and tissues. Recent studies with gene-targeted mice expressing mutations homologous to those found in cryopyrin-associated periodic syndrome patients have advanced the understanding of NLRP3-associated autoinflammation. In this Viewpoint, we will discuss the mechanisms of NLRP3 inflammasome activation and its induction of Th17-cell-dominant immunologic responses.

DOI: 10.1002/eji.200940191

PMCID: PMC3729261

PMID: 20201022 [Indexed for MEDLINE]

3317. Eur J Immunol. 2010 Mar;40(3):643-8. doi: 10.1002/eji.200940225.

Genetics of inflammasome-associated disorders: a lesson in the guiding principals of inflammasome function.

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Human genetics research has had a great impact on the genesis of the inflammasome field and the treatment of certain inflammasomopathies. The identification of mutations causing rare autoinflammatory syndromes, reproductive wastage disorders and of single nucleotide polymorphisms influencing susceptibility to complex diseases such as vitiligo, sepsis, and Crohn's disease has not only led to the characterization of novel proteins involved in NOD-like receptor-coupled inflammatory signaling pathways but also to greater insights into pathogenic mechanisms.

DOI: 10.1002/eji.200940225

PMID: 20201021 [Indexed for MEDLINE]

3318. Eur J Immunol. 2010 Mar;40(3):631-4. doi: 10.1002/eji.200940162.

The NLRP3 inflammasome, a target for therapy in diverse disease states.

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A role for NLRP3 inflammasome in recurrent and chronic inflammation was initially described in a group of rare autoinflammatory conditions, termed cryopyrin-associated periodic syndrome. Subsequently, inflammasomes have been implicated in the pathology of many common diseases, including cancer, gout and diabetes. Despite diverse pathologies, the central role of the inflammasome in innate defences and tumour elimination suggests common therapeutic approaches to reduce inflammation where appropriate.

DOI: 10.1002/eji.200940162

PMID: 20201018 [Indexed for MEDLINE]

3319. *Pediatr Dermatol*. 2010 Jan-Feb;27(1):69-73. doi: 10.1111/j.1525-1470.2009.01060.x.

Sporadic Blau syndrome with onset of widespread granulomatous dermatitis in the newborn period.

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Blau syndrome is a dominantly inherited, chronic autoinflammatory disorder characterized by the clinical triad of granulomatous dermatitis, symmetric arthritis, and recurrent uveitis with onset below 4 years of age. It is caused by activating mutations in the nucleotide-binding oligomerization domain 2 (NOD2) gene, previously referred to as CARD15 gene. Noncaseating granulomas in affected tissues are the pathologic hallmark of the condition. We report the lifelong

severe disease course in a 14-year-old Caucasian boy with sporadic Blau syndrome. Unusually, granulomatous dermatitis started in the first week of life. Whereas skin involvement faded away spontaneously in subsequent years, polyarthritides and anterior uveitis appeared in the second and third year of life respectively. Mutational analysis of the NOD2 gene revealed a missense mutation (R334W) previously detected in other Blau syndrome pedigrees. With this report, we would like to stress the rare possibility of Blau syndrome in generalized papular rashes of infancy and the importance of histopathologic study for clarification. The finding of early-onset widespread granulomatous dermatitis should prompt eye and joint examination in regular intervals and entail mutational analysis of the NOD2 gene.

DOI: 10.1111/j.1525-1470.2009.01060.x

PMID: 20199415 [Indexed for MEDLINE]

3320. J Rheumatol. 2010 Apr;37(4):865-9. doi: 10.3899/jrheum.090687. Epub 2010 Mar 1.

Familial Mediterranean fever in children presenting with attacks of fever alone.

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**OBJECTIVE:** Familial Mediterranean fever (FMF) is an inherited disease characterized by attacks of febrile polyserositis. In children, attacks of fever alone, or with headache and malaise, may precede other forms of attacks. Our objective was clinical and genetic characterization of FMF and its development in pediatric patients who first presented with attacks of fever alone.

**METHODS:** Clinical characterization and MEFV genotype of all FMF patients < 16 years of age at disease onset and first presenting with attacks of fever alone were analyzed and compared for age, sex, and disease duration with matched FMF patients presenting with serositis at the onset of the disease.

**RESULTS:** There were 814 patients with FMF in our registry. Fifty patients formed the study group and 234 patients the control group. In the study group, the first (febrile) attacks appeared at a younger age than in the control group (1.7 +/- 1.6 yrs vs 5.0 +/- 4.1 yrs, respectively;  $p < 0.0001$ ), diagnosis was made earlier

(4.2 +/- 2.7 yrs vs 6.7 +/- 4.1 yrs;  $p < 0.0001$ ), despite a trend for a longer delay in diagnosis. In the study group, attacks were shorter (1.6 +/- 0.8 days vs 2.1 +/- 1.0 days;  $p = 0.023$ ) and homozygosity to the M694V mutation was more prevalent (46% vs 31%;  $p = 0.03$ ). Attack rate, colchicine dose, and the MEFV mutation carrier rates were comparable between the groups. In 40/50 (80%) of the patients with fever alone, serositis had developed over a course of 2.9 +/- 2.2 years after disease onset.

**CONCLUSION:** FMF in young children may begin with attacks of fever alone, but it progresses to typical FMF disease over the next 2.9 +/- 2.2 years. Our study demonstrates that clinical heterogeneity at presentation is more likely to indicate a feature of a disease in development, rather than to mark distinct phenotypes of FMF.

DOI: 10.3899/jrheum.090687

PMID: 20194447 [Indexed for MEDLINE]

3321. Pediatrics. 2010 Apr;125(4):e964-8. doi: 10.1542/peds.2009-1774. Epub 2010 Mar 1.

A novel missense mutation in MVK associated with MK deficiency and dyserythropoietic anemia.

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Mevalonate kinase deficiency (MKD) is a rare inborn error of metabolism caused by mutations in the mevalonate kinase (MVK) gene. The clinical phenotype is variable, ranging from the hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) to mevalonic aciduria (MA), a severe metabolic disease. We report here for the first time (to our knowledge) the case of a patient with MKD and congenital dyserythropoietic anemia. Clinical and laboratory characteristics of inflammatory attacks were compatible with HIDS, but mild dysmorphic features and elevated urinary mevalonic acid levels in the absence of an inflammatory attack suggested an intermediate phenotype between HIDS and MA. Genomic sequencing of the MVK gene revealed compound heterozygosity for a missense mutation previously described in

MA (V310M) and a novel missense mutation (Y116H). By contrast, sequencing of the novel CDAll (SEC23B) gene revealed no mutations, suggesting that the bone marrow abnormalities were causally related to the MKD. Treatment with corticosteroids and colchicine directed at controlling the autoinflammatory disease resulted in improvement of the anemia.

DOI: 10.1542/peds.2009-1774

PMID: 20194276 [Indexed for MEDLINE]

3322. Immunol Rev. 2010 Jan;233(1):218-32. doi: 10.1111/j.0105-2896.2009.00860.x.

Mechanisms of uric acid crystal-mediated autoinflammation.

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Gout is an arthritis characterized by elevated uric acid in the bloodstream. In this condition, crystals of uric acid are formed and accumulate in the synovial fluids. Crystal deposition leads to acute inflammation, which is associated with the spontaneous resolution of the disease. Recent studies have led to significant advances in the understanding of the basic biology of crystal-mediated inflammation. Uric acid has been identified as a danger signal that triggers a cytosolic sensor, the inflammasome. This signaling platform is required for the activation of interleukin-1, a cytokine that is critical to the initiation of acute inflammation in gout. Importantly, both molecular and pathological evidence support the notion that gout is a prototypical member of the growing family of autoinflammatory diseases. This review discusses the role of the inflammasome in gout and the emerging new therapeutic strategies aimed at controlling inflammation in crystal arthritis.

DOI: 10.1111/j.0105-2896.2009.00860.x

PMID: 20193002 [Indexed for MEDLINE]

3323. Arthritis Care Res (Hoboken). 2010 Feb;62(2):143-8. doi: 10.1002/acr.20061.

Pregnancy outcomes in women with familial Mediterranean fever receiving colchicine: is amniocentesis justified?

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**OBJECTIVE:** To evaluate the outcome of pregnancies in women with familial Mediterranean fever (FMF) who are taking colchicine, and to reconsider the justification for amniocentesis in these women.

**METHODS:** The outcome of 179 pregnancies in a group of women with FMF taking colchicine was compared with the outcome of 197 pregnancies in women with FMF who did not take colchicine during pregnancy and with 312 pregnancies in another cohort of healthy pregnant women of similar age and ethnicity.

**RESULTS:** There was no difference in the 3 groups regarding early abortions, late abortions, or congenital malformations. There was a mild trend towards a better outcome for the colchicine-treated group but these results did not reach statistical significance.

**CONCLUSION:** Treatment with colchicine during pregnancy in patients with FMF is beneficial in controlling the disease while not affecting the outcome of the pregnancy; therefore there is no justification for recommending amniocentesis in women taking colchicine solely because of this treatment.

DOI: 10.1002/acr.20061

PMID: 20191511 [Indexed for MEDLINE]

3324. Eur Rev Med Pharmacol Sci. 2010 Jan;14(1):1-18.

The protean visage of systemic autoinflammatory syndromes: a challenge for inter-professional collaboration.

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Systemic autoinflammatory syndromes are a group of inherited and acquired disorders of the innate immunity characterized by recurrence of seemingly unprovoked febrile attacks of variable duration and multi-district inflammation of different severity. The vast majority of these conditions when observed in pediatrics is caused by mutations in genetic systems involved in the orchestration of inflammation and apoptosis. The group includes hereditary recurrent fevers, idiopathic febrile syndromes, hereditary pyogenic disorders, bone autoinflammatory diseases, immune-mediated granulomatous diseases, complement disorders, hemophagocytic and vasculitic syndromes. Diagnostic identification derives from the combination of genotype studies and clinical/bioluminal data showing the spontaneous activation of cells of the innate immunity in the absence of specific ligands, although diagnosis remains only clinical for idiopathic febrile syndromes such as systemic-onset juvenile idiopathic arthritis and PFAPA syndrome. Meeting the needs of patients with complex chronic diseases as systemic autoinflammatory syndromes requires the provision of collaborative multidisciplinary care and the expertise of a number of health care providers across varied health care settings.

PMID: 20184084 [Indexed for MEDLINE]

3325. Eur J Pediatr. 2010 Aug;169(8):971-4. doi: 10.1007/s00431-010-1158-y. Epub 2010 Feb 24.

Decrease in the rate of secondary amyloidosis in Turkish children with FMF: are we doing better?

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Familial Mediterranean fever (FMF) is the most common autoinflammatory disease in the world. The most serious complication of FMF is the development of secondary amyloidosis. Besides genetic factors, environment has been implicated in the development of this complication. The main objective of this study is to analyze whether there has been a substantial decrease of secondary amyloidosis in Turkey



and possible effective factors. For this purpose, clinical features of the patients diagnosed with secondary amyloidosis between the years 1978 and 1990 were compared with those diagnosed between 2000 and 2009. Severity scores were determined by the use of a scoring system modified for children. Median ages of the group diagnosed between 1978 and 1990 (n = 115; 12.1% among a total of 947 renal biopsies) and diagnosed after 2000 (n = 19; 2% among a total of 974 renal biopsies) were 12 and 13 years, respectively. There were no significant differences between the two patient groups according to gender, age, age of onset, disease duration, and disease severity. There was, however, a clear decrease in the percentage of biopsies with secondary amyloidosis from 12.1% (1978-1990) to 2% (after 2000;  $p < 0.001$ ). Our results have shown that there has been a significant decrease in the rate of secondary amyloidosis in Turkey. The main reason for this decrease is better medical care with increased awareness and treatment of the disease. However, we suggest that the improvement of infectious milieu may possibly have had a positive effect on the course of this monogenic disease, since inflammatory pathways related to innate immunity are deregulated.

DOI: 10.1007/s00431-010-1158-y

PMID: 20179967 [Indexed for MEDLINE]

3326. Open Rheumatol J. 2010 Jan 29;4:1-6. doi: 10.2174/1874312901004010001.

Familial mediterranean Fever: a retrospective clinical and molecular study in the East of anatolia region of Turkey.

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Erratum in

Open Rheumatol J. 2010;4:23.

Familial Mediterranean Fever (FMF) is an autoinflammatory periodic disorder. We aim to identify the distribution and the frequency of the Mediterranean Fever (MEFV) gene mutations in the east of Anatolia in Turkey and perform a genotype/phenotype correlation in the patients' cohort. The study was carried out

on 415 clinically diagnosed Turkish FMF patients and 103 healthy controls. The tested individuals were screened for the most common twelve MEFV mutations. The most important features were the predominance of the M694V and E148Q mutations in patient group and the earlier onset of the disease in M694V mutation carriers compared with the carriers of other mutations ( $P=0.00$ ). We discuss the high frequency of E148Q mutations in patient group compared with controls, genetic counseling in intermarriage families and the variations in mutation frequency according to regions of Turkey.

DOI: 10.2174/1874312901004010001

PMCID: PMC2825617

PMID: 20177433

3327. Nat Rev Rheumatol. 2010 Apr;6(4):232-41. doi: 10.1038/nrrheum.2010.4. Epub 2010 Feb 23.

IL-1 pathways in inflammation and human diseases.

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Interleukin (IL)-1 was first cloned in the 1980s, and rapidly emerged as a key player in the regulation of inflammatory processes. The term IL-1 refers to two cytokines, IL-1 $\alpha$  and IL-1 $\beta$ , which are encoded by two separate genes. The effects of IL-1 are tightly controlled by several naturally occurring inhibitors, such as IL-1 receptor antagonist (IL-1Ra), IL-1 receptor type II (IL-1RII), and other soluble receptors. Numerous IL-1 inhibitors have been developed and tested primarily in rheumatoid arthritis, with only modest effects. By contrast, the use of IL-1 antagonists has been uniformly associated with beneficial effects in patients with hereditary autoinflammatory conditions associated with excessive IL-1 signaling, such as cryopyrinopathies and IL-1Ra deficiency. Successful treatment with IL-1 blockers has also been reported in other hereditary autoinflammatory diseases, as well as in nonhereditary inflammatory diseases, such as Schnitzler syndrome, systemic-onset juvenile idiopathic arthritis and

adult Still disease. The role of microcrystals in the regulation of IL-1 $\beta$  processing and release has provided the rationale for the use of IL-1 inhibitors in crystal-induced arthritis. Finally, preliminary results indicating that IL-1 targeting is efficacious in type 2 diabetes and smoldering myeloma have further broadened the spectrum of IL-1-driven diseases.

DOI: 10.1038/nrrheum.2010.4

PMID: 20177398 [Indexed for MEDLINE]

3328. Nat Rev Endocrinol. 2010 Mar;6(3):158-66. doi: 10.1038/nrendo.2009.271.

Blockade of interleukin 1 in type 1 diabetes mellitus.

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Interleukin 1 (IL-1) is a 17 kDa protein highly conserved through evolution and is a key mediator of inflammation, fever and the acute-phase response. IL-1 has important functions in the innate immune defense against microbes, trauma and stress, and is also an effector molecule involved in tissue destruction and fibrosis. The inhibition of IL-1 action has clinical efficacy in many inflammatory diseases, such as hereditary autoinflammatory disorders, familial hereditary fever, gout, rheumatoid arthritis and type 2 diabetes mellitus (T2DM). The latter is a common metabolic condition caused by insulin resistance and pancreatic beta-cell failure, the causes of both of which have inflammatory components. IL-1 signaling has roles in beta-cell dysfunction and destruction via the NF $\kappa$ B and mitogen-activated-protein-kinase pathways, leading to endoplasmic reticulum and mitochondrial stress and eventually activating the apoptotic machinery. In addition, IL-1 acts on T-lymphocyte regulation. The modulating effect of IL-1 on the interaction between the innate and adaptive immune systems and the effects of IL-1 on the beta-cell point to this molecule being a potential interventional target in autoimmune diabetes mellitus. Genetic or pharmacological abrogation of IL-1 action reduces disease incidence in animal models of type 1 diabetes mellitus (T1DM) and clinical trials have been started to study the feasibility, safety and efficacy of IL-1 therapy in patients with

T1DM. Here, we review the rationale for blocking IL-1 in patients with T1DM.

DOI: 10.1038/nrendo.2009.271

PMID: 20173777 [Indexed for MEDLINE]

3329. Mod Rheumatol. 2010 Jun;20(3):311-5. doi: 10.1007/s10165-010-0273-y. Epub 2010 Feb 19.

Variable intrafamilial expressivity of the rare tumor necrosis factor-receptor associated periodic syndrome-associated mutation I170N that affects the TNFR1A cleavage site.

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We report on a 33-year-old female patient with a relatively mild clinical case of TNF-receptor associated periodic syndrome (TRAPS) and her 58-year-old father in whom end-stage renal disease due to TRAPS-related AA-amyloidosis has already developed. TRAPS was caused by a I170N mutation that has previously not been associated with amyloidosis. It remains unclear if an only mildly affected patient such as ours would benefit from treatment considering her father's severe course of disease. The relevant literature on this problem is reviewed.

DOI: 10.1007/s10165-010-0273-y

PMCID: PMC3074501

PMID: 20169391 [Indexed for MEDLINE]

3330. Sao Paulo Med J. 2009 Sep;127(5):314-6.

Autoinflammatory syndromes: report on three cases.

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CONTEXT: Autoinflammatory syndromes are diseases manifested by recurrent episodes of fever and inflammation in multiple organs. There is no production of autoantibodies, but interleukins play an important role and acute-phase reactants show abnormalities. Our aim was to report on three cases of autoinflammatory syndromes that are considered to be rare entities.

CASE REPORTS: The authors describe the clinical features of three patients whose diagnosis were the following: tumor necrosis factor receptor-associated periodic syndrome (TRAPS), chronic infantile neurological cutaneous articular (CINCA) syndrome and familial Mediterranean fever (FMF). All of the patients presented fever, joint or bone involvement and increased acute phase reactants. The genetic analysis confirmed the diagnoses of two patients. The great diversity of manifestations and the difficulties in genetic analyses make the diagnosing of these diseases a challenge.

PMID: 20169282 [Indexed for MEDLINE]

3331. Arerugi. 2009 Nov;58(11):1502-12.

[Diagnostic approach for the autoinflammatory syndromes based on the molecular mechanism of innate immunity].

[Article in Japanese]

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PMID: 20168068 [Indexed for MEDLINE]

3332. Mol Biol Rep. 2011 Jun;38(5):3195-200. doi: 10.1007/s11033-010-9991-7. Epub 2010 Feb 18.

Prevalence of known mutations in the MEFV gene in a population screening with high rate of carriers.

Ozdemir O(1), Sezgin I, Kurtulgan HK, Candan F, Koksall B, Sumer H, Icagasioglu D, Uslu A, Yildiz F, Arslan S, Cetinkaya S, Citli S, Oztemur Z, Kayatas M.

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The Familial Mediterranean Fever (FMF) shows an autosomal recessive pattern of inheritance and affects certain ethnic groups. Disease is caused by mutations in MEFV gene and more than 180 mutations have been defined in affected individuals. Current study aimed to determine the frequency-type of the mutations for MEFV gene in Sivas-middle Anatolian city. The cohort was composed of 3340 patients. MEFV gene mutations were studied by multiplex PCR based reverse hybridization stripAssay method. Patients' clinical features were; family history: 68%, erysipelas-like erythema: 17.6%, fever: 89.9%, abdominal pain: 84.2%, peritonitis: 90.2%, arthritis: 33%, pleuritis: 14.2%, parental consanguinity: 21.2%. Current results revealed that M694V is the most frequent mutation (43.12%), followed by E148Q (20.18), M680I(G/C) (15.00%) and V726A (11.32%). The study population has a high rate of carriers and the E148Q mutation frequency was found to be highest when compared to the other regions of Turkey and other Mediterranean groups.

DOI: 10.1007/s11033-010-9991-7

PMID: 20165923 [Indexed for MEDLINE]

3333. Genet Test Mol Biomarkers. 2010 Apr;14(2):263-8. doi: 10.1089/gtmb.2009.0180.

MEFV gene mutations in Egyptian patients with familial Mediterranean fever.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent attacks of fever and serositis. The disease affects mainly Mediterranean populations and is caused by mutations in the MEFV gene.

**AIM:** This work was carried out to identify and determine the frequencies of MEFV gene mutations in Egyptian patients in whom FMF was diagnosed.

**METHODS:** We investigated 316 patients with a clinical diagnosis of FMF for 12 MEFV mutations including the 5 most common known mutations M694V, V726A, M694I, M680I, and E148Q by allele-specific hybridization.

**RESULTS:** Mutations were detected in 182 (57.6%) patients: 20 were homozygous, 80 were compound heterozygous, and 82 had only one identifiable mutant allele. In patients with clinically definite FMF (n = 112), no mutations were detected in 28 patients; whereas in patients with clinically unlikely FMF (n = 48), genetic analysis established the diagnosis in 6 patients. Overall, 10 mutations were detected in our patients. The most common were M694I (34%), E148Q (22.7%), V726A (15.6%), M680I (12.1%), and M694V (7.8%). M694V was observed in severe disease and in patients with amyloidosis.

**CONCLUSION:** We were able to identify a wide spectrum of MEFV mutations in Egyptian patients in whom FMF was diagnosed. Frequencies of individual mutations showed some differences from those in other Mediterranean populations.

DOI: 10.1089/gtmb.2009.0180

PMID: 20151816 [Indexed for MEDLINE]

3334. Curr Opin Rheumatol. 2010 May;22(3):246-51. doi: 10.1097/BOR.0b013e3283373fa0.

Actual status of antiinterleukin-1 therapies in rheumatic diseases.

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**PURPOSE OF REVIEW:** Several studies have evaluated the efficacy and safety of novel therapeutic options targeting interleukin-1 (IL-1), which not only plays a significant role in rheumatoid arthritis, but also in other rheumatic diseases,

for which only limited therapeutical options exist.

RECENT FINDINGS: Three different strategies have been pursued and evaluated in the past years: preventing IL-1 binding by occupying IL-1 receptors with anakinra, an imitation of the naturally occurring IL-1 receptor antagonist, anakinra; development of the fully human monoclonal anti-IL-1 $\beta$  antibody canakinumab; and synthesis of the dimeric fusion protein rilonacept, consisting of the ligand-binding domain of interleukin-1 receptor type I and its accessory protein, bound to human IgG1. Each of these three anti-IL-1 agents proved efficacy in distinct clinical situations and disease entities.

SUMMARY: Owing to the observation that IL-1 is not only involved in signaling processes resulting in autoimmune and crystal-induced joint destruction but also in several hereditary autoinflammatory syndromes, its value both in pathophysiology as well as for novel advances in medication has significantly improved in the past years leading to an enrichment of the current therapeutic armamentarium for the affected patients.

DOI: 10.1097/BOR.0b013e3283373fa0

PMID: 20150813 [Indexed for MEDLINE]

3335. Nat Rev Rheumatol. 2010 Mar;6(3):146-56. doi: 10.1038/nrrheum.2009.278. Epub 2010 Feb 9.

Sensors of the innate immune system: their link to rheumatic diseases.

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Evidence strongly suggests that excessive or protracted signaling, or both, by cell-surface or intracellular innate immune receptors is central to the pathogenesis of most autoimmune and autoinflammatory rheumatic diseases. The initiation of aberrant innate and adaptive immune responses in autoimmune diseases can be triggered by microbes and, at times, by endogenous molecules--particularly nucleic acids and related immune complexes--under sterile



conditions. By contrast, most autoinflammatory syndromes are generally dependent on germline or de novo gene mutations that cause or facilitate inflammasome assembly. The consequent production of proinflammatory cytokines, principally interferon-alpha/beta and tumor necrosis factor in autoimmune diseases, and interleukin-1beta in autoinflammatory diseases, leads to the creation of autoamplification feedback loops and chronicity of these syndromes. These findings have resulted in a critical reappraisal of pathogenetic mechanisms, and provide a basis for the development of novel diagnostic and therapeutic modalities for these diseases.

DOI: 10.1038/nrrheum.2009.278

PMCID: PMC4437225

PMID: 20142813 [Indexed for MEDLINE]

3336. Pediatrics. 2010 Mar;125(3):e683-6. doi: 10.1542/peds.2009-2630. Epub 2010 Feb 8.

Autoimmune hepatitis type 2 arising in PFAPA syndrome: coincidences or possible correlations?

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PFAPA syndrome is a chronic disease classified in the group of autoinflammatory syndromes characterized by periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis in young children. The etiology of this disorder is still unknown, but a primary dysfunction of the innate immune system seems to be involved. According to Marshall criteria, it is not possible to diagnose PFAPA in the presence of autoimmune diseases. We present here the case report of an 8-month girl with PFAPA who developed autoimmune hepatitis type 2 at the age of 18 months. We suppose that the dysregulation in innate immunity that is typical of patients with PFAPA could trigger autoimmune disorders such as autoimmune hepatitis in susceptible subjects. The possible relationships between immune-system dysfunction peculiar to this syndrome and autoimmune hepatitis are discussed.

DOI: 10.1542/peds.2009-2630

PMID: 20142286 [Indexed for MEDLINE]

3337. Klin Padiatr. 2010 Jul;222(4):266-8. doi: 10.1055/s-0029-1239527. Epub 2010 Feb 4.

[Improvement of sensoneurinal hearing loss in a patient with Muckle-Wells syndrome treated with anakinra].

[Article in German]

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Muckle Wells syndrome is an autoinflammatory disease in the group of cryopyrin associated periodic syndromes (CAPS). We report the case of an 8 year old girl with MWS who presented with remitting fever, urticaria, remitting coxitis, osteitis, bilateral uveitis anterior, elevated levels of C-reactive protein (CRP) and Serum amyloid A (SAA) and progressive sensoneurinal hearing loss. After starting treatment with anakinra, clinical symptoms dissolved almost completely for about two years now. CRP and SAA levels normalized quickly and sustained and as a consequence the risk of amyloidosis may be minimized. Notable is the complete recovery from sensoneurinal hearing loss merely two months after start of treatment. This brings up questions about pathophysiology of sensoneurinal hearing loss in MWS and emphasizes the benefits of an early diagnosis, as an early start of treatment possibly reduces long-term damage.

(c) Georg Thieme Verlag KG Stuttgart-New York.

DOI: 10.1055/s-0029-1239527

PMID: 20135584 [Indexed for MEDLINE]

3338. Arthritis Rheum. 2010 Apr;62(4):1158-66. doi: 10.1002/art.27342.

A somatic NLRP3 mutation as a cause of a sporadic case of chronic infantile neurologic, cutaneous, articular syndrome/neonatal-onset multisystem inflammatory disease: Novel evidence of the role of low-level mosaicism as the pathophysiologic mechanism underlying mendelian inherited diseases.

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**OBJECTIVE:** Chronic infantile neurologic, cutaneous, articular syndrome (CINCA), also known as neonatal-onset multisystem inflammatory disease (NOMID), is a severe, early-onset autoinflammatory disease characterized by an urticaria-like rash, arthritis/arthropathy, variable neurologic involvement, and dysmorphic features, which usually respond to interleukin-1 blockade. CINCA/NOMID has been associated with dominant Mendelian inherited NLRP3 mutations. However, conventional sequencing analyses detect true disease-causing mutations in only approximately 55-60% of patients, which suggests the presence of genetic heterogeneity. We undertook the current study to assess the presence of somatic, nongermine NLRP3 mutations in a sporadic case of CINCA/NOMID.

**METHODS:** Clinical data, laboratory results, and information on treatment outcomes were gathered through direct interviews. Exhaustive genetic studies, including Sanger method sequencing, subcloning, restriction fragment length polymorphism assay, and pyrosequencing, were performed.

**RESULTS:** The patient's CINCA/NOMID was diagnosed based on clinical features (early onset of the disease, urticaria-like rash, knee arthropathy, and dysmorphic features). The patient has exhibited a successful response to anakinra within the last 28 months. Analysis of NLRP3 identified a novel heterozygous variant (p.D303H) that was detected in approximately 30-38% of circulating leukocytes. The absence of this variant in healthy controls and in the patient's parents suggested a de novo true disease-causing mutation. Additional analyses showed that this novel mutation was present in both leukocyte subpopulations and epithelial cells.

**CONCLUSION:** Our findings identify the novel p.D303H NLRP3 variant in a Spanish patient with CINCA/NOMID as a new disease-causing mutation, which was detected as a somatic, nongermine mutation in hematopoietic and nonhematopoietic cell

lineages. Our data provide new insight into the role of low-level mosaicism in NLRP3 as the pathophysiologic mechanism underlying cryopyrin-associated periodic syndrome.

DOI: 10.1002/art.27342

PMID: 20131270 [Indexed for MEDLINE]

3339. Arthritis Rheum. 2010 Apr;62(4):1051-9. doi: 10.1002/art.27335.

Nucleotide-binding oligomerization domain 2 and Toll-like receptor 2 function independently in a murine model of arthritis triggered by intraarticular peptidoglycan.

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**OBJECTIVE:** Blau syndrome is an autoinflammatory disease resulting from mutations in the NOD2 gene, wherein granulomatous arthritis, uveitis, and dermatitis develop. The mechanisms by which aberrant NOD2 causes joint inflammation are poorly understood. Indeed, very few studies have addressed the function of nucleotide-binding oligomerization domain 2 (NOD-2) in the joint. This study was undertaken to investigate NOD-2 function in an experimental model of arthritis and to explore the potential interplay between Toll-like receptor 2 (TLR-2) and NOD-2 in joint inflammation.

**METHODS:** Mice deficient in TLR-2, myeloid differentiation factor 88 (MyD88), or NOD-2 and their wild-type controls were given an intraarticular injection of muramyl dipeptide (MDP), peptidoglycan (PG; a metabolite of which is MDP), or palmitoyl-3-cysteine-serine-lysine-4 (Pam(3)CSK(4)), a synthetic TLR-2 agonist. Joint inflammation was assessed by near-infrared fluorescence imaging and histologic analysis.

**RESULTS:** Locally administered PG resulted in joint inflammation, which was markedly reduced in mice deficient in either TLR-2 or the TLR signaling mediator MyD88. In addition to TLR-2 signaling events, NOD-2 mediated joint inflammation, as evidenced by the fact that mice deficient in NOD-2 showed significantly reduced PG-induced arthritis. TLR-2 or MyD88 deficiency did not influence arthritis induced by the specific NOD-2 agonist MDP. In addition, NOD-2

deficiency did not alter the TLR-2-dependent joint inflammation elicited by the synthetic TLR-2 agonist Pam(3)CSK(4).

CONCLUSION: Whereas NOD-2 and TLR-2 are both critical for the development of PG-induced arthritis, they appear to elicit inflammation independently of each other. Our findings indicate that NOD-2 plays an inflammatory role in arthritis.

DOI: 10.1002/art.27335

PMCID: PMC2945367

PMID: 20131263 [Indexed for MEDLINE]

3340. Arthritis Rheum. 2010 Apr;62(4):1176-85. doi: 10.1002/art.27326.

Functional consequences of a germline mutation in the leucine-rich repeat domain of NLRP3 identified in an atypical autoinflammatory disorder.

Jéru I(1), Marlin S, Le Borgne G, Cochet E, Normand S, Duquesnoy P, Dastot-Le Moal F, Cuisset L, Hentgen V, Fernandes Alnemri T, Lecron JC, Dhote R, Grateau G, Alnemri ES, Amselem S.

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Comment in

Arthritis Rheum. 2010 Oct;62(10):3123-4; author reply 3124-5.

OBJECTIVE: To gain insight into the pathophysiology of an atypical familial form of an autoinflammatory disorder, characterized by autosomal-dominant sensorineural hearing loss, systemic inflammation, increased secretion of interleukin-1beta (IL-1beta), and the absence of any cutaneous manifestations, and to assess the functional consequences of a missense mutation identified in the leucine-rich repeat (LRR) domain of NLRP3.

METHODS: Microsatellite markers were used to test the familial segregation of the NLRP3 locus with the disease phenotype. All NLRP3 exons were screened for mutations by sequencing. Functional assays were performed in HEK 293T cells to determine the effects of mutated (versus normal) NLRP3 proteins on NF-kappaB activation, caspase 1 signaling, and speck formation.

**RESULTS:** A heterozygous NLRP3 missense mutation (p.Tyr859Cys) was identified in exon 6, which encodes the LRR domain of the protein. This mutation was found to segregate with the disease phenotype within the family, and had a moderate activating effect on speck formation and procaspase 1 processing and did not alter the inhibitory properties of NLRP3 on NF-kappaB signaling.

**CONCLUSION:** This report is the first to describe a familial form of a cryopyrinopathy associated with a mutation outside of exon 3 of NLRP3. This finding, together with the known efficacy of anti-IL-1 treatments in these disorders, underlines the importance of screening all exons of NLRP3 in patients who present with atypical manifestations. In addition, the gain of function associated with this mutation in terms of activation of caspase 1 signaling was consistent with the observed inflammatory phenotype. Therefore, this study of the functional consequences of an LRR mutation sheds new light on the clinical relevance of in vitro assays.

DOI: 10.1002/art.27326

PMID: 20131254 [Indexed for MEDLINE]

3341. Ann Clin Lab Sci. 2010 Winter;40(1):10-4.

Increased serum concentrations of homocysteine and lipoprotein (a) in familial Mediterranean fever.

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Serum homocysteine, folic acid, lipoprotein (a) (Lp(a)), fibrinogen, and C-reactive protein (CRP) concentrations and erythrocyte sedimentation rates (ESR) were measured in 52 patients with familial Mediterranean fever (FMF) during attack-free periods and in 30 healthy control subjects. Serum homocysteine levels were significantly higher in the FMF patients (median 17.8 microg/dl; range 5.6-80.8) than in controls (median 11.7; range 5.6-42.2;  $p = 0.013$ ). Serum homocysteine levels were elevated above the upper reference limit (15 microg/dl) in 56% of the FMF patients compared to 27% of the controls ( $p = 0.011$ ). Serum

Lp(a) levels were significantly higher in the FMF patients (median 39.3 mg/dl; range 6.6-124.5) than in controls (median 27.2; range 11.1-78.1;  $p = 0.035$ ). Serum Lp(a) levels were elevated above the upper reference limit (30 mg/dl) in 71% of the FMF patients compared to 47% of the controls ( $p = 0.028$ ). The ESR, fibrinogen, CRP, and folic acid levels were similar in both groups. In conclusion, serum homocysteine and Lp(a) concentrations are often increased in FMF patients during attack-free periods. The elevated homocysteine and Lp(a) levels, which are markers of sub-clinical inflammation, may be mediators of atherosclerotic disease in FMF patients.

PMID: 20124324 [Indexed for MEDLINE]

3342. Eur J Neurol. 2010 Jun 1;17(6):861-5. doi: 10.1111/j.1468-1331.2010.02948.x. Epub 2010 Jan 20.

Rapidly progressive Creutzfeldt-Jakob disease in patients with Familial Mediterranean Fever.

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**BACKGROUND:** The largest cluster of familial Creutzfeldt-Jakob disease (fCJD) exists in Jews of Libyan origin. Familial Mediterranean fever (FMF) is an inflammatory disease also common in this population.

**OBJECTIVES:** We hypothesized that FMF, as a pro-inflammatory condition, may affect the course of CJD.

**METHODS:** Three hundred and seventy-two consecutive patients diagnosed clinically and genetically as CJD were included in the study. Two hundred and thirty-six had fCJD, and 136 had sporadic disease (sCJD). Review of the patient's records revealed three patients with FMF-CJD co-morbidity. In addition, 50 DNA samples of patients with CJD were genotyped as homozygote, heterozygote, and non-carriers of the FMF mutation. The demographic and clinical variables of the groups were

compared.

RESULTS: The three patients with FMF had an earlier age of onset and significantly shorter disease duration than the patients without FMF.

Heterozygote carriers did not differ in disease onset and duration from patients without FMF.

CONCLUSIONS: The shorter disease duration of CJD patients with FMF may indicate the importance of pro-inflammatory factors in the disease.

DOI: 10.1111/j.1468-1331.2010.02948.x

PMCID: PMC2895685

PMID: 20113338 [Indexed for MEDLINE]

3343. IUBMB Life. 2010 Apr;62(4):303-12. doi: 10.1002/iub.304.

Worms to the rescue: can worm glycans protect from autoimmune diseases?

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Autoimmune and autoinflammatory diseases represent a significant health burden, especially in Western societies. For the majority of these diseases, no cure exists. Recently, research on parasitic worms (helminths) has demonstrated great potential for whole worms, their eggs or their excretory/secretory proteins in down-regulating inflammatory responses both in vitro and in vivo, in various disease models and, in some cases, even in clinical trials. The worms are thought to induce Th2 and regulatory T cells, interfere with Toll-like receptor (TLR) signaling and to down-regulate Th17 and Th1 responses. The molecular mechanisms underlying the worms' ability to modulate the host immune response are not well understood, and many hypotheses have been proposed to explain the observed immune modulation. Increasing evidence suggests that carbohydrate structures (glycans), for example, phosphorylcholine-modified glycans or Galbeta1-4(Fucalpha1-3)GlcNAc-(Lewis X, Le(X)) containing glycans, expressed by the worms contribute to these modulating properties by their interaction with antigen presenting cells. Helminths express a broad variety of protein- and lipid-linked glycans on their surface and on secretory products. These glycans differ in amount and composition



and several of these structures are species specific. However, worms also express glycan antigens that are found in a wide variety of different species. Some of these "common" worm glycans are particularly interesting with regard to regulating host responses, because they have the potential to interact with C-type lectins on dendritic cells and thereby may interfere with T-cell polarization. Helminths and helminth-derived molecules form a novel and promising group of therapeutics for autoinflammatory diseases. However, much has to be learned about the molecular mechanisms behind the helminth-mediated antiinflammatory properties. This review will describe some of the emerging evidence in selected disease areas as well as discuss the putative role of glycans in helminth-mediated immunosuppression.

DOI: 10.1002/iub.304

PMID: 20101628 [Indexed for MEDLINE]

3344. Clin Exp Rheumatol. 2009 Jul-Aug;27(4 Suppl 55):S10-4.

Differences in pathophysiology between rheumatoid arthritis and ankylosing spondylitis.

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Rheumatoid arthritis and ankylosing spondylitis are common and severe chronic inflammatory skeletal diseases. Recognizing the differences rather than emphasizing similarities is important for a better understanding of the disease processes, the identification of specific therapeutic targets and in the long-term better treatment options for the individual patients. We discuss a number of pathophysiological differences between rheumatoid arthritis and ankylosing spondylitis by looking at the anatomical characteristics, differences and similarities in the autoimmune and autoinflammatory reactions, association with other immune mediated inflammatory diseases, structural outcome, and their potential significance for further therapeutic developments. Further research into the differences between these diseases should focus on the specific nature

of the immune/inflammatory components, the role of resident cells in the joint and joint-associated tissues, the types and mechanisms of tissue remodeling and the characteristics of the articular cartilage. Better insights into their individual characteristics may lead to better therapeutic strategies, specific targets and useful biomarkers.

PMID: 19822039 [Indexed for MEDLINE]

3345. Trends Endocrinol Metab. 2010 May;21(5):261-7. doi: 10.1016/j.tem.2009.12.010. Epub 2010 Jan 22.

Cytokine production by islets in health and diabetes: cellular origin, regulation and function.

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Islets produce a variety of cytokines and chemokines in response to physiologic and pathologic stimulation by nutrients. The cellular source of these inflammatory mediators includes alpha-, beta-, endothelial-, ductal- and recruited immune cells. Islet-derived cytokines promote alpha- and beta-cell adaptation and repair in the short term. Eventually, chronic metabolic stress can induce a deleterious autoinflammatory process in islets leading to insulin secretion failure and type 2 diabetes. Understanding the specific role of islet derived cytokines and chemokines has opened the door to targeted clinical interventions aimed at remodeling islet inflammation from destruction to adaptation. In this article, we review the islet cellular origin of various cytokines and chemokines and describe their regulation and respective roles in physiology and diabetes.

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DOI: 10.1016/j.tem.2009.12.010

PMID: 20096598 [Indexed for MEDLINE]

3346. J Nephrol. 2010 Jan-Feb;23(1):119-23.

No regression of renal amyloid mass despite remission of nephrotic syndrome in a patient with TRAPS following etanercept therapy.

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Reactive systemic (AA) amyloidosis leading to renal failure is the most severe complication of tumor necrosis factor receptor-associated periodic syndrome (TRAPS). There is now growing evidence to suggest that anti-tumor necrosis factor (anti-TNF) agents may be an attractive treatment option for amyloidosis not only in TRAPS but in several forms of secondary amyloidosis complicating inflammatory rheumatic diseases. In most of the reported cases, anti-TNF agents were deemed successful on the basis of regression of proteinuria and either improvement or stabilization of creatinine clearance, while objective proof of renal amyloid regression either by serum amyloid P scintigraphy or biopsy is limited. We herein report a case of TRAPS complicated with nephrotic syndrome due to AA amyloidosis in which treatment with etanercept was associated with remission of the nephrotic syndrome but no regression of amyloid mass on the follow-up renal biopsy. Indeed, amyloid deposition was noted to be more pronounced on the second renal biopsy, particularly at tubular basement membranes. Although the variable relation between reduction in amyloid load and changes in organ function is well-known, the basis for renal recovery in association with stable or even progressive amyloid deposition is challenging. We suggest that in patients with secondary AA amyloidosis, mechanisms other than the reduction of amyloid mass could have contributed to the observed improvement of renal function with anti-TNF agents.

PMID: 20091495 [Indexed for MEDLINE]

3347. Sci Signal. 2010 Jan 19;3(105):cm1. doi: 10.1126/scisignal.3105cm1.

Interleukin-1 (IL-1) pathway.

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The interleukin-1 (IL-1) family of cytokines comprises 11 proteins (IL-1F1 to IL-1F11) encoded by 11 distinct genes in humans and mice. IL-1-type cytokines are major mediators of innate immune reactions, and blockade of the founding members IL-1alpha or IL-1beta by the interleukin-1 receptor antagonist (IL-1RA) has demonstrated a central role of IL-1 in a number of human autoinflammatory diseases. IL-1alpha or IL-1beta rapidly increase messenger RNA expression of hundreds of genes in multiple different cell types. The potent proinflammatory activities of IL-1alpha and IL-1beta are restricted at three major levels: (i) synthesis and release, (ii) membrane receptors, and (iii) intracellular signal transduction. This pathway summarizes extracellular and intracellular signaling of IL-1alpha or IL-1beta, including positive- and negative-feedback mechanisms that amplify or terminate the IL-1 response. In response to ligand binding of the receptor, a complex sequence of combinatorial phosphorylation and ubiquitination events results in activation of nuclear factor kappaB signaling and the JNK and p38 mitogen-activated protein kinase pathways, which, cooperatively, induce the expression of canonical IL-1 target genes (such as IL-6, IL-8, MCP-1, COX-2, IkappaBalpha, IL-1alpha, IL-1beta, MKP-1) by transcriptional and posttranscriptional mechanisms. Of note, most intracellular components that participate in the cellular response to IL-1 also mediate responses to other cytokines (IL-18 and IL-33), Toll-like-receptors (TLRs), and many forms of cytotoxic stresses.

DOI: 10.1126/scisignal.3105cm1

PMID: 20086235 [Indexed for MEDLINE]

3348. Int J Immunopathol Pharmacol. 2009 Oct-Dec;22(4):1051-8.

Idiopathic recurrent pericarditis refractory to colchicine treatment can reveal tumor necrosis factor receptor-associated periodic syndrome.

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Recurrences develop in up to 20-50% of patients with acute pericarditis. Although different causes of recurrent pericarditis have been identified, the etiology remains obscure in most cases which are therefore labelled as idiopathic. Autoinflammatory syndromes include familial Mediterranean fever (FMF), due to mutations in the MEFV gene, and tumor necrosis factor receptor-associated periodic syndrome (TRAPS), due to mutations in the TNFRSF1A gene. Recurrent pericarditis is a common feature of both conditions, but it rarely occurs alone. Colchicine is the standard treatment for FMF, while patients with TRAPS do not respond to colchicine therapy, but are responsive to corticosteroids. Based on the proven efficacy of colchicine in preventing polyserositis in FMF, colchicine has been proposed for the treatment of recurrent pericarditis and is able to decrease the recurrence rate. Our aim was to investigate the possible involvement of TNFRSF1A mutations in a group of patients with idiopathic recurrent pericarditis who were refractory to colchicine treatment. Thirty consecutive patients (17 males, 13 females) diagnosed with idiopathic recurrent pericarditis, who were characterized by a poor response to colchicine treatment, were enrolled in the study. Mutations of the TNFRSF1A gene were searched for by amplifying, using polymerase chain reaction (PCR), genomic DNA, and direct sequencing. TNFRSF1A mutations were found in 4 of the 30 patients. None of these 4 patients had a family history of recurrent inflammatory syndromes or history of pericarditis. One of the 4 patients had a novel heterozygous deletion (DeltaY103-R104) and three patients carried a heterozygous low-penetrance R92Q mutation. Our data suggest that TRAPS should be kept in mind in the differential diagnosis of recurrent pericarditis, and mutation analysis of the TNFRSF1A gene should be considered, in addition to MEFV analysis, in patients of Mediterranean origin. A poor response to colchicine treatment and/or a steroid-dependence may be the clue to investigate TNFRSF1A mutations in patients with idiopathic recurrent pericarditis.

DOI: 10.1177/039463200902200421

PMID: 20074469 [Indexed for MEDLINE]

3349. Ann N Y Acad Sci. 2009 Dec;1182:111-23. doi: 10.1111/j.1749-6632.2009.05159.x.

Blocking interleukin-1 in rheumatic diseases.

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The role of the potent proinflammatory cytokine IL-1 in disease could clinically be investigated with the development of the IL-1 blocking agent anakinra (Kineret), a recombinant IL-1 receptor antagonist. It was first tested in patients with sepsis without much benefit but was later FDA approved for the treatment of patients with rheumatoid arthritis. More recently IL-1 blocking therapies are used successfully to treat a new group of immune-mediated inflammatory conditions, autoinflammatory diseases. These conditions include rare hereditary fever syndromes and pediatric and adult conditions of Still's disease. Recently the FDA approved two additional longer acting IL-1 blocking agents, for the treatment of cryopyrin-associated periodic syndromes (CAPS), an IL-1 dependent autoinflammatory syndrome. The study of autoinflammatory diseases revealed mechanisms of IL-1 mediated organ damage and provided concepts to a better understanding of the pathogenesis of more common diseases such as gout and Type 2 diabetes which show initial promising results with IL-1 blocking therapy.

DOI: 10.1111/j.1749-6632.2009.05159.x

PMCID: PMC3080043

PMID: 20074280 [Indexed for MEDLINE]

3350. Rheumatology (Oxford). 2010 Feb;49(2):382-90. doi: 10.1093/rheumatology/kep327.

Low TNF-induced NF-kappaB and p38 phosphorylation levels in leucocytes in tumour necrosis factor receptor-associated periodic syndrome.

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Comment in

Rheumatology (Oxford). 2011 Aug;50(8):1525-6; author reply 1526-9.

**OBJECTIVE:** TNF receptor-associated periodic syndrome (TRAPS) is a systemic autoinflammatory disorder caused by mutations in the type 1 TNF receptor (TNFRSF1A) gene. Because the pathomechanism of TRAPS may involve aberrant TNF-mediated intracellular signalling, we examined phosphorylation levels of nuclear factor kappaB (NF-kappaB) and p38 in response to TNF in 10 patients with three different TNFRSF1A mutations (C73R, C88Y and F112I).

**METHODS:** Phosphorylation levels of NF-kappaB p65 and p38 were determined in fresh leucocytes stimulated with TNF (0-100 ng/ml) for 2.5-20 min and permeabilized for phospho-specific antibodies in a whole blood flow cytometry assay. As control agonists, we used bacterial lipopolysaccharide (LPS) and IFN-gamma, the latter mediating phosphorylation of the signal transducer and activator of transcription 1. Areas under curve values for dose-response and time course of NF-kappaB and p38 phosphorylation were calculated for the comparison of patients and reference subjects.

**RESULTS:** NF-kappaB and p38 phosphorylation levels of monocytes, lymphocytes and neutrophils stimulated with TNF were significantly lower in TRAPS patients than in reference subjects. Phosphorylation levels induced by LPS, or by IFN-gamma, in patient and reference samples were comparable, indicating that the defect was confined to TNF-mediated signalling.

**CONCLUSIONS:** In the three families studied, TRAPS was associated with low TNF-mediated signalling in leucocytes. This deficiency of the innate immune system may result in the activation of as yet unidentified compensatory regulatory mechanisms yielding the hyperinflammatory phenotype of TRAPS.

DOI: 10.1093/rheumatology/kep327

PMID: 20071450 [Indexed for MEDLINE]

3351. Drugs Today (Barc). 2009 Oct;45(10):731-5. doi: 1396674/dot.2009.45.10.1416583.

Canakinumab for the treatment of cryopyrin-associated periodic syndromes.

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Familial cold-induced autoinflammatory syndrome, Muckle-Wells syndrome and neonatal-onset multisystem inflammatory disease make up cryopyrin-associated periodic syndromes (CAPS). These are autoinflammatory inherited disorders caused by autosomal dominant gain-of-function mutations in the NLRP3 gene, located on chromosome 1q44. Cryopyrin/NALP3/NLRP3 is an essential component of intracellular inflammasomes that activate caspase-1, which in turn converts interleukin-1beta (IL-1beta) to its active form. IL-1beta is a potent cytokine that activates diverse elements of the immune and inflammatory systems leading to the pathogenic changes characteristic of CAPS. There is therefore much interest in the development of IL-1beta blocking agents as novel biologic treatments for these conditions. Canakinumab (ACZ-885; Ilaris, Novartis Pharma) is a fully humanized monoclonal antibody (mAb) specific for IL-1beta and is indicated for a wide range of inflammatory disorders including CAPS. This review will assess the utility of canakinumab as a treatment for CAPS.

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DOI: 1396674/dot.2009.45.10.1416583

PMID: 20069137 [Indexed for MEDLINE]

3352. Curr Opin Rheumatol. 2010 May;22(3):278-83. doi: 10.1097/BOR.0b013e3283368099.

Interferon therapy in rheumatic diseases: state-of-the-art 2010.

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PURPOSE OF REVIEW: Interferons are natural glycoproteins that have antiviral,



antiproliferative and immune regulatory functions. They are not only involved in the pathogenesis of certain autoimmune conditions but are also useful in the treatment of some rheumatologic disorders, notably Behçet's syndrome.

RECENT FINDINGS: Interferon alpha (IFNalpha) has been recommended for severe eye involvement in Behçet's syndrome, especially when there is a significant drop in visual acuity and/or retinal involvement. It can induce a high rate of complete remission that may also persist after its discontinuation. When given early at the beginning, interferon might be effective in ameliorating the attacks of familial Mediterranean fever resistant to colchicine treatment. The combination of PEGylated IFNalpha with ribavirin and rituximab emerges as a novel and promising treatment providing complete clinical response and viral clearance in hepatitis C virus-associated mixed cryoglobulinemia. Limited data also suggest that interferon may induce remissions in Churg-Strauss patients who fail to respond to conventional immunosuppressive treatment.

SUMMARY: Among several rheumatologic diseases, IFNalpha has found more widespread use in Behçet's syndrome and hepatitis C virus-associated mixed cryoglobulinemia despite a paucity of formal studies. Patients should be carefully monitored for the frequent and dose-dependent adverse effects.

DOI: 10.1097/BOR.0b013e3283368099

PMID: 20061957 [Indexed for MEDLINE]

3353. Rheumatol Int. 2010 Jun;30(8):1121-4. doi: 10.1007/s00296-009-1342-4. Epub 2010 Jan 6.

Altered cytokine profiles of mononuclear cells after stimulation in a patient with Blau syndrome.

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Autoinflammatory Blau syndrome (BS) is associated with NOD2 gene mutations that lead to constitutive NFkappaB activation. NOD2 functions as an intracellular receptor for the muramyl dipeptide (MDP) component of peptidoglycan (PGN). The objectives of this study are to analyse whether NFkappaB activation in BS affects

immune cell functions, and whether NOD2 and toll-like receptor (TLR) pathways interact. Peripheral blood mononuclear cells (MNCs) from a BS patient and three normal donors were analyzed for their ability to produce pro- and anti-inflammatory cytokines in the presence and absence of MDP, PGN, and lipopolysaccharide (LPS). The results obtained showed that the basal TNF-alpha and IL-10 production by MNCs over 24 h of incubation was very low for both the patient and the normal donors. However, upon stimulation with MDP, LPS, and PGN, the cells from the BS patient produced much lower levels of TNF-alpha, IL-10, G-CSF, and IFN-gamma than the normal donor cells. We conclude that the pathogenic mechanism responsible for the chronic inflammation that characterizes BS may relate to the impaired production of both pro- and anti-inflammatory cytokines to stimuli. The NOD2 pathway possibly interacts with either the TLR2 or TLR4 pathways.

DOI: 10.1007/s00296-009-1342-4

PMID: 20052476 [Indexed for MEDLINE]

3354. Respiration. 2010;79(6):508-10. doi: 10.1159/000272314. Epub 2009 Dec 24.

Isolated recurrent pleuritis revealing familial mediterranean Fever in adulthood.

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Comment in

Respiration. 2010;80(3):260-1; author reply 262.

Familial Mediterranean fever (FMF) is a genetic autoinflammatory disease especially affecting populations of Mediterranean origin with an autosomal recessive inheritance. The cardinal manifestations consist of short febrile and painful attacks of peritonitis, arthritis and pleuritis developing during childhood. We report the case of a 26-year-old man of Tunisian descent who had febrile episodes of right-sided pleuritis without any extrathoracic complaints. Disappearance of attacks with one dose of colchicine (1 mg/day) strengthened the

presumptive diagnosis of atypical FMF, which was further confirmed by genetic testing identifying the homozygous mutation M694I/M694I of the MEFV gene.

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DOI: 10.1159/000272314

PMID: 20051664 [Indexed for MEDLINE]

3355. Rheumatol Int. 2012 Mar;32(3):783-5. doi: 10.1007/s00296-009-1326-4. Epub 2010 Jan 5.

An infant with severe refractory Crohn's disease and homozygous MEFV mutation who dramatically responded to colchicine.

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Previous studies have suggested that inflammatory bowel disease is particularly frequent and severe in familial Mediterranean fever (FMF) families. An 8-month-old boy was admitted to our hospital with chronic bloody diarrhea, failure to thrive and high-grade fever. He was diagnosed as Crohn's disease (CD) based on clinical, laboratory and histological findings and, corticosteroid therapy was started. The patient did not respond to intensive medical therapy including intravenous corticosteroid, mesalazine, azathioprine, intravenous cyclosporine and enteral feeding. MEFV gene mutation analysis revealed homozygous M694V mutation. In addition to azathioprine and cyclosporine therapy, with the diagnosis of FMF, colchicine therapy was started and partial remission was observed within 2 weeks. To the best of our knowledge, this is the first report of association of CD and FMF in an infant. In cases of CD resistant to medical therapy, possibility of underlying FMF should be considered, especially in countries where FMF is prevalent.

DOI: 10.1007/s00296-009-1326-4

PMID: 20049453 [Indexed for MEDLINE]

3356. Rheumatol Int. 2011 May;31(5):623-8. doi: 10.1007/s00296-009-1334-4. Epub 2010 Jan 5.

Health-related quality of life and its associations with mood condition in familial Mediterranean fever patients.

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The aim of the present study was to investigate the health-related quality of life (HRQOL) and mood conditions in familial Mediterranean fever (FMF) patients. Ninety FMF patients (F/M 60/30, median age 29) and 67 control subjects (F/M 46/21, median age 30) were included in this study. HRQOL was assessed with short form-36 (SF-36) and mood conditions were assessed with hospital anxiety depression scale (HADS). FMF patients had significantly lower mean scores on SF-36 physical components compared to the control group. However, mental components were comparable between groups. FMF patients were significantly more likely to have depression and anxiety compared to the control group [30 (33%) vs. 8 (12%), respectively,  $\chi^2(2) = 9.58$ , OR (95% CI) = 3.7 (1.5-8.7),  $p < 0.01$  for depression and 48 (53%) and 11 (16%), respectively,  $\chi^2(2) = 22.31$ , OR (95% CI) = 5.8 (2.7-12.5),  $p < 0.001$  for anxiety]. When frequency of anxious subjects was adjusted for the presence of concomitant depressive status as a confounding factor, the difference between the groups remained statistically significant [ $\chi^2(2) = 11.86$ , OR (95% CI) = 5.4 (2.1-13.7),  $p < 0.01$ ]. However, the difference of depression status between groups was not statistically significant when adjusted for the presence of concomitant anxiety status [ $\chi^2(2) = 0.08$ , OR (95% CI) = 1.3 (0.5-3.8),  $p = 0.78$ ] and FMF was found to be independently associated with only anxiety [OR (95% CI) = 7.1 (2.3-20.3)]. In addition, pure anxious FMF subgroup had significantly lower scores of mental health and mental component summary when compared to normal mood subgroup. In conclusion, FMF might adversely affect HRQOL. Depression and anxiety are more frequent in FMF patients than healthy subjects.

DOI: 10.1007/s00296-009-1334-4

PMID: 20049448 [Indexed for MEDLINE]

3357. Joint Bone Spine. 2010 Mar;77(2):102-7. doi: 10.1016/j.jbspin.2009.10.011. Epub 2009 Dec 31.

Anti-IL-1 molecules: new comers and new indications.

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The interleukin 1 family is composed by the interleukin 1 (IL-1) and its natural occurring inhibitor, the interleukin 1 receptor antagonist (IL-1Ra). The role of both molecules in rheumatoid arthritis has been widely established, and in this sense new molecules blocking IL-1 actions are under investigation. Anakinra is the recombinant form of IL-1Ra, and has proven to be well tolerated and indicated in the treatment of rheumatoid arthritis. Nevertheless, other molecules such as mAb anti-IL-1 and IL-1 Trap are being developed. Moreover, the recent relation of IL-1 in the inflammasome and pathways of innate immunity has lead to new indications of anti-IL-1 molecules, especially in the autoinflammatory syndromes as well as in other inflammatory diseases. Herein we have performed a review of the literature, limited to English language journals (PUBMED search: combination of descriptors IL-1 and anakinra, systemic juvenile idiopathic arthritis, adult's onset Still's disease, autoinflammatory syndromes, gout, pseudogout, ankylosing spondylitis, and systemic lupus erythematosus from January 1985-December 2008) emphasizing the possible new indications. Although sufficient data is not yet available to fully assess the efficacy and safety of anti-IL-1 molecules in patients with inflammatory disorders other than rheumatoid arthritis, new data is promising.

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DOI: 10.1016/j.jbspin.2009.10.011

PMID: 20045371 [Indexed for MEDLINE]

3358. Rheumatol Int. 2012 Feb;32(2):465-7. doi: 10.1007/s00296-009-1331-7. Epub 2010 Jan 1.

Systemic-onset juvenile idiopathic arthritis complicated by early onset amyloidosis in a patient carrying a mutation in the MEFV gene.

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Systemic juvenile idiopathic arthritis (SJIA) is a disorder characterized by arthritis in children starting before 16 years of age associated with daily high fever, persisting for more than 2 weeks, and at least one of the following clinical features: evanescent cutaneous rash, lymphadenopathy, serositis or hepatosplenomegaly. SJIA patients carry a significantly higher frequency of MEFV mutations, the gene responsible for familial Mediterranean fever, and may be characterized by a more aggressive disease. In this line, we describe a 9-year-old girl affected with SJIA who carried a heterozygous G196W mutation in MEFV. Our patient was characterized by an aggressive disease course, resistance to conventional immunosuppressive agents and developed renal amyloidosis just 2 years after the disease onset.

DOI: 10.1007/s00296-009-1331-7

PMID: 20044784 [Indexed for MEDLINE]

3359. J Inflamm Res. 2010;3:1-8. Epub 2010 Jan 19.

Riloncept in the management of cryopyrin-associated periodic syndromes (CAPS).

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Cryopyrin-associated periodic syndromes (CAPS) are a subgroup of the hereditary periodic fever syndromes, which are rare autoinflammatory and inherited disorders, characterized by recurrent inflammation and varying degrees of severity. CAPS are thought to be driven by excessive production of interleukin-1 $\beta$  (IL-1 $\beta$ ), through over-activation of the inflammasome by gain of function mutations in the gene encoding cryopyrin (NLRP3). This conclusion is supported by the remarkable efficacy of IL-1 $\beta$  blockade in these conditions. Rilonacept (Arcalyst(TM); Regeneron) is the first us Food and Drug Administration-approved treatment for familial cold autoinflammatory syndrome and Muckle-Wells syndrome and the first in a new line of drugs designed for longer-acting IL-1 blockade. Rilonacept has been associated with a decrease in disease activity, high-sensitivity C-reactive protein (hsCRP) and serum amyloid A (SAA) in the treatment of CAPS. The clinical safety and efficacy of rilonacept in CAPS and non-CAPS populations will be summarized in this review. Rilonacept is also beneficial for patients who tolerate injections poorly, due to an extended half-life over the unapproved CAPS treatment, anakinra, requiring weekly rather than daily self-administration. Other autoinflammatory disorders may also benefit from rilonacept treatment, with clinical trials in progress for systemic onset juvenile idiopathic arthritis, gout and familial mediterranean fever.

PMCID: PMC3218731

PMID: 22096352

3360. Clin Med Insights Case Rep. 2010;3:59-62. doi: 10.4137/CCRep.S5910. Epub 2010 Oct 12.

Delay in diagnosis of intestinal obstruction in a patient with familial mediterranean Fever.

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Familial Mediterranean Fever (FMF) is a recurrent disease characterized by

inflammatory process effecting synovial membranes such as peritoneum, pericardium and joints. It usually presents with acute abdominal pain. Intestinal obstruction secondary to adhesions may be observed in FMF patients. Sometimes diagnosing intestinal obstruction can be a challenging problem. We were presented a patient with FMF and adhesive intestinal obstruction. He was operated on after 10 days of symptoms. Delay in diagnosis and treatment of the case discussed with literature review.

DOI: 10.4137/CCRep.S5910

PMCID: PMC3046008

PMID: 21769256

3361. Front Microbiol. 2011 Jan 20;1:148. doi: 10.3389/fmicb.2010.00148. eCollection 2010.

Profiles of Microbial Fatty Acids in the Human Metabolome are Disease-Specific.

Ktsoyan ZA(1), Beloborodova NV, Sedrakyan AM, Osipov GA, Khachatryan ZA, Kelly D, Manukyan GP, Arakelova KA, Hovhannisyan AI, Olenin AY, Arakelyan AA, Ghazaryan KA, Aminov RI.

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The human gastrointestinal tract is inhabited by a diverse and dense symbiotic microbiota, the composition of which is the result of host-microbe co-evolution and co-adaptation. This tight integration creates intense cross-talk and signaling between the host and microbiota at the cellular and metabolic levels. In many genetic or infectious diseases the balance between host and microbiota may be compromised resulting in erroneous communication. Consequently, the composition of the human metabolome, which includes the gut metabolome, may be different in health and disease states in terms of microbial products and metabolites entering systemic circulation. To test this hypothesis, we measured the level of hydroxy, branched, cyclopropyl and unsaturated fatty acids, aldehydes, and phenyl derivatives in blood of patients with a hereditary autoinflammatory disorder, familial Mediterranean fever (FMF), and in patients with peptic ulceration (PU) resulting from *Helicobacter pylori* infection.



Discriminant function analysis of a data matrix consisting of 94 cases as statistical units (37 FMF patients, 14 PU patients, and 43 healthy controls) and the concentration of 35 microbial products in the blood as statistical variables revealed a high accuracy of the proposed model (all cases were correctly classified). This suggests that the profile of microbial products and metabolites in the human metabolome is specific for a given disease and may potentially serve as a biomarker for disease.

DOI: 10.3389/fmicb.2010.00148

PMCID: PMC3109323

PMID: 21687748

3362. *Dermatoendocrinol.* 2010 Jan;2(1):9-16. doi: 10.4161/derm.2.1.12490.

Comorbidities of hidradenitis suppurativa (acne inversa).

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Comorbidities of hidradenitis suppurativa (acne inversa) were reviewed by extracting original and review publications included in MEDLINE, EMBASE and COCHRANE libraries using the terms "hidradenitis," "Verneuil" and "acne inversa." Follicular occlusion disorders, inflammatory bowel diseases, especially Crohn disease, spondylarthropathy, other hyperergic diseases, genetic keratin disorders associated with follicular occlusion and squamous cell carcinoma were the most common hidradenitis suppurativa comorbid diseases. A first classification of these major comorbidities and their possible genetic background reveals a list of chromosome loci and genes, which could be hidradenitis suppurativa candidates. Most of these diseases belong to the group of autoinflammatory disorders, where th17 cell cytokines seem to play a central role.

DOI: 10.4161/derm.2.1.12490

PMCID: PMC3084959

PMID: 21547142

3363. PLoS One. 2009 Dec 30;4(12):e8480. doi: 10.1371/journal.pone.0008480.

Missense mutations in the MEFV gene are associated with fibromyalgia syndrome and correlate with elevated IL-1beta plasma levels.

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**BACKGROUND:** Fibromyalgia syndrome (FMS), a common, chronic, widespread musculoskeletal pain disorder found in 2% of the general population and with a preponderance of 85% in females, has both genetic and environmental contributions. Patients and their parents have high plasma levels of the chemokines MCP-1 and eotaxin, providing evidence for both a genetic and an immunological/inflammatory origin for the syndrome (Zhang et al., 2008, Exp. Biol. Med. 233: 1171-1180).

**METHODS AND FINDINGS:** In a search for a candidate gene affecting inflammatory pathways, among five screened in our patient samples (100 probands with FMS and their parents), we found 10 rare and one common alleles for MEFV, a gene in which various compound heterozygous mutations lead to Familial Mediterranean Fever (FMF). A total of 2.63 megabases of genomic sequence of the MEFV gene were scanned by direct sequencing. The collection of rare missense mutations (all heterozygotes and tested in the aggregate) had a significant elevated frequency of transmission to affecteds ( $p = 0.0085$ , one-sided, exact binomial test). Our data provide evidence that rare missense variants of the MEFV gene are, collectively, associated with risk of FMS and are present in a subset of 15% of FMS patients. This subset had, on average, high levels of plasma IL-1beta ( $p = 0.019$ ) compared to FMS patients without rare variants, unaffected family members with or without rare variants, and unrelated controls of unknown genotype. IL-1beta is a cytokine associated with the function of the MEFV gene and thought to be responsible for its symptoms of fever and muscle aches.

**CONCLUSIONS:** Since misregulation of IL-1beta expression has been predicted for patients with mutations in the MEFV gene, we conclude that patients heterozygous for rare missense variants of this gene may be predisposed to FMS, possibly

triggered by environmental factors.

DOI: 10.1371/journal.pone.0008480

PMCID: PMC2794536

PMID: 20041150 [Indexed for MEDLINE]

3364. Arthritis Rheum. 2010 Jan;62(1):258-67. doi: 10.1002/art.25057.

Long-term efficacy of the interleukin-1 receptor antagonist anakinra in ten patients with neonatal-onset multisystem inflammatory disease/chronic infantile neurologic, cutaneous, articular syndrome.

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**OBJECTIVE:** Cryopyrin-associated periodic syndromes (CAPS) are a group of rare autoinflammatory diseases. Neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic, cutaneous, articular syndrome (CINCA syndrome) is the most severe phenotype, with fever, rash, articular manifestations, and neurologic and neurosensory involvement. CAPS are caused by mutations in CIAS1, the gene encoding NLRP3, which plays a critical role in interleukin-1 (IL-1) processing. Anakinra, an IL-1 receptor antagonist, has been shown to be an effective treatment; however, data on long-term efficacy and safety have been sparse. This study was undertaken to assess the long-term efficacy and safety of anakinra treatment in patients with NOMID/CINCA syndrome. **METHODS:** We retrospectively analyzed the medical records of NOMID/CINCA syndrome patients referred to 2 centers, who had started anakinra treatment before June 2007.

**RESULTS:** There were 10 patients with NOMID/CINCA syndrome who had been treated with anakinra. The patients' ages at the time anakinra treatment was initiated ranged from 3 months to 20 years. They had been followed up for 26-42 months. Sustained efficacy in the treatment of systemic inflammation and, in some cases, neurologic involvement and growth parameters, was achieved. The dosage of

anakinra required for efficacy ranged from 1 to 3 mg/kg/day in the 8 oldest patients and from 6 to 10 mg/kg/day in the 2 youngest. Residual central nervous system inflammation and deafness persisted in some patients, especially if there had been a delay in diagnosis and treatment. Secondary amyloidosis persisted in cases in which it was present at treatment initiation, but no new lesions developed. No effect on overgrowth arthropathy was observed. Adverse events consisted of mild injection-site reactions.

CONCLUSION: The present results indicate that anakinra treatment is effective over the long term in NOMID/CINCA syndrome. However, treatment has to be initiated before irreversible lesions develop, and, particularly in very young patients, dosage adjustment is required.

DOI: 10.1002/art.25057

PMID: 20039428 [Indexed for MEDLINE]

3365. J Biol Chem. 2010 Feb 26;285(9):6477-88. doi: 10.1074/jbc.M109.064907. Epub 2009 Dec 28.

Constitutively active inflammasome in human melanoma cells mediating autoinflammation via caspase-1 processing and secretion of interleukin-1beta.

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Interleukin-1beta (IL-1beta) is a pleiotropic cytokine promoting inflammation, angiogenesis, and tissue remodeling as well as regulation of immune responses. Although IL-1beta contributes to growth and metastatic spread in experimental and human cancers, the molecular mechanisms regulating the conversion of the inactive IL-1beta precursor to a secreted and active cytokine remains unclear. Here we demonstrate that NALP3 inflammasome is constitutively assembled and activated with cleavage of caspase-1 in human melanoma cells. Late stage human melanoma cells spontaneously secrete active IL-1beta via constitutive activation of the NALP3 inflammasome and IL-1 receptor signaling, exhibiting a feature of autoinflammatory diseases. Unlike human blood monocytes, these melanoma cells require no exogenous stimulation. In contrast, NALP3 functionality in

intermediate stage melanoma cells requires activation of the IL-1 receptor to secrete active IL-1 $\beta$ ; cells from an early stage of melanoma require stimulation of the IL-1 receptor plus the co-stimulant muramyl dipeptide. The spontaneous secretion of IL-1 $\beta$  from melanoma cells was reduced by inhibition of caspase-1 or the use of small interfering RNA directed against ASC. Supernatants from melanoma cell cultures enhanced macrophage chemotaxis and promoted in vitro angiogenesis, both prevented by pretreating melanoma cells with inhibitors of caspases-1 and -5 or IL-1 receptor blockade. These findings implicate IL-1-mediated autoinflammation as contributing to the development and progression of human melanoma and suggest that inhibiting the inflammasome pathway or reducing IL-1 activity can be a therapeutic option for melanoma patients.

DOI: 10.1074/jbc.M109.064907

PMCID: PMC2825443

PMID: 20038581 [Indexed for MEDLINE]

3366. J Clin Pharmacol. 2010 Jul;50(7):835-41. doi: 10.1177/0091270009351882. Epub 2009 Dec 24.

Safety and pharmacokinetics of subcutaneously administered riloncept in patients with well-controlled end-stage renal disease (ESRD).

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The safety and pharmacokinetics of a single dose of the IL-1 inhibitor, riloncept (IL-1 Trap; 160 mg, subcutaneously), was studied in a group of 6 patients with well-controlled end-stage renal disease (ESRD) who were observed for a period of 42 days following dosing. The safety of riloncept administration was ascertained by regular monitoring of patients for adverse events, by periodic determination of a battery of standard laboratory and hematology tests, and by testing for binding and neutralizing antibodies to riloncept. Two of the 6 patients had treatment-emergent adverse events that were moderate in intensity and unrelated to administration of riloncept. There were no deaths, serious

adverse events, or withdrawals due to adverse events. No patient developed binding or neutralizing antibodies to rilonacept by the 42nd day postdosing. Mean C(max) estimated by a noncompartmental analysis was 17.2 mg/L; t(max,) 2.80 days; terminal t(1/2), 7.63 days; and AUC(0-infinity), 199.3 d.mg/L. Comparison of these results to those obtained in a population of patients with cryopyrin-associated periodic syndromes, a group of rare, inherited, autoinflammatory disorders (mean [SD] eGFR of 73.1 [13.3] mL/min/1.73m<sup>2</sup>), shows that ESRD and related hemodialysis procedures do not prolong the elimination of rilonacept, and therefore no dose adjustment should be needed relative to individuals with normal renal function.

DOI: 10.1177/0091270009351882

PMID: 20035038 [Indexed for MEDLINE]

3367. Clin Rheumatol. 2010 Apr;29(4):375-9. doi: 10.1007/s10067-009-1330-9. Epub 2009 Dec 22.

Depression and anxiety in children and adolescents with familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is the most common autoinflammatory disease which requires a lifelong treatment. The aim of this study was to evaluate the depression and anxiety in pediatric FMF patients. The Children's Depression Inventory and the Screen for Child Anxiety-related Emotional Disorders were the instruments used. Forty-three patients with FMF and 53 healthy controls were compared. Both study and control groups were divided into two age groups, 7-12 and 13-18 years. The depression scores of patients with FMF were significantly higher than their healthy peers ( $p = 0.001$ ). However, there was no significant difference between patients with FMF and control group regarding the anxiety scores ( $p = 0.78$ ). The disease duration was not significantly correlated with depression and anxiety scores. There was a significant correlation between depression score and FMF severity score ( $p = 0.01$ ). The mean depression and

anxiety scores of the FMF patients were positively correlated with the number of attacks ( $p = 0.000$  and  $p = 0.001$ , respectively). This study suggested that patients with FMF were considerably more depressed than their healthy peers and that the depression scores were negatively affected from disease severity score and number of attacks. Psychosocial assessment of children with FMF has potential clinical implications and individualized counseling and interventions are needed.

DOI: 10.1007/s10067-009-1330-9

PMID: 20033242 [Indexed for MEDLINE]

3368. FASEB J. 2010 May;24(5):1365-75. doi: 10.1096/fj.09-145573. Epub 2009 Dec 23.

Uncovering an IL-10-dependent NF-kappaB recruitment to the IL-1ra promoter that is impaired in STAT3 functionally defective patients.

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The interleukin 1 receptor antagonist (IL-1ra) is an important negative regulator of the inflammatory response, whose genetic deficiency has been recently shown to cause a severe autoinflammatory syndrome in humans. In this study we characterized the molecular mechanisms whereby interleukin 10 (IL-10) potentiates IL-1ra transcription in LPS-stimulated monocytes and neutrophils. Using chromatin immunoprecipitation, we show that although NF-kappaBp65 and NF-kappaBp50 proteins accumulate into the nuclei and bind to the IkappaB alpha promoter during LPS stimulation, they are not recruited to the kappaB sites of the IL-1ra promoter. However, in response to LPS plus IL-10, which were found to induce chromatin acetylation, recruitment of both NF-kappaBp65 and NF-kappaBp50 to the IL-1ra promoter efficiently occurs in a STAT3-dependent manner. Accordingly, in neutrophils from hyper-IgE syndrome patients, who carry a nonfunctional STAT3, IL-10 failed to promote NF-kappaBp65 recruitment to the IL-1ra promoter and consequently to potentiate LPS-induced IL-1ra transcription. Altogether our findings uncover a novel mechanism whereby IL-10-activated STAT3 modulates IL-1ra transcription in LPS-treated phagocytes by making IL-1ra promoter accessible to

readily available nuclear NF-kappaB.

DOI: 10.1096/fj.09-145573

PMID: 20032313 [Indexed for MEDLINE]

3369. Joint Bone Spine. 2010 Jan;77(1):32-5. doi: 10.1016/j.jbspin.2009.08.006. Epub 2009 Dec 23.

Prevalence and significance of MEFV gene mutations in a cohort of patients with rheumatoid arthritis.

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**OBJECTIVES:** Pyrin/marenostrin, an inhibitory regulator of inflammation, is encoded by MEditerranean FeVer (MEFV) gene. Mutations of this gene are the cause of familial Mediterranean fever (FMF). A connection between MEFV gene mutations and rheumatic diseases has been suggested. The aim of this study was to explore the frequency and clinical significance of MEFV gene mutations in a cohort of Turkish patients with rheumatoid arthritis (RA).

**METHODS:** The study included 103 patients with RA and 103 age-, sex- and origin-matched healthy controls (HC). In all participants, genomic DNA was isolated and genotyped using amplification refractory mutation system or restriction fragment length polymorphism for the eight MEFV gene mutations (E148Q, M694V, M694I, M680I, V726A, A744S, R761H, and P369S). In the RA group, disease activity was determined using the disease activity score-28 (DAS-28), and radiological damage was evaluated by the modified Larsen scoring method.

**RESULTS:** Carrier rates of MEFV gene mutations were 26/103 (25.2%) and 24/103 (23.3%) in the RA and HC groups, respectively ( $p>0.05$ , OR: 0.9, 95% CI: 0.48-1.71). In the RA group, while deformed joint count was significantly higher in the mutation carrier group than those of the non-carrier group ( $p<0.05$ ), the level of C-reactive protein, DAS-28 and modified-Larsen scores were slightly but not significantly higher in the carrier group.

**CONCLUSION:** The results of this study suggest that MEFV gene mutations appear to be an aggravating factor for the severity of RA, and consequently, patients with



RA might be screened for MEFV gene mutations in countries where FMF is frequent. Whether the searching of MEFV gene mutations in RA patients is cost-effective deserves further investigations.

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DOI: 10.1016/j.jbspin.2009.08.006

PMID: 20031469 [Indexed for MEDLINE]

3370. Rheumatol Int. 2012 Jan;32(1):249-51. doi: 10.1007/s00296-009-1322-8. Epub 2009 Dec 18.

Etanercept and anakinra can prolong febrile episodes in patients with hyperimmunoglobulin D and periodic fever syndrome.

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Hyperimmunoglobulin D and periodic fever syndrome (HIDS) is a rare, hereditary autoinflammatory condition, characterized by recurrent inflammatory episodes. There is no proven treatment for HIDS, but various drugs including, non-steroidal anti-inflammatory drugs, colchicine, steroids, statins and thalidomide have all been tried. Recently, some patients have demonstrated a good clinical response to either etanercept or anakinra. We report a case of a 10-year-old girl who experienced prolonged and severe inflammatory attacks, when she was treated with etanercept, and later with anakinra.

DOI: 10.1007/s00296-009-1322-8

PMID: 20020131 [Indexed for MEDLINE]

3371. Eur J Pediatr. 2010 Jul;169(7):825-8. doi: 10.1007/s00431-009-1120-z. Epub 2009 Dec 17.

The effect of colchicine on physical growth in children with familial mediterranean fever.

Ozçakar ZB(1), Kadioğlu G, Siklar Z, Kavaz A, Nur Aksanal F, Berberoğlu M, Ekim M, Ocal G, Yalçinkaya F.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease, characterized by recurrent, self-limited attacks of fever with serositis involving the peritoneum, pleura, and joints. There is very scarce information on physical growth of affected children. The aim of this study was to determine whether there is significant improvement in growth parameters in FMF patients after colchicine treatment. Patient files were retrospectively evaluated and patients that used colchicine for more than 1 year were included in the study. Demographic features, clinical findings before and after colchicine therapy, duration and dosage of therapy, weight, height, parentally adjusted height, and body mass index before and after colchicine therapy were noted and transformed into standard deviation scores (SDS). The study group consisted of 50 FMF (25 male and 25 female) patients. Median age at the time of diagnosis was 6.5 years. Median follow-up period was 3.6 (1-12.5) years. Mean height SDS increased from  $-0.19 \pm 1.01$  to  $0.13 \pm 0.99$  ( $p = 0.026$ ), and mean parentally adjusted height increased from  $-0.18 \pm 1.23$  to  $0.13 \pm 1.24$  ( $p = 0.027$ ), and both of them were found to be statistically significant. Mean body mass index SDS increased from  $-0.61 \pm 1.32$  to  $-0.32 \pm 1.33$ , but this improvement was statistically insignificant ( $p = 0.18$ ). In this study, we found that colchicine significantly improved height development in FMF patients.

DOI: 10.1007/s00431-009-1120-z

PMID: 20016916 [Indexed for MEDLINE]

3372. J Rheumatol. 2010 Feb;37(2):422-5. doi: 10.3899/jrheum.090401. Epub 2009 Dec 15.

Familial Mediterranean fever in Ashkenazi Jews: the mild end of the clinical spectrum.

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Comment in

J Rheumatol. 2010 Oct;37(10):2190; author reply 2190-1.

**OBJECTIVE:** To characterize familial Mediterranean fever (FMF) in Ashkenazi patients, a Jewish subgroup in which FMF has rarely been described before.

**METHODS:** A retrospective analysis, comparing demographic, clinical, and genetic measures of the cohort of Ashkenazi Jewish patients with FMF (n = 57), followed at the National Center for FMF in Israel, to age and sex matched patients of Iraqi Jewish (n = 62) and North African Jewish (NAJ; n = 61) origin.

**RESULTS:** Age at disease onset and diagnosis was earlier in NAJ than among Ashkenazi and Iraqi patients. Family history of FMF was described by only 30% of Ashkenazi patients as opposed to the majority of Iraqi and NAJ patients (p = 0.001). The frequency of abdominal and febrile attacks was similar among the 3 groups, while chest and joint attacks were far less common in Ashkenazi and Iraqi compared to NAJ patients. A good response to colchicine was noted in a similar proportion of Ashkenazi and Iraqi patients (82-84%) as opposed to only 56% of NAJ patients (p = 0.0001). Proteinuria, renal failure, and amyloidosis were most frequent among the NAJ patients (18, 6.6, and 9.8% compared to 5.3, 0, and 3.5% and 1.6, 0, and 0% in Ashkenazi and Iraqi patients, respectively).

**CONCLUSION:** Ashkenazi patients with FMF stand at the mildest end of the clinical spectrum of FMF. This is notwithstanding the tendency for amyloidosis, the frequency of which is not trivial and which deserves particular awareness.

DOI: 10.3899/jrheum.090401

PMID: 20008924 [Indexed for MEDLINE]

3373. J Rheumatol. 2010 Jan;37(1):182-9. doi: 10.3899/jrheum.090273. Epub 2009 Dec 15.

Unresponsiveness to colchicine therapy in patients with familial Mediterranean fever homozygous for the M694V mutation.

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**OBJECTIVE:** More than 50 disease-associated mutations of the Mediterranean fever gene (MEFV) have been identified in familial Mediterranean fever (FMF), some of which were shown to have different clinical, diagnostic, prognostic, and therapeutic implications. The aim of our study was to define the frequency of mutation type, genotype-phenotype correlation, and response to colchicine treatment in patients with FMF.

**METHODS:** This study included 222 pediatric FMF patients. All patients were investigated for 6 MEFV mutations. Then patients were divided into 3 groups according to the presence of M694V mutation on both of the alleles (homozygotes), on only 1 allele (heterozygotes), and on none of the alleles, and compared according to their phenotypic characteristics and response to treatment.

M694V/M694V was denoted Group A, M694V/Other Group B, and Other/Other, Group C.

**RESULTS:** Complete colchicine response was significantly lower while the rate of unresponsiveness was significantly higher in Group A compared to Groups B and C ( $p = 0.031$ ,  $p < 0.001$  and  $p = 0.005$ ,  $p = 0.029$ , respectively). No differences except proteinuria were found between the phenotypic features of 3 groups. Group C had the lowest rate of proteinuria development ( $p = 0.024$ ). All the amyloidosis patients were in Group A.

**CONCLUSION:** Our results indicate that the M694V/M694V mutation is associated with lower response to colchicine treatment. Therefore, patients homozygous for M694V/M694V may be carrying an increased risk for development of amyloidosis.

DOI: 10.3899/jrheum.090273

PMID: 20008920 [Indexed for MEDLINE]

3374. J Immunol. 2009 Dec 15;183(12):7623-9. doi: 10.4049/jimmunol.0902425.

Inflammasome-associated nucleotide-binding domain, leucine-rich repeat proteins and inflammatory diseases.

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The nucleotide-binding domain, leucine-rich repeat (NLR) proteins are a recently discovered family of intracellular pathogen and danger signal sensors. NLRs have emerged as important contributors to innate immunity in animals. The physiological impact of these genes is increasingly evident, underscored by the genetic association of variant family members with an array of inflammatory diseases. The association of mutations in NLR genes with autoinflammatory diseases indicates an important function of these genes in inflammation *in vivo*. This review summarizes the role of the inflammasome NLR proteins in innate immunity and inflammatory diseases and explores the possible utility of some of these NLRs as pharmacological targets.

DOI: 10.4049/jimmunol.0902425

PMCID: PMC3666034

PMID: 20007570 [Indexed for MEDLINE]

3375. J Fr Ophtalmol. 2010 Jan;33(1):36-9. doi: 10.1016/j.jfo.2009.11.003. Epub 2009 Dec 10.

[CINCA syndrome: a rare cause of papilledema. The case of homozygous twins].

[Article in French]

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CINCA syndrome is an autoinflammatory disease in childhood characterized by multisystemic manifestations: cutaneous, articular, and neurological including sensory organs. We report the case of homozygous twins affected by CINCA syndrome. The diagnosis was evoked on the basis of multiple systemic symptoms (multiple episodes of fever of unknown origin, mental retardation, short stature, meningitis, hearing loss, bilateral papilledema) and confirmed by the presence of a CIAS1 mutation on genetic analysis. After few months of treatment by anakinra

(an interleukin-1 receptor antagonist) the children began to grow again and we noted regression of the biological inflammatory syndrome.

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DOI: 10.1016/j.jfo.2009.11.003

PMID: 20005004 [Indexed for MEDLINE]

3376. J Allergy Clin Immunol. 2009 Dec;124(6):1141-9; quiz 1150-1. doi: 10.1016/j.jaci.2009.11.016.

Autoinflammation: the prominent role of IL-1 in monogenic autoinflammatory diseases and implications for common illnesses.

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The discovery of the genetic causes of a rare group of immune-mediated inflammatory conditions that mimic infections and allergic conditions in their clinical presentation and the molecular understanding of the function of the mutated molecules in these diseases has led to a revolution in our understanding of the pathogenesis of systemic and local inflammation. The proteins mutated in a number of these so-called autoinflammatory diseases are part of, or regulate the activity of, intracellular molecular complexes, the inflammasomes, that sense "danger" to the body and coordinate an initial immune response. Our understanding of specific triggers of the inflammasomes, coupled with the recognition that inflammasomes are critical for activation of the proinflammatory cytokine IL-1, has provided a rational and very effective target in the treatment of a number of these rare autoinflammatory diseases. In addition, the ongoing discovery of the role of inflammasomes and IL-1 activation and secretion in a number of genetically complex disorders have fundamentally changed our view of disease pathogenesis in a growing number of disorders that were heretofore not even thought of as "immunologic" diseases.

DOI: 10.1016/j.jaci.2009.11.016

PMCID: PMC2995268

PMID: 20004775 [Indexed for MEDLINE]

3377. J Allergy Clin Immunol. 2009 Dec;124(6):1129-38; quiz 1139-40. doi: 10.1016/j.jaci.2009.11.001.

Therapy of autoinflammatory syndromes.

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Comment in

J Allergy Clin Immunol. 2011 Dec;128(6):1352-4.

The therapy of autoinflammatory syndromes is an excellent example of the power of translational research. Recent advances in our understanding of the molecular and immunologic basis of this newly identified classification of disease have allowed for the application of novel, effective, targeted treatments with life-changing effects on patients. Although colchicine and TNF-alpha inhibitors are important therapies for specific autoinflammatory syndromes, the novel IL-1-targeted drugs are particularly effective for many of these diseases. Recently, the pharmaceutical industry has adopted a strategy of confirming the efficacy of new targeted drugs in often-ignored patients with orphan diseases, and US Food and Drug Administration policies have allowed for accelerated approval of these drugs, creating a win-win situation for patients and industry. This article reviews the general approach to the therapy of autoinflammatory diseases, focusing on current approved therapies and novel approaches that might be used in the future.

DOI: 10.1016/j.jaci.2009.11.001

PMCID: PMC4508191

PMID: 20004774 [Indexed for MEDLINE]

3378. Ocul Immunol Inflamm. 2009 Nov-Dec;17(6):403-14. doi: 10.3109/09273940903072443.

Clinical review: Anti-TNFalpha therapies in uveitis: perspective on 5 years of clinical experience.

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Despite a lack of robust evidence, anti-TNF therapies are in wide use for the treatment of noninfectious ocular inflammatory diseases. There is a clear rationale, based on mechanistic and preclinical efficacy data, for their use in posterior segment intraocular inflammation. However, their increasing use for other indications has been largely extrapolated from the benefit observed in autoinflammatory and autoimmune systemic diseases. Given their cost and the potential for significant adverse events, this review highlights the evidence for their continued use, possibilities for switching anti-TNF agents, and ways of reducing the risk of therapy.

DOI: 10.3109/09273940903072443

PMID: 20001261 [Indexed for MEDLINE]

3379. Hokkaido Igaku Zasshi. 2009 Nov;84(6):419-22.

A Japanese case of familial Mediterranean fever with a MEFV gene mutation.

Kawabata H(1), Murakami M, Nishikomori R, Saito M, Takaoka Y, Nanao K, Maezawa M.

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A 17-year-old Japanese male with a three-year history of recurrent episodic chest pain and fever, each lasting for one to three days, was diagnosed with familial Mediterranean fever (FMF) because of the following: 1) short attacks of chest pain and fever recurring at varying intervals; 2) no symptoms with a sense of well-being between attacks; and 3) identification of the Mediterranean fever gene



(MEFV) mutation demonstrating M694I. Although FMF has been described primarily in several limited ethnic groups, a limited number of cases have been reported in Japan. No specific diagnostic tests are commercially available for FMF so identifying the characteristic clinical picture of FMF is important.

PMID: 19998717 [Indexed for MEDLINE]

3380. *Mod Rheumatol*. 2010 Apr;20(2):193-5. doi: 10.1007/s10165-009-0249-y. Epub 2009 Dec 8.

A case of familial Mediterranean fever associated with compound heterozygosity for the pyrin variant L110P-E148Q/M680I in Japan.

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Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent and self-limited fever attacks and serositis/arthritis. The M694V, M694I, M680I, V726A, and E148Q mutations in MEFV, the gene responsible for FMF, account for most FMF cases in Mediterranean populations. In Japan, M694I and E148Q are most frequently detected; M694V, M680I, and V726A have not been identified so far. We report the first case of FMF associated with M680I in Japan.

DOI: 10.1007/s10165-009-0249-y

PMID: 19967574 [Indexed for MEDLINE]

3381. *Autoimmun Rev*. 2010 Apr;9(6):436-40. doi: 10.1016/j.autrev.2009.11.021. Epub 2009 Dec 3.

Innate versus acquired immune response in the pathogenesis of recurrent idiopathic pericarditis.

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Erratum in

Autoimmun Rev. 2011 Nov;11(1):76. Luca, Cantarini [corrected to Cantarini, Luca]; Massimo, Imazio [corrected to Imazio, Massimo]; Antonio, Brucato [corrected to Brucato, Antonio]; Maria, Lucherini Orso [corrected to Lucherini, Orso Maria]; Mauro, Galeazzi [corrected to Galeazzi, Mauro].

The pathogenesis of recurrent pericarditis is still poorly understood and may be related either to viral infections or autoimmune and autoinflammatory disorders. The immune system plays a major role in the pathogenesis of the disease, modulating individual responses to different noxa and explaining the variable reported recurrence rate (ranging from 20% to 50% of patients) following an attack of acute or recurrent pericarditis. Increasing interest is currently being devoted to autoinflammatory disorders, a group of conditions characterized by spontaneously relapsing and remitting bouts of systemic inflammation without apparent involvement of antigen-specific T cells or significant production of auto-antibodies. Ongoing basic and clinical research is needed to provide further evidence for the understanding of this common and troublesome disease, and to develop targeted and more efficacious therapies.

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DOI: 10.1016/j.autrev.2009.11.021

PMID: 19948252 [Indexed for MEDLINE]

3382. Eurasian J Med. 2009 Dec;41(3):154-7.

Celiac disease in childhood: evaluation of 140 patients.

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**OBJECTIVE:** Celiac disease (CD) is a lifelong gluten-sensitive intestinal enteropathy that is multifactorial in its etiology. In the present study, we evaluated basic anthropometric, clinical, laboratory, and histological features of 140 Turkish children with CD. We particularly underscored the association of CD with other autoimmune diseases.

**MATERIALS AND METHODS:** During the period from 1999 to 2005, CD was diagnosed in 140 children according to ESPGAN criteria. The age, gender, clinical findings, hematological, and biochemical parameters at diagnosis were noted. Symptoms and signs were recorded. Endoscopic intestinal biopsies were taken from all children.

**RESULTS:** Of the 140 children with CD, 75 (53.6%) were female, and 65 (46.4%) were male. Mean age was  $8.56 \pm 4.43$  years (range 13 months to 18 years). The most frequent symptom was failure to thrive (81.4%), followed by chronic diarrhea (60%). Of the children with CD, nine (6.4%) had type 1 diabetes mellitus (DM), six (4.3%) had familial Mediterranean fever, three (2.1%) had alopecia areata, three (2.1%) had vitiligo, three (2.1%) had Down syndrome, two (1.4%) had lung tuberculosis, two (1.4 %) had autoimmune hepatitis, two (1.4%) had growth hormone deficiency, one (0.7%) had osteogenesis imperfecta, and one (0.7%) had Floating Harbor Syndrome. Elevated serum levels of ALT, CK and AST were detected in 48(34.8%), 50 (38.2%) and 67 (48.6%) children, respectively.

**CONCLUSION:** The spectrum of clinical findings is very wide. In order to avoid overlooking CD in patients with extra intestinal symptoms and signs, physicians, especially pediatricians, should be informed about new atypical manifestations of CD.

**Publisher:** Çölyak Hastalığı (ÇH) multifaktöryel etyolojili hayat boyu devam eden glutene duyarlı incebarsak hastalığıdır. Bu çalışmada ÇH lıklı 140 Türk çocuğunun histolojik, laboratuvar, klinik, antropometrik bulguları değerlendirildi.2000–2008 yılları arasında ESPGAN tanı kriterlerine göre 140 çocuk ÇH tanısı aldı.

Çocukların tanı anındaki yaş, cins, klinik bulguları, hematolojik ve biyokimyasal parametreleri belirlendi. Endoskopik ince barsak biyopsisi tüm olgulardan alındı.ÇH’ lıklı 140 çocuğun 75(% 53,6)’ i kız, 65 (% 46,4)’ ü erkek idi.

Olguların ortalama yaşları  $8,56 \pm 4,43$  yıl (13 ay–18 yaş). En sık görülen semptom

büyüme gelişme geriliği idi. ÇH' çocuklardan 9 (% 6,4)' unda tip 1 diabetes mellitus (DM), 6 (% 4,3)' sında ailevi akdeniz ateşi, 3 (% 2,1)' ünde alopesia areata, 3 (% 2,1)' ünde vitiligo, 3 (% 2,1)' ünde Down sendromu, 2 (% 1,4)' sinde akciğer tüberkülozu, 2 (% 1,4)' sinde otoimmün hepatit, 2 (% 1,4)' sinde büyüme hormonu eksikliği, birinde (% 0,7) osteogenezis imperfekta, birinde (% 0,7) Floathing Harbor sendromu saptandı. ALT, AST ve CK' nın serum düzeylerinde artış sırası ile şöyle idi: 48 (% 34,8), 50 (% 38,2), and 67 (% 48,6). ÇH' lıklı çocuklarda klinik bulguların dağılımı çok geniş idi. Ekstra intestinal semptomlu hastalarda ÇH tanısını gözden kaçırmamak için hekimler, özellikle çocuk hekimleri ÇH' nın yeni atipik bulguları hakkında düzenli olarak bilgilendirilmelidirler.

PMCID: PMC4261272

PMID: 25610093

3383. Immunol Lett. 2010 Feb 16;128(2):154-5. doi: 10.1016/j.imlet.2009.11.008. Epub 2009 Nov 24.

AHR activation by tryptophan--pathogenic hallmark of Th17-mediated inflammation in eosinophilic fasciitis, eosinophilia-myalgia-syndrome and toxic oil syndrome?

Rieber N, Belohradsky BH.

The aryl-hydrocarbon-receptor (AHR) is involved as receptor and transcription factor in dioxin toxicity. Recently, its role in Th17-mediated autoimmunity and autoinflammation has been described, yet a disease-associated AHR ligand is still elusive. L-tryptophan and its metabolites are assumed to trigger the autoinflammatory disorders eosinophilic fasciitis, eosinophilia-myalgia-syndrome and toxic oil syndrome. Since L-tryptophan and metabolites are well known as AHR ligands we hypothesize that it is their interaction with AHR that induces Th17 cell differentiation and autoinflammation in these disorders. This, for the first time would link disease-causing environmental factors to a well-defined cellular receptor and the subsequent pathogenic pathway.

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DOI: 10.1016/j.imlet.2009.11.008

PMID: 19941898 [Indexed for MEDLINE]

3384. Neurol India. 2009 Sep-Oct;57(5):672-3. doi: 10.4103/0028-3886.57790.

The co-incidence of multiple sclerosis in a patient with familial Mediterranean fever.

Unal A, Emre U, Dursun A, Aydemir S.

DOI: 10.4103/0028-3886.57790

PMID: 19934575 [Indexed for MEDLINE]

3385. Ann Rheum Dis. 2010 Jul;69(7):1383-8. doi: 10.1136/ard.2009.113415. Epub 2009 Nov 23.

Clinical features and functional significance of the P369S/R408Q variant in pyrin, the familial Mediterranean fever protein.

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**OBJECTIVES:** Familial Mediterranean fever (FMF) is caused by mutations in MEFV, which encodes pyrin. The nature of substitutions P369S and R408Q in exon 3 remains unclear. Exon 3 encoding pyrin's B-box domain is necessary for interactions with proline serine threonine phosphatase interacting protein 1 (PSTPIP1). The aim was to characterise the phenotype of patients with these substitutions and to determine their functional significance.

**METHODS:** A database of genetic tests undertaken at the US National Institutes of Health was interrogated. Symptoms and signs were classified according to Tel-Hashomer criteria. Coimmunoprecipitation techniques were employed to determine the variants' effects on pyrin/PSTPIP1 interactions.

**RESULTS:** A total of 40 symptomatic and 4 asymptomatic family members with these substitutions were identified. P369S and R408Q were found in cis, and cosegregated in all patients sequenced. Clinical details were available on 22

patients. In all, 5 patients had symptoms and signs fulfilling a clinical diagnosis of FMF, and 15 received colchicine. In patients not achieving the criteria, trials of anti-tumour necrosis factor (TNF) agents resulted in partial or no benefit; resolution of symptoms was noted in those receiving anakinra. The carrier frequency was higher in the patient cohort than in controls but was not statistically significant. Coimmunoprecipitation studies demonstrated that these pyrin variants did not affect binding to PSTPIP1.

CONCLUSIONS: P369S/R408Q substitutions are associated with a highly variable phenotype, and are infrequently associated with typical FMF symptoms, however a trial of colchicine is warranted in all. Functional and modelling studies suggest that these substitutions do not significantly affect pyrin's interaction with PSTPIP1. This study highlights the need for caution in interpreting genetic tests in patients with atypical symptoms.

DOI: 10.1136/ard.2009.113415

PMCID: PMC3570240

PMID: 19934105 [Indexed for MEDLINE]

3386. Nephrol Dial Transplant. 2010 Aug;25(8):2520-3. doi: 10.1093/ndt/gfp632. Epub 2009 Nov 23.

MEFV gene compound heterozygous mutations in familial Mediterranean fever phenotype: a retrospective clinical and molecular study.

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BACKGROUND: Familial Mediterranean fever (FMF) is an autosomal-recessive inherited inflammatory disease caused by mutations in the MEFV gene that encodes pyrin/marenostrin. It is characterized by recurrent short episodes of fever, abdominal pain and serositis affecting mainly Mediterranean and Middle Eastern populations. We determined the frequency of the compound heterozygous mutations which has been rarely reported. The present study not only investigated clinical features of child-onset FMF patients with compound heterozygous mutations but also determined whether there is a phenotype-genotype correlation in the same

patient population.

**METHODS:** The medical records of 66 heterozygous patients with FMF were retrospectively reviewed and assessed. Patients were investigated regarding the mutation type, clinical characteristics at the time of inflammatory attacks such as fever, abdominal pain, arthritis, chest pain, erysipelas-like erythema and oedema, epidemiological data, consanguinity, severity score and family history of FMF and amyloidosis.

**RESULTS:** The most frequent mutation was M694V, identified in 32% of the alleles examined, followed by E148Q in 20.6%, V726A in 17% and M680I in 14.5%, respectively. Consequently, we determined that P369S (n = 10; 8%) was the most frequent rare mutation in Turkish FMF patients. Frequency of the other rare mutations were R761H (3%), F479L (3%), A744S (1.5%) and K695R (0.7%). Fever was seen in 96.5%, abdominal pain in 98.5%, arthralgia in 85%, chest pain in 45.5% and erysipelas-like lesions in 23%. None of these patients had amyloidosis, but 16 had a family history of chronic renal failure, 44% had vomiting and 35% had diarrhoea during the attack. Although regular colchicine treatment was effective in 83% of the patients, the percentage of patients that did not start colchicine therapy was 18%. In addition, the patients were divided into four groups according to the presence of the mutation types and we compared genotype-phenotype correlations.

**CONCLUSIONS:** We suggest that regular colchicine therapy may be administered to symptomatic patients with MEVF gene compound heterozygous mutations, regardless of the mutation type.

DOI: 10.1093/ndt/gfp632

PMID: 19934083 [Indexed for MEDLINE]

3387. *Pediatr Neurol.* 2009 Dec;41(6):448-50. doi: 10.1016/j.pediatrneurol.2009.06.008.

Cerebrospinal fluid neopterin and cryopyrin-associated periodic syndrome.

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Cryopyrin-associated periodic syndrome is a category of autoinflammatory

disorders caused by mutations of the NLRP3 gene, with chronic infantile neurologic cutaneous and articular syndrome being the severest clinical phenotype. Various pterins have been reported as mediating immunologic functions in the central nervous system, but to date studies of pterin cerebrospinal fluid (CSF) values and cryopyrin-associated periodic syndrome have been lacking. A 2-year-old child was affected with a severe atypical form of cryopyrin-associated periodic syndrome, suspected based on the analysis of neopterin in CSF. He initially presented isolated neurologic manifestations mimicking a neuroregressive disorder. Blood and CSF analyses did not present any routine inflammatory markers, but CSF neopterin was elevated. Later, the patient developed arthritis and recurrent episodes of fever, and the cryopyrin-associated periodic syndrome diagnosis was confirmed by genetic studies. Neopterin was the most altered indicator over the time. Child neurologists should be on the alert when unexplained neurologic signs appear, giving consideration to the possibility of inflammatory or immune-mediated diseases. The present case demonstrates the clinical utility of measurement of CSF neopterin levels in screening for these immune-mediated diseases, especially when neurologic symptoms are associated with normal results on routine CSF tests.

DOI: 10.1016/j.pediatrneurol.2009.06.008

PMID: 19931168 [Indexed for MEDLINE]

3388. Genet Test Mol Biomarkers. 2010 Feb;14(1):149-51. doi: 10.1089/gtmb.2009.0087.

Common Mediterranean fever gene mutations in the Azeri Turkish population of Iran.

Bonyadi M, Esmaeili M, Karimi A, Dastgiri S.

Familial Mediterranean fever (FMF) is an autosomal recessive disorder primarily affecting the Mediterranean populations. It is characterized by recurrent attacks of fever and inflammation of serosal membranes and gradual development of nephropathic amyloidosis. More than 70 disease-associated mutations have been identified in the Mediterranean fever gene (MEFV) responsible for FMF. The aim of this study was to determine the mutation carrier rate in the Iranian Azeri Turkish population. A cohort of 200 unrelated healthy individuals was screened for the five most common MEFV mutations (M694V, V726A, M680I, M694I, and E148Q) using the amplification refractory mutation system for the first four and by



polymerase chain reaction-restriction-digestion testing for E148Q. Genotyping revealed that the carrier rate in the Azeri Turkish population was 25.5%, with E148Q being the most common mutation (11.5%) followed by V726A (1.75%). The remaining common mutations were not found in this cohort. Our data indicate that the FMF carrier rate and E148Q mutation frequency are high in the Iranian Azeri Turkish population.

DOI: 10.1089/gtmb.2009.0087

PMID: 19929404 [Indexed for MEDLINE]

3389. Cell Cycle. 2009 Dec;8(23):3925-42. Epub 2009 Dec 17.

Identification of intergenic trans-regulatory RNAs containing a disease-linked SNP sequence and targeting cell cycle progression/differentiation pathways in multiple common human disorders.

Glinskii AB(1), Ma J, Ma S, Grant D, Lim CU, Sell S, Glinsky GV.

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Meta-analysis of genomic coordinates of SNP variations identified in genome-wide association studies (GWAS) of up to 712,253 samples (comprising 221,158 disease cases, 322,862 controls, and 168,233 case/control subjects of obesity GWAS) reveals that 39% of SNPs associated with 22 common human disorders are located within intergenic regions. Chromatin-state maps based on H3K4me3-H3K36me3 signatures show that many intergenic disease-linked SNPs are located within the boundaries of the K4-K36 domains, suggesting that SNP-harboring genomic regions are transcribed. Here we report identification of 13 trans-regulatory RNAs (transRNAs) 100 to 200 nucleotides in length containing intergenic SNP sequences associated with Crohn's disease, rheumatoid arthritis, type 1 diabetes, vitiligo, hypertension and multiple types of epithelial malignancies (prostate, breast, ovarian and colorectal cancers). We demonstrate that NALP1 loci intergenic SNP sequence, rs2670660, is expressed in human cells and may contribute to clinical manifestations of autoimmune and autoinflammatory phenotypes by generating

distinct allelic variants of transRNAs. Stable expression of allele-specific sense and anti-sense variants of transRNAs markedly alters cellular behavior, affect cell cycle progression, and interfere with monocyte/macrophage transdifferentiation. On a molecular level, forced expression of allele-specific sense and anti-sense variants of transRNAs asserts allele-specific genome-wide effects on abundance of hundreds microRNAs and mRNAs. Using lentiviral gene transfer, microarray and Q-RT-PCR technologies, we identify rs2670660 allele-specific gene expression signatures (GES) which appear useful for detecting the activated states of innate immunity/inflammasome pathways in approximately 700 clinical samples from 185 control subjects and 350 patients diagnosed with nine common human disorders, including Crohn's disease, ulcerative colitis, rheumatoid arthritis, Huntington disease, autism, Alzheimer disease, obesity, prostate and breast cancers. Microarray analysis of clinical samples demonstrates that rs2670660 allele-specific GES are engaged in patients' peripheral blood mononuclear cells (PBMC) which encounter pathological conditions in coherent tissues of a human body during immune surveillance and homeostasis monitoring. These data indicate that expression of transRNAs encoded by specific intergenic sequences can trigger activation of innate immunity/inflammasome pathways and contribute to clinical development of autoinflammatory and autoimmune syndromes. Documented in this work single-base substitution-driven molecular and biological antagonisms of intergenic SNP-containing transRNAs suggest a guiding mechanism of selection and retention of phenotype-compatible intergenic variations during evolution. According to this model, random genetic variations which generate transRNAs asserting antagonistic phenotype-altering effects compared to ancestral alleles will be selected and retained as SNP variants.

DOI: 10.4161/cc.8.23.10113

PMID: 19923886 [Indexed for MEDLINE]

3390. Clin Exp Rheumatol. 2009 Sep-Oct;27(5):890-1.

Tumour necrosis factor receptor-associated periodic syndrome caused by a rare mutation in the TNFRSF1A gene, and with excellent response to etanercept treatment.

Cantarini L, Lucherini OM, Galeazzi M, Fanti F, Simonini G, Baldari CT, Laghi Pasini F, De Martino M, Cimaz R.

PMID: 19917181 [Indexed for MEDLINE]

3391. Ann Rheum Dis. 2010 Jul;69(7):1408-9. doi: 10.1136/ard.2009.118661. Epub 2009 Nov 12.

Imaging evidence for persistent subclinical fasciitis and arthritis in tumour necrosis factor receptor-associated periodic syndrome (TRAPS) between febrile attacks.

Quillinan N, Mohammad A, Mannion G, O'Keeffe D, Bergin D, Coughlan R, McDermott MF, McGonagle D.

DOI: 10.1136/ard.2009.118661

PMID: 19914902 [Indexed for MEDLINE]

3392. Perit Dial Int. 2009 Nov-Dec;29(6):676-8.

Fulminant acute pancreatitis in a patient with familial mediterranean fever on CAPD: what caused the pancreatitis?

Ardalan MR, Shoja MM, Ghabili K, Taheri S, Shakeri A, Etemadi J, Einollahi B.

PMID: 19910573 [Indexed for MEDLINE]

3393. J Allergy Clin Immunol. 2009 Dec;124(6):1245-50. doi: 10.1016/j.jaci.2009.09.035.

Familial atypical cold urticaria: description of a new hereditary disease.

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**BACKGROUND:** Acquired cold urticaria (ACU) is usually a self-limited, sporadic, cutaneous disease diagnosed based on history and a positive cold stimulation time test (CSTT) result. We describe 3 unrelated families (A, B, and C) with lifelong atypical cold urticaria distinguished from ACU and familial cold autoinflammatory syndrome.

**OBJECTIVE:** We sought to describe a new hereditary disease of cold urticaria and study its pathogenesis.

**METHODS:** Questionnaires, interviews, physical examinations, skin testing, and biopsies were performed. Absolute values, means, and prevalence percentages of data are reported.

**RESULTS:** Thirty-five subjects are described with familial atypical cold urticaria (FACU; family A, 17; family B, 8; and family C, 10) displaying an autosomal dominant pattern of inheritance. All tested subjects had negative CSTT results. Completed questionnaires from affected and unaffected members of families A and B (n = 35) revealed that all affected subjects had lifelong symptoms that began in early childhood with pruritus, erythema, and urticaria after cold exposure.

Angioedema (family A, 23%; family B, 42%) and syncope, near syncope, or both (family A, 46%; family B, 86%) were also present. Triggers included cold atmosphere (100%), aquatic activities (family A, 92%; family B, 100%), handling cold objects (family A, 54%; family B, 71%), and ingestion of cold foods or beverages (family A, 69%; family B, 100%). Skin biopsy specimens demonstrated a mast cell infiltrate with the appearance of degranulation after cold challenge.

**CONCLUSIONS:** FACU is a new cold-induced inherited disease that is different than ACU in its natural history, atmospheric cold elicitation, severity of systemic reactions, and CSTT results. FACU differs from familial cold autoinflammatory syndrome in symptom timing and the absence of fever, chills, and joint pain. The cause is suspected to be mast cell related. Treatment of reactions is similar to that for ACU. Further evaluation of pathogenesis and genetics is warranted.

DOI: 10.1016/j.jaci.2009.09.035

PMCID: PMC2794966

PMID: 19910034 [Indexed for MEDLINE]

3394. Clin Exp Rheumatol. 2009 Mar-Apr;27(2 Suppl 53):S106-7.

A case of amyloid myopathy in a patient with familial Mediterranean fever.

Cantarini L, Volpi N, Lucherini OM, Giannini F, Galeazzi M.

PMID: 19796547 [Indexed for MEDLINE]

3395. Clin Exp Rheumatol. 2009 Mar-Apr;27(2 Suppl 53):S105.

Intravenous colchicine treatment for six months: adjunctive therapy in familial Mediterranean fever (FMF) unresponsive to oral colchicine.

Rozenbaum M, Boulman N, Feld J, Avshovich N, Petrovich S, Elias M, Slobodin G, Rosner I.

PMID: 19796546 [Indexed for MEDLINE]

3396. Clin Exp Rheumatol. 2009 Mar-Apr;27(2 Suppl 53):S103-4.

The 3435T polymorphism in the ABCB1 gene and colchicine unresponsiveness in familial Mediterranean fever.

Bezalel Y, Gershoni-Baruch R, Dagan E, Lidar M, Livneh A.

PMID: 19796545 [Indexed for MEDLINE]

3397. Clin Exp Rheumatol. 2009 Mar-Apr;27(2 Suppl 53):S96-101.

Health-related quality of life of school-age children with familial Mediterranean fever.

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**OBJECTIVES:** To describe and compare the parent proxy-reported and child self-reported physical and psychosocial HRQOL of school age children who have FMF with healthy peers.

**METHODS:** The Pediatric Quality of Life Inventory 4.0 (Peds QL 4.0) Generic Core Scales was used to measure HR-QOL. Fifty-one patients and 81 healthy peers were enrolled in the study. Patients were grouped according to their ages as : 1) Children (8-12 years) and 2) Adolescents (13-18 years). An accompanying parent completed the parent proxy-report of the Peds QL 4.0.

**RESULTS:** Peds QL scores of children (8-12 years) with FMF were significantly lower than healthy peers for physical and psychosocial functioning for both child self-report and parent proxy-report. The parent proxy-report and child self-reported Peds QL scores of adolescent patients (13-18 years) with FMF were lower than the healthy group for physical, emotional and school functioning; however no significant difference was detected regarding the social functioning. Adolescents with FMF had significantly higher social scores when compared to the younger age group (8-12 years) with FMF, 92.6 +/- 8.5 and 82.2 +/- 17.6, respectively ( $p=0.028$ ). The scores of physical, emotional and school functioning were similar in both groups ( $p=0.73$ ,  $p=0.93$ , and  $p=0.028$ ). Correlations among child self-report subscales and proxy-report subscales were all significant and varied from moderate to high.

**CONCLUSION:** This study suggested that assessment of HRQOL has potential clinical implications for the healthcare needs of children and adolescents with FMF. Given the degree of reported impairment in their health-related quality of life, individualized counseling and interventions are needed.

PMID: 19796543 [Indexed for MEDLINE]

3398. Clin Exp Rheumatol. 2009 Mar-Apr;27(2 Suppl 53):S29-31.

Mutations/polymorphisms in a monogenetic autoinflammatory disease may be susceptibility markers for certain rheumatic diseases: lessons from the bedside for the benchside.

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Certain vasculitides have an increased prevalence among patients with familial Mediterranean fever (FMF). Subsequently, it was noticed that patients with certain rheumatic diseases had an increased carrier rate for mutations in the MEFV gene including seronegative spondyloarthritis, Henoch Schönlein purpura, polyarteritis nodosa and some forms of juvenile idiopathic arthritis. Furthermore in populations where the disease is rare, certain polymorphisms have been associated with a severe inflammatory complication in arthritis. The effect of these polymorphisms are probably through the upregulation of the innate immune system which serves as the initial response to the environmental trigger. It may be suggested for the aforementioned clinical associations that mutations/polymorphisms in the MEFV gene may well be susceptibility factors for the disease or a more severe course of the disease for a number of rheumatic diseases.

PMID: 19796529 [Indexed for MEDLINE]

3399. Clin Exp Rheumatol. 2009 Mar-Apr;27(2 Suppl 53):S4-5.

The use of diseased control groups in genetic association studies.

Esen F, Celik A, Yazici H.

PMID: 19796523 [Indexed for MEDLINE]

3400. Clin Exp Rheumatol. 2009 Mar-Apr;27(2 Suppl 53):S1-3.

About colchicine compliance, resistance and virulence.

Ben-Chetrit E, Aamar S.

PMID: 19796522 [Indexed for MEDLINE]

3401. Rheumatology (Oxford). 2010 Jan;49(1):198; author reply 198-9. doi: 10.1093/rheumatology/kep341. Epub 2009 Nov 10.

Comment on: Web resources for rare auto-inflammatory diseases: towards a common patient registry.

Yazici Y, Yazici H.

Comment on

Rheumatology (Oxford). 2009 Jun;48(6):665-9.

DOI: 10.1093/rheumatology/kep341

PMID: 19903728 [Indexed for MEDLINE]

3402. Cytokine Growth Factor Rev. 2009 Oct-Dec;20(5-6):467-73. doi: 10.1016/j.cytogfr.2009.10.009. Epub 2009 Nov 8.

Bone morphogenetic protein signaling and arthritis.

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Chronic joint diseases have a major impact on society as patients suffer from pain and disability. The spectrum of arthritic disorders is wide including autoimmune and autoinflammatory diseases such as rheumatoid arthritis, ankylosing spondylitis and related spondyloarthritides but also the more prevalent osteoarthritic diseases. The latter appear to be mainly the consequence of injury, strain and aging in a predisposing genetic background. The therapeutic options for chronic inflammatory and immune joint diseases have greatly increased over the last decade by the use of targeted anti-cytokine or anti-immune cell drugs. However, such a shift towards successful treatment has not been achieved for osteoarthritis. In addition, control of inflammation does not equal cure of



the disease as relapse occurs as soon as the treatment is interrupted, and only limited tissue repair has been observed. Bone morphogenetic proteins are potent regulators of cell proliferation, differentiation and apoptosis and they have come into the spotlight in arthritis research. Here, we summarize the recent data on the role of bone morphogenetic proteins in joint protection and repair and but also their potential disease promoting or controlling roles. These data are presented in the context of a systems biology view of joint diseases based on their histomorphological phenotype rather than on existing clinical classifications.

DOI: 10.1016/j.cytogfr.2009.10.009

PMID: 19900833 [Indexed for MEDLINE]

3403. Reumatismo. 2009 Jul-Sep;61(3):187-96.

[Utility of denaturing high performance liquid chromatography (DHPLC) for the diagnosis of mevalonate kinase deficiency in periodic disease].

[Article in Italian]

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**OBJECTIVES:** We developed a genetic investigation using denaturing high performance liquid chromatography (DHPLC), in order to identify polymorphisms of the gene MVK in patients with autoinflammatory syndrome suspicion.

**METHODS:** We evaluated 19 patients affected by recurrent fevers and other clinical manifestations usually found in autoinflammatory syndromes and not correlated with infections or autoimmune disease and 10 healthy controls. IgD level was measured in all patients. Molecular testing was performed in DNA extracted from PBMC and MVK gene was analysed either with DHPLC or with automatic sequencer. Primers for PCR amplifications, amplicon lengths and PCR conditions were designed in our laboratory.

**RESULTS:** IgD level was normal in 14 patients. Healthy controls did not show any

alteration of the DHPLC-profiles and of the DNA sequences. Twelve patients had at least one altered DHPLC-profile and these data have been confirmed by sequencing. In particular we detected the polymorphisms c.78+61A>G, S52N, S135S, D170D, c.632-18A>G, c.885+24G>A already described in the database INFEVERS. With DHPLC we got the results in shorter time (10 hours/patient) and with lower cost (40 euro/patient) in comparison to direct sequencing (25 hours and 150 euro/patient). CONCLUSIONS: High IgD levels do not represent an essential marker for diagnosis of MKD, as already reported in literature. DHPLC is a rapid low cost technique in order to screen mutations in patients with MKD suspicion. Twelve patients carried at the same time D170D and c.632-18A>G: such event suggests that these SNPs could be in linkage disequilibrium and that such polymorphisms could predispose to MKD.

PMID: 19888504 [Indexed for MEDLINE]

3404. PLoS One. 2009 Oct 30;4(10):e7676. doi: 10.1371/journal.pone.0007676.

Involvement of the modifier gene of a human Mendelian disorder in a negative selection process.

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BACKGROUND: Identification of modifier genes and characterization of their effects represent major challenges in human genetics. SAA1 is one of the few modifiers identified in humans: this gene influences the risk of renal amyloidosis (RA) in patients with familial Mediterranean fever (FMF), a Mendelian autoinflammatory disorder associated with mutations in MEFV. Indeed, the SAA1 alpha homozygous genotype and the p.Met694Val homozygous genotype at the MEFV locus are two main risk factors for RA.

METHODOLOGY/PRINCIPAL FINDINGS: HERE, WE INVESTIGATED ARMENIAN FMF PATIENTS AND

CONTROLS FROM TWO NEIGHBORING COUNTRIES: Armenia, where RA is frequent (24%), and Karabakh, where RA is rare (2.5%). Sequencing of MEFV revealed similar frequencies of p.Met694Val homozygotes in the two groups of patients. However, a

major deficit of SAA1 alpha homozygotes was found among Karabakhian patients (4%) as compared to Armenian patients (24%) ( $p = 5.10(-5)$ ). Most importantly, we observed deviations from Hardy-Weinberg equilibrium (HWE) in the two groups of patients, and unexpectedly, in opposite directions, whereas, in the two control populations, genotype distributions at this locus were similar and complied with (HWE).

**CONCLUSIONS/SIGNIFICANCE:** The excess of SAA1alpha homozygotes among Armenian patients could be explained by the recruitment of patients with severe phenotypes. In contrast, a population-based study revealed that the deficit of alpha/alpha among Karabakhian patients would result from a negative selection against carriers of this genotype. This study, which provides new insights into the role of SAA1 in the pathophysiology of FMF, represents the first example of deviations from HWE and selection involving the modifier gene of a Mendelian disorder.

DOI: 10.1371/journal.pone.0007676

PMCID: PMC2765618

PMID: 19888326 [Indexed for MEDLINE]

3405. Rheumatol Int. 2011 Jan;31(1):39-43. doi: 10.1007/s00296-009-1214-y. Epub 2009 Nov 1.

Heart rate variability in familial Mediterranean fever.

Nussinovitch N(1), Livneh A, Katz K, Langevitz P, Feld O, Nussinovitch M, Volovitz B, Lidar M, Nussinovitch U.

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Familial Mediterranean fever (FMF) is a hereditary disease, characterized by recurrent episodes of fever and polyserositis. Heart rate variability (HRV) is a powerful, simple and reliable technique to evaluate autonomic nervous system function. Previous studies of physiologic parameters during tilt-test have suggested that patients with FMF have abnormal cardiovascular reactivity and occult dysautonomia. Prompted by these findings, the present study sought to evaluate HRV in patients with FMF, at rest and in the standing position. The

study sample included 34 patients with FMF and 34 sex- and age-matched control subjects. All underwent electrocardiography according to strict criteria. HRV parameters were computed with custom-made software. There was no significant difference in HRV parameters, in either the supine or standing position, between the FMF and control groups. In both groups, the upright position was associated with a significant decrease, when compared with the supine position, in maximal RR interval, minimal RR, average RR, root square of successive differences in RR interval, number of intervals differing by >50 ms from preceding interval (NN50), NN50 divided by total number of intervals (pNN50) and high-frequency components as well as a significant increase in average heart rate, very low frequency or low-frequency components, low-frequency/high-frequency components ratio and total power. In conclusion, patients with FMF who are continuously treated with low-dose colchicine have not developed amyloidosis and have normal HRV parameters in the supine and upright position. Further investigation of occult dysautonomia in FMF is needed.

DOI: 10.1007/s00296-009-1214-y

PMID: 19882341 [Indexed for MEDLINE]

3406. Rev Pneumol Clin. 2009 Oct;65(5):313-7. doi: 10.1016/j.pneumo.2009.05.001. Epub 2009 Sep 19.

[Thoracic impairment from familial Mediterranean fever: review of the literature and a case study].

[Article in French]

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Familial Mediterranean fever (FMF) is a recessive autosomal disease, predominantly affecting the population around the Mediterranean. The main clinical signs consist of attacks of fever associated with abdominal, articular and thoracic pain. Based on a case report, the authors describe the main thoracic forms of this illness comprising pleural pain, pleural effusion and pulmonary

amyloidosis. The authors also discuss the association of mesothelioma and FMF. Colchicine is successfully used in the treatment of FMF.

DOI: 10.1016/j.pneumo.2009.05.001

PMID: 19878808 [Indexed for MEDLINE]

3407. Arthritis Rheum. 2009 Nov;60(11):3476-84. doi: 10.1002/art.24905.

The 423Q polymorphism of the X-linked inhibitor of apoptosis gene influences monocyte function and is associated with periodic fever.

Ferretti M(1), Gattorno M, Chiocchetti A, Mesturini R, Orilieri E, Bensi T, Sormani MP, Cappellano G, Cerutti E, Nicola S, Biava A, Bardelli C, Federici S, Ceccherini I, Baldi M, Santoro C, Dianzani I, Martini A, Dianzani U.

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**OBJECTIVE:** Hereditary periodic fever syndromes (HPFs) develop as a result of uncontrolled activation of the inflammatory response, with a substantial contribution from interleukin-1 $\beta$  or tumor necrosis factor  $\alpha$  (TNF $\alpha$ ). The HPFs include familial Mediterranean fever (FMF), hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), TNF receptor-associated syndrome (TRAPS), and cryopyrinopathies, which are attributable to mutations of the MEFV, MVK, TNFRSF1A, and CIAS1 genes, respectively. However, in many patients, the mutated gene has not been determined; therefore, the condition in these patients with an HPF-like clinical picture is referred to as idiopathic periodic fever (IPF). The aim of this study was to assess involvement of X-linked inhibitor of apoptosis (XIAP), which plays a role in caspase inhibition and NF-kappaB signaling, both of which are processes that influence the development of inflammatory cells.

**METHODS:** The XIAP gene (X-linked) was sequenced in 87 patients with IPF, 46 patients with HPF (13 with HIDS, 17 with TRAPS, and 16 with FMF), and 182 healthy control subjects. The expression of different alleles was evaluated by sequencing XIAP-specific complementary DNA mini-libraries and by real-time polymerase chain reaction and Western blot analyses. The functional effect of XIAP on caspase 9 activity was assessed by a fluorimetric assay, and cytokine secretion was evaluated by enzyme-linked immunosorbent assay.

**RESULTS:** Sequencing disclosed a 1268A>C variation that caused a Q423P amino acid substitution. The frequency of 423Q-homozygous female patients and 423Q-hemizygous male patients was significantly higher in the IPF group than in the control group (69% versus 51%; odds ratio 2.17, 95% confidence interval 1.23-3.87,  $P = 0.007$ ), whereas no significant difference was detected in the HPF group (59%) compared with controls. In primary lymphocytes and transfected cell lines, 423Q, as compared with 423P, was associated with higher XIAP protein and messenger RNA expression and lower caspase 9 activation. In lipopolysaccharide-activated monocytes, 423Q was associated with higher secretion of TNF $\alpha$ .

**CONCLUSION:** These results suggest that 423Q is a predisposing factor for IPF development, possibly through its influence on monocyte function.

DOI: 10.1002/art.24905

PMID: 19877056 [Indexed for MEDLINE]

3408. Clin Genet. 2009 Nov;76(5):477-80. doi: 10.1111/j.1399-0004.2009.01270.x.

MEFV mutations in Iranian Azeri Turkish patients with familial Mediterranean fever.

Bonyadi M(1), Esmaeili M, Jalali H, Somi MH, Ghaffari A, Rafeey M, Sakha K, Lotfalizadeh N, Pourhassan A, Khoshbaten M, Ardalan MR, Laghaeian N.

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Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disorder with more than 60 disease-associated mutations in the responsible gene, MEFV. In the present study, we determined 15 MEFV mutations in Iranian Azeri Turkish FMF patients. Five hundred and twenty-four unrelated patients were tested for 15 known mutations in the MEFV gene using amplification refractory mutation system-polymerase chain reaction and polymerase chain reaction-restriction fragment length polymorphism methods. Thirty-five different genotypes were characterized among the studied patients. Of the alleles investigated, the most common mutation was p.M694V (42.4%), followed by p.V726A (17%), p.E148Q (16.2%), and p.M680I (c.2040G>C) (15.2%). The p.R761H mutation (4.7%) was found to be the

most frequent among the rare mutations. The mutations p.M680I (c.2040G>A), p.I692del, p.M694del and p.K695R were not found in this cohort. The remaining mutations account for 7.7% of the identifiable mutations. Five different types of complex alleles were also identified. The results show the diversity and the frequency of the mutations in the Iranian Azeri Turkish FMF patients. The p.R761H mutation is rather prevalent in Azeri Turks; therefore, it should be included in the routine molecular diagnosis of FMF patients from this ethnic group.

DOI: 10.1111/j.1399-0004.2009.01270.x

PMID: 19863562 [Indexed for MEDLINE]

3409. Best Pract Res Clin Rheumatol. 2009 Oct;23(5):655-64. doi: 10.1016/j.berh.2009.08.003.

Systemic JIA: new developments in the understanding of the pathophysiology and therapy.

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Systemic juvenile idiopathic arthritis (sJIA) is a rare, systemic inflammatory disease classified as a subtype of JIA. Besides arthritis, it is characterised by systemic features such as spiking fever, skin rash, hepatosplenomegaly or serositis. It is becoming clear now that abnormalities in the innate immunity (cytokines such as interleukin (IL)-1, IL-6 and IL-18, and neutrophils and monocytes/macrophages rather than lymphocytes) play a major role in the pathogenesis of sJIA, distinguishing it from other JIA subtypes. Another distinctive feature of sJIA is its strong association with macrophage activation syndrome (MAS). Based on this, consensus is emerging that sJIA should be viewed as an autoinflammatory syndrome rather than a classic auto-immune disease. As a consequence of the progression in understanding the underlying mechanisms of sJIA, major changes in the management are evolving. So far, treatment has been based on glucocorticosteroids in combination with disease-modifying drugs such as methotrexate. Recently, remarkable improvement has been observed with IL-1 and

IL-6 targeted therapies. These therapies might also change the long-term outcome of this disease. However, controlled trials set up in international collaboration are needed to determine the optimal treatment strategies for all sJIA patients.

DOI: 10.1016/j.berh.2009.08.003

PMCID: PMC2774820

PMID: 19853830 [Indexed for MEDLINE]

3410. J Paediatr Child Health. 2009 Nov;45(11):641-5. doi: 10.1111/j.1440-1754.2009.01587.x. Epub 2009 Oct 19.

Familial Mediterranean fever gene mutations in the inner northern region of Turkey and genotype-phenotype correlation in children.

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**AIM:** Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterised by recurrent episodes of fever, polyserositis and rash. The aim of this study was to determine the most common mutations and clinical features, and their relationships.

**METHODS:** The medical records of 78 patients were evaluated retrospectively. All of the patients had been diagnosed with FMF according to Tel Hashomer criteria between January 2005 and May 2008 in general paediatric clinics of the School of Medicine at Gaziosmanpasa University. Twelve mutations were detected in the 78 patients by polymerase chain reaction-enzyme-linked immunosorbent assay. The patients were classified into three groups according to allele status.

**RESULTS:** The most prominent clinical symptoms were abdominal pain (95%), fever (90%), arthritis (33%) and pleuritis (31%). Seventeen different genotypes were identified. The mutations were homozygous in 25 (32%) patients, compound heterozygous in 28 (36%) patients and heterozygous in 22 (28%) patients. No mutation was detected in three (4%) patients. The most frequent mutations were M694V (55%), M680I (16%), E148Q (10%) and P369S (4%). The mean symptom severity score was highest in the homozygous group, and high levels of C-reactive protein were also detected in this group.



**CONCLUSIONS:** In addition to clinical criteria, molecular studies for detecting disease-causing mutations are needed to establish the diagnosis of FMF. FMF patients who were homozygous for MEFV gene mutations had a higher symptom severity score and higher incidence of appendectomy. The broad spectrum of mutations may reflect intercultural interactions of ethnic groups in Anatolia. Nation-wide studies may help to determine the relationships among demographic, clinical and genetic features of FMF.

DOI: 10.1111/j.1440-1754.2009.01587.x

PMID: 19845843 [Indexed for MEDLINE]

3411. Z Rheumatol. 2009 Nov;68(9):726-32. doi: 10.1007/s00393-009-0487-6.

[Autoinflammatory diseases in childhood].

[Article in German]

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Autoinflammatory diseases are a group of monogenic inflammatory diseases with an early onset in childhood. Previously these diseases were summarized as "periodic fever syndromes." Included in this spectrum are familial Mediterranean fever, mevalonate kinase deficiency, and tumor necrosis factor receptor-associated disease. They are characterized by periodic or recurrent episodes of systemic inflammation causing fever, accompanied by rash, serositis, lymphadenopathy, arthritis, and other clinical manifestations. The other large group of autoinflammatory diseases consists of the cryopyrin-associated periodic syndromes, which include the cryopyrinopathies. The mildest form is familial cold-associated syndrome, a more severe form is Muckle-Wells syndrome, and the most severe is neonatal-onset multisystem inflammatory disease/chronic infantile neurological cutaneous and articular syndrome. These are characterized by chronic or recurrent systemic inflammation associated with various clinical

presentations, including urticaria-like rash, arthritis, sensorineural deafness, and central nervous system and bone involvement. In our review we focus on the clinical presentation of these diseases.

DOI: 10.1007/s00393-009-0487-6

PMID: 19841924 [Indexed for MEDLINE]

3412. Z Rheumatol. 2009 Nov;68(9):733-9. doi: 10.1007/s00393-009-0489-4.

[Crystal-induced activation of the inflammasome: gout and pseudogout].

[Article in German]

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Crystals in tissues lead the innate immune system to the same kind of acute response seen with pathogens. Via activation of the inflammasome, interleukin-1 (IL-1) is released, which upregulates mediators such as cyclooxygenase, tumor necrosis factor, and IL-8 and induces an acute granulocytic inflammation. Therefore, in addition to nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, and colchicine, IL-1 blockers appear to be effective. Large clinical trials have already been initiated. Such an approach could constitute a valuable alternative for patients with contraindications or insufficient response to NSAIDs. After the attack has subsided, control of uric acid metabolism is central. At least several of the responsible urate transporters have been unraveled, which could lead to more focused therapy in the future. At present, diet and blockade of uric acid synthesis remain the main pillars of therapy. The new xanthine oxidase inhibitor febuxostat constitutes a novel option for patients with renal insufficiency or intolerance to allopurinol.

DOI: 10.1007/s00393-009-0489-4

PMID: 19838718 [Indexed for MEDLINE]

3413. Z Rheumatol. 2009 Nov;68(9):740-6. doi: 10.1007/s00393-009-0490-y.

[Adult-onset Still's disease, Schnitzler syndrome, and autoinflammatory syndromes in adulthood].

[Article in German]

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Adult-onset Still's disease (AoSD), Schnitzler syndrome, and cases of adult-onset autoinflammatory syndromes [10-15% of cases of familial Mediterranean fever (FMF) and tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS)] are characterized by a genetic predisposition, with increased interleukin (IL)-1beta and IL-18 production and TNF-alpha signaling, respectively. As a result, periodic fever and inflammation at barrier tissues (synovial tissues, serous membranes, and the skin) are encountered in such patients.

Pathophysiological insights into these diseases have renewed interest in research on IL-1beta in rheumatic diseases and have opened new therapeutic avenues. Recently published studies have shown that patients with Schnitzler syndrome, methotrexate-refractory AoSD, and colchicine-refractory FMF or contraindications to colchicines in FMF respond well to treatment with the soluble IL-1 receptor antagonist anakinra. For TRAPS patients, the p75 TNF-alpha receptor/Fc-IgG1 fusion protein etanercept is the treatment of first choice.

DOI: 10.1007/s00393-009-0490-y

PMID: 19838717 [Indexed for MEDLINE]

3414. Rheumatology (Oxford). 2009 Nov;48(11):1455-9. doi: 10.1093/rheumatology/kep296.

The spectrum of MEFV clinical presentations--is it familial Mediterranean fever only?

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**OBJECTIVE:** FMF is an autosomal recessive hereditary disease, associated with a single gene named MEFV. This gene is considered to be responsible only for FMF. In the present study, we tried to find out whether the MEFV gene is associated with or responsible for clinical conditions other than FMF.

**METHODS:** We looked for patients who presented with signs and symptoms not typical for FMF but carried MEFV mutations. We also searched for reports about similar conditions in the English medical literature, and we surveyed the website 'Infervers' for MEFV mutations defined as associated with 'atypical FMF'.

**RESULTS:** We encountered three patients carrying MEFV mutations who presented with distinct clinical presentations not typical of FMF. We identified additional reports about MEFV-related non-FMF disease entities such as palindromic rheumatism. By screening the 'Infervers' website, we further disclosed 13 cases with MEFV mutations that were defined as 'atypical FMF' and 4 cases categorized as 'recurrent arthritis'.

**CONCLUSIONS:** These findings suggest that the MEFV gene is associated with clinical conditions other than FMF. Changing our concept regarding the MEFV gene and its link to such clinical phenotypes may call for a higher awareness of the existence of additional autoinflammatory diseases. Furthermore, a correct diagnosis of these MEFV gene mutation-associated syndromes will justify a therapeutic trial with colchicine, thereby relieving suffering of many patients who up to now have been misdiagnosed.

DOI: 10.1093/rheumatology/kep296

PMID: 19837680 [Indexed for MEDLINE]

3415. Z Rheumatol. 2009 Nov;68(9):720-5. doi: 10.1007/s00393-009-0486-7.

[Molecular diagnostics of hereditary fever syndromes. Familial Mediterranean fever (FMF), hyperimmunoglobulin D syndrome (HIDS), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndrome (CAPS: FCAS, MWS, NOMID/CINCA)].

[Article in German]

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Periodic episodes of fever and inflammation can have a genetic origin. Nowadays, the identification of the causative genetic variants in the majority of cases allows molecular genetic confirmation of the clinical diagnosis, which enables approaches with specific drug treatment and improves patient compliance as well as genetic counseling. Besides a detailed clinical examination a medical history including family history and an assessment of the ethnic origin are required. In order to make genetic testing straightforward and cost effective an iterative procedure should be followed which should include, in addition to clinical data, the frequencies of causative mutations in the various gene segments involved.

DOI: 10.1007/s00393-009-0486-7

PMID: 19830438 [Indexed for MEDLINE]

3416. Z Rheumatol. 2009 Nov;68(9):712-9. doi: 10.1007/s00393-009-0488-5.

[Interleukin-1 cytokines, inflammasomes, NOD-signalosomes and autoinflammation].

[Article in German]

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The understanding of the genetic and immunological basis of human periodic fever syndromes, in particular cryopyrin-associated periodic syndromes (CAPS), has led to important new insights into the pathogenesis of monogenic and complex interleukin-1beta-associated autoinflammatory diseases. Currently the focus of attention is on the nucleotide-binding oligomerization domain (NOD)-like receptors (NLR), which take part in the regulation of the synthesis and

maturation of cytokines in the IL-1 families, NOD-signalosomes and inflammasomes.

DOI: 10.1007/s00393-009-0488-5

PMID: 19830437 [Indexed for MEDLINE]

3417. Eur Cytokine Netw. 2009 Sep;20(3):108-11. doi: 10.1684/ecn.2009.0164.

Free circulating interleukin-18 is increased in Schnitzler syndrome: a new autoinflammatory disease?

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Schnitzler syndrome is a rare disease characterised by chronic urticaria and arthralgia. The recent evidence that the IL-1 receptor antagonist IL-1Ra could induce rapid and complete remission of Schnitzler symptoms has pointed to IL-1 as a major pathological factor in this disease. To examine the possibility that Schnitzler syndrome may be considered to be an autoinflammatory disease, in this study we measured the serum levels of IL-18, another cytokine of the IL-1 family that is cleaved by caspase-1, in two recently diagnosed Schnitzler patients before and after treatment with IL-1Ra. In parallel, mRNA expression of IL-1 family cytokines and caspase-1 were assessed in isolated blood monocytes. Treatment with IL-1Ra significantly inhibited IL-1beta gene expression, indicating that IL-1beta activity in Schnitzler syndrome is central to IL-1beta gene upregulation in a type of auto-amplification loop. While no IL-1beta was detected in serum, free circulating IL-18 was increased in patients with Schnitzler syndrome, despite low IL-18 gene expression in monocytes. This suggests constitutive activation of the IL-1beta/IL-18-producing inflammasome, and supports the hypothesis that Schnitzler's syndrome is a new autoinflammatory disease.

DOI: 10.1684/ecn.2009.0164

PMID: 19825519 [Indexed for MEDLINE]

3418. Eur Cytokine Netw. 2009 Sep;20(3):101-7. doi: 10.1684/ecn.2009.0163.

Specific increase in caspase-1 activity and secretion of IL-1 family cytokines: a putative link between mevalonate kinase deficiency and inflammation.

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The mevalonate kinase deficiency (MKD), including hyperimmunoglobulinemia D periodic fever syndrome (HIDS) and the more severe mevalonic aciduria are rare, autosomal recessive, autoinflammatory diseases belonging to the hereditary periodic fever (HPF) family. Other members include: familial mediterranean fever (FMF), the cryopyrin-associated periodic syndromes (CAPS) and TNFR-associated periodic syndromes (TRAPS). MKD is caused by mutations in the gene encoding mevalonate kinase (MK), an enzyme of the cholesterol pathway, leading to its inactivation. The molecular mechanisms linking MKD and abnormalities of isoprenoid biosynthesis to cytokine production and inflammation have yet to be fully elucidated. Statins, which are extensively prescribed for lowering cholesterol, are potent inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase, the enzyme directly upstream of MK. In this review, we discuss recent reports demonstrating that in vitro inhibition of the mevalonate pathway by statins specifically increases the production, by activated monocytes, of cytokines of the IL-1 family, by enhancing caspase-1 activity, the enzyme responsible for IL-1 $\beta$  and IL-18 maturation. The molecular mechanisms involve geranylgeranylation and the enhancement of the activity of G proteins such as Rac-1. Interestingly, activated fibroblasts from MKD patients secrete more IL-1 $\beta$  than fibroblasts from healthy donors. Taken together, these data highlight the specific enhancement of the IL-1 family of cytokines, the maturation of which is caspase-1-dependent in MKD. Finally, the spectacular decrease in febrile attacks in patients with severe HIDS under IL-1 receptor antagonist (anakinra) treatment, reinforces this hypothesis. Deregulated caspase-1 activation could be responsible for the inflammatory component of MKD, thereby mechanistically linking MKD to FMF and CAPS through cytokines of the IL-1 family.

DOI: 10.1684/ecn.2009.0163

PMID: 19825518 [Indexed for MEDLINE]

3419. Rheumatol Int. 2010 Jul;30(9):1269-71. doi: 10.1007/s00296-009-1167-1. Epub 2009 Oct 13.

TNF receptor-associated periodic fever syndrome caused by sequence alterations in exonic splicing enhancers: comment on the article by Trübenbach et al.

Martorana D, Neri TM.

Comment on

Rheumatol Int. 2010 Apr;30(6):805-9.

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS), an autosomal disease belonging to human autoinflammatory syndromes, is caused by mutations in Tumor Necrosis Factor Receptor Superfamily Member 1A (TNFRSF1A) gene. Trübenbach and colleagues described a patient with two heterozygotic nucleotide transversions in exon 4 of TNFRSF1A gene: the first is a substitution from guanine to cytosine at position 263 of the nucleotide sequence (c.263 G>C); the second is a substitution from cytosine to adenine at position 264 (c.264 C>A); the two mutations affect the amino acid number 88 of the protein. To date, this was the first report of a double monoallelic mutation in a gene related to autoinflammatory syndromes. Using two web interfaces (ESEfinder and RESCUE-ESE), we provide evidence that the double nucleotide change may affect an exonic splicing enhancer (ESE), a sequence element distinct from the canonical splice sites that are needed for normal splicing. ESEs are short and degenerate sequences found within coding exons and required for efficient splicing and splice site recognition. In order to verify if these changes really affect an ESE, it would be useful to analyze the described index case TNFRSF1A cDNA, because if this analysis will evidence an exon skipping in the TNFRSF1A coding sequence, it would then represent the first mutation in autoinflammatory syndromes demonstrated to be caused by ESE elements alteration.

DOI: 10.1007/s00296-009-1167-1

PMID: 19823838 [Indexed for MEDLINE]



3420. Acta Reumatol Port. 2009 Jul-Sep;34(3):561-2.

Do MTHFR mutations kick in during familial mediterranean fever attacks?

Dönmez G, Dönmez AD, Ozçakar L.

PMID: 19820684 [Indexed for MEDLINE]

3421. Acta Reumatol Port. 2009 Jul-Sep;34(3):520-4.

Surgery for acute abdomen and MEFV mutations in patients with FMF.

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**OBJECTIVES:** Familial Mediterranean Fever (FMF) is an autosomal recessive disease characterized by recurrent fever, peritonitis, arthritis, pleuritis, and

secondary amyloidosis. In the current study, we sought to determine the frequency of acute surgical abdominal intervention and MEFV gene mutations in FMF patients.

**PATIENTS AND METHODS:** A total of 159 patients were referred to our department with a diagnosis of FMF. Twenty-six patients (16.4%) had a history of surgical intervention. Of these, 17 (10.7%) were operated on due to appendicitis, and 9 (5.7%) were operated on due to other acute abdomen reasons. Genomic DNA was isolated from the blood samples, and in the isolated DNA samples, 12 MEFV gene mutations were studied.

**RESULTS:** Mutation frequency was detected to be 80.8% in the patients with acute abdomen surgery intervention and 56.4% in the patients without acute abdomen surgical intervention. Upon mutational evaluation of these patients, we noted that the M694V (40.5%) and E148Q (21.4%) mutations occurred most frequently.

**CONCLUSIONS:** The MEFV gene mutation frequency in FMF patients with acute abdomen surgical intervention was significantly higher than that in patients without such intervention. Increased mutation scanning in FMF patients will significantly decrease unnecessary surgical interventions in this patient group.

PMID: 19820675 [Indexed for MEDLINE]

3422. J Rheumatol. 2009 Oct;36(10):2372. doi: 10.3899/jrheum.090250.

Is E148Q a benign polymorphism or a disease-causing mutation?

Marek-Yagel D, Bar-Joseph I, Pras E, Berkun Y.

DOI: 10.3899/jrheum.090250

PMID: 19820229 [Indexed for MEDLINE]

3423. Diagn Interv Radiol. 2009 Dec;15(4):252-5. doi: 10.4261/1305-3825.DIR.2252-08.2. Epub 2009 Oct 5.

Diffusion-weighted MRI of the kidneys in patients with familial Mediterranean fever: initial experience.

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**PURPOSE:** To evaluate the feasibility of diffusion-weighted magnetic resonance imaging (DW-MRI) in the assessment of renal function in patients with familial Mediterranean fever (FMF).

**MATERIALS AND METHODS:** Thirty healthy volunteers who had no history of renal disease, hypertension or vascular disease and 60 patients with FMF were included in the study. Transverse diffusion-weighted multisection echo-planar MRI was performed with the following diffusion gradient b values: 0, 111, 222, 333, 444, 556, 667, 778, 889 and 1000 s/mm<sup>2</sup>. The apparent diffusion coefficient (ADC) values, urine protein and serum creatinine levels, and glomerular filtration rates of the healthy volunteers, patients with renal involvement, and patients without were compared by using ANOVA test. ADCs of the kidneys were calculated separately for low (ADC(low); b = 0, 111, 222, 333 s/mm<sup>2</sup>), average (ADC(avg); of all b values), and high (ADC(high); b = 778, 889, 1000 s/mm<sup>2</sup>) b values to

enable the differentiation of the relative influence of perfusion fraction and true diffusion. ADC(high) reflects almost only diffusion, whereas ADC(low) is composed of both diffusion and perfusion.

RESULTS: There was statistically significant difference between ADC(low) values of the FMF patients with renal involvement and the control group ( $P < 0.05$ ).

Negative correlation was found between the duration of disease and ADC(low) values of the kidneys ( $r = -0.223$ ,  $P = 0.087$ ).

CONCLUSION: DW-MRI of the kidneys might allow early detection of the renal changes in patients with FMF. This might prevent the progression of disease by giving proper medical treatment. Further studies with larger numbers of FMF patients and more experience on MRI technique are required to help define more conclusively the precise role of DW imaging in detection of renal changes.

DOI: 10.4261/1305-3825.DIR.2252-08.2

PMID: 19813167 [Indexed for MEDLINE]

3424. Z Rheumatol. 2009 Nov;68(9):711. doi: 10.1007/s00393-009-0485-8.

[Autoinflammation and inflammation. The dark energy in the universe of rheumatology].

[Article in German]

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DOI: 10.1007/s00393-009-0485-8

PMID: 19809827 [Indexed for MEDLINE]

3425. J Cell Biol. 2009 Oct 5;187(1):61-70. doi: 10.1083/jcb.200903124.

Glyburide inhibits the Cryopyrin/Nalp3 inflammasome.

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Inflammasomes activate caspase-1 for processing and secretion of the cytokines interleukin-1beta (IL-1beta) and IL-18. Cryopyrin/NALP3/NLRP3 is an essential component of inflammasomes triggered by microbial ligands, danger-associated molecular patterns (DAMPs), and crystals. Inappropriate Cryopyrin activity has been incriminated in the pathogenesis of gouty arthritis, Alzheimer's, and silicosis. Therefore, inhibitors of the Nalp3 inflammasome offer considerable therapeutic promise. In this study, we show that the type 2 diabetes drug glyburide prevented activation of the Cryopyrin inflammasome. Glyburide's cyclohexylurea group, which binds to adenosine triphosphatase (ATP)-sensitive K(+) (K(ATP)) channels for insulin secretion, is dispensable for inflammasome inhibition. Macrophages lacking K(ATP) subunits or ATP-binding cassette transporters also activate the Cryopyrin inflammasome normally. Glyburide analogues inhibit ATP- but not hypothermia-induced IL-1beta secretion from human monocytes expressing familial cold-associated autoinflammatory syndrome-associated Cryopyrin mutations, thus suggesting that inhibition occurs upstream of Cryopyrin. Concurrent with the role of Cryopyrin in endotoxemia, glyburide significantly delays lipopolysaccharide-induced lethality in mice. Therefore, glyburide is the first identified compound to prevent Cryopyrin activation and microbial ligand-, DAMP-, and crystal-induced IL-1beta secretion.

DOI: 10.1083/jcb.200903124

PMCID: PMC2762099

PMID: 19805629 [Indexed for MEDLINE]

3426. Int J Immunogenet. 2010 Feb;37(1):21-5. doi: 10.1111/j.1744-313X.2009.00884.x. Epub 2009 Oct 5.

A novel Y331X nonsense mutation in TNFRSF1A gene in two unrelated Turkish families with periodic fever syndrome.

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The autoinflammatory disorders differ in severity, as well as age of onset, duration, and manifestations, but they all share some common features: recurring fever peaks, inflammation of serosal membranes, musculoskeletal involvement, varying types of skin rash, amyloidosis as a sequel of the disease. TRAPS is very rare in Turkish population and we present two unrelated Turkish children with similar clinical phenotypes and laboratory findings related with autoinflammatory disorders and with novel p. Y331X mutation in TNFRSF1A gene. Both of the patients were male and they had recurrent fever without abdominal pain and arthralgia. Full cDNA and exon-intron binding regions of TNFRSF1A, MEFV, MVK, CIAS1 genes were analysed by direct DNA sequencing methods in order to differentiate TRAPS, FMF, HIDS, CINCA/MWS/FCAS respectively. We screened ten exons of TNFRSF1A gene, and detected a heterozygous c.1080C>G nucleotide substitution in exon 10 in both of the unrelated patients, resulting p.Y360X nonsense (protein truncated) mutation. According to classical TNFRSF1A gene nomenclature and the agreement of 30th amino acid as the first one, it is accepted as p.Y331X. It was interesting to determine same mutations in fathers of two patients. In one of the cases, E148Q heterozygous mutation, which is one of the disease-causing mutations of MEFV gene, was detected. No nucleotide substitution was identified in exon and exon-intron splicing regions encoding 396 amino acid of MVK gene in both of the patients. In CIAS1 gene, two different nucleotide substitutions resulting synonymous amino acid mutation were detected in exon 3: c.[732G>A] and c.[786A>G] nucleotide substitutions and compatible p.A242A (according to c.DNA p.A244A) and p.R260R (according to c.DNA p.R262R) synonymous amino acid mutations. These nucleotide substitutions were also detected in parents and were reported to be normal variations in Turkish population. In conclusion, in Turkish patients, with dominantly inherited recurrent fever, TRAPS is a diagnosis worthy of attention and novel mutations have to be reported with phenotype associations.

DOI: 10.1111/j.1744-313X.2009.00884.x

PMID: 19804406 [Indexed for MEDLINE]

3427. Future Cardiol. 2008 Nov;4(6):599-607. doi: 10.2217/14796678.4.6.599.

Colchicine for the treatment of pericarditis.

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Colchicine has been effectively used in the treatment of several inflammatory conditions, such as gouty attacks, serositis related to familial Mediterranean fever, Behçet syndrome and more recently, in acute and recurrent pericarditis. Colchicine concentrates in white blood cells, particularly polymorphonuclear cells, inhibiting tubulin polymerization, thus interfering with migration and phagocytosis, and reducing the inflammatory cycle. Although the exact number of responders is unknown, the drug has been successfully used for the treatment and prevention of recurrences and to taper corticosteroids in patients with recurrent pericarditis in several retrospective studies and an open-label, randomized trial, where the recurrence rate was halved in the treatment arm. Less evidence supports the use of the drug for the treatment of acute pericarditis, where colchicine remains optional and requires further multicenter confirmatory studies. At present, colchicine has been recommended by the 2004 European guidelines on the management of pericardial diseases for acute (class IIa) and recurrent pericarditis (class I), but its use is still unlabeled and informed consent is required for prescription. A careful monitoring of possible contraindications, drug interactions and side effects is necessary. The aim of this paper is to review the evidence that supports the use of the drug in acute and recurrent pericarditis, as well as dosing and precautions for clinical use.

DOI: 10.2217/14796678.4.6.599

PMID: 19804354

3428. Med Princ Pract. 2009;18(6):441-6. doi: 10.1159/000235892. Epub 2009 Sep 30.

Prevention of amyloidosis in familial Mediterranean fever with colchicine: a case-control study in Armenia.

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**OBJECTIVE:** To determine whether or not the use of colchicine decreases the risk of amyloidosis among Armenian patients with familial Mediterranean fever (FMF).

**SUBJECTS AND METHODS:** The study included 99 Armenian patients from the Center of Medical Genetics database with genetically ascertained FMF; 33 had renal amyloidosis and 66 were randomly selected control patients without renal amyloidosis. Self-reported colchicine use was assessed by interviewer-based questionnaire.

**RESULTS:** The patients with incident amyloidosis were more likely to be older men, but younger at the time of disease onset, and more likely to have had a family history of amyloidosis and M694F mutation in the MEFV gene compared to patients without amyloidosis. The risk of amyloidosis decreased with adequate colchicine use rather than nonadequate use (adjusted odds ratio, OR, 0.48, 95% confidence interval, CI, 0.16-1.43), continuous colchicine use rather than interrupted use (adjusted OR 0.15, 95% CI 0.04-0.53), earlier rather than later initiation age of colchicine treatment (adjusted OR 0.95, 95% CI 0.90-1.01), current colchicine rather than ever/never colchicine use (adjusted OR 0.20, 95% CI 0.05-0.89).

**CONCLUSION:** The study demonstrated that colchicine treatment is effective in preventing amyloidosis among Armenian patients with FMF and that earlier initiation and continuous therapy at an adequate dose of 1.2-1.8 mg/day may be associated with a decreased amyloidosis risk among Armenian patients with FMF.

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DOI: 10.1159/000235892

PMID: 19797919 [Indexed for MEDLINE]

3429. Joint Bone Spine. 2009 Oct;76(5):567-9. doi: 10.1016/j.jbspin.2009.08.002. Epub 2009 Sep 30.

TNF receptor-associated periodic syndrome (TRAPS): a new cause of joint destruction?

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TNF receptor-associated periodic syndrome (TRAPS) is a highly polymorphic autoinflammatory syndrome related to mutations in the TNFRSF1A gene encoding the type 1 TNF receptor. Arthralgia and nonerosive synovitis are among the most common manifestations. We report the case of a 73-year-old woman who presented with chronic erosive joint disease that progressed by flare-ups. Moderate nonspecific abdominal and cutaneous abnormalities were noted, suggesting TRAPS. This diagnosis was confirmed when genetic tests identified the R92Q mutation in the TNFRSF1A gene. Although glucocorticoid therapy was effective in alleviating the symptoms, combination therapy with methotrexate and etanercept neither decreased the frequency of the flare-ups nor slowed the pace of joint destruction. Treatment with anakinra is being considered. To our knowledge, this is the first reported case of joint destruction related to TRAPS. In patients with refractory inflammatory joint disease, the presence of extraarticular manifestations, however mundane, should suggest TRAPS.

DOI: 10.1016/j.jbspin.2009.08.002

PMID: 19796978 [Indexed for MEDLINE]

3430. Nat Rev Neurol. 2009 Oct;5(10):528-9. doi: 10.1038/nrneurol.2009.154.

Multiple sclerosis. TNFRSF1A, TRAPS and multiple sclerosis.

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A genome-wide association study has identified the R92Q variant of the TNFRSF1A gene as a new susceptibility locus for multiple sclerosis. This locus is of special interest because the R92Q substitution was previously detected in a group of multiple sclerosis patients who had additional symptoms compatible with the autoinflammatory syndrome TRAPS.



DOI: 10.1038/nrneurol.2009.154  
PMID: 19794511 [Indexed for MEDLINE]

3431. Arthritis Rheum. 2009 Oct 15;61(10):1447-53. doi: 10.1002/art.24458.

Familial mediterranean Fever in the world.

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DOI: 10.1002/art.24458  
PMID: 19790133 [Indexed for MEDLINE]

3432. Pediatrics. 2009 Oct;124(4):e721-8. doi: 10.1542/peds.2009-0088. Epub 2009 Sep 28.

Differentiating PFAPA syndrome from monogenic periodic fevers.

Gattorno M(1), Caorsi R, Meini A, Cattalini M, Federici S, Zulian F, Cortis E, Calcagno G, Tommasini A, Consolini R, Simonini G, Pelagatti MA, Baldi M, Ceccherini I, Plebani A, Frenkel J, Sormani MP, Martini A.

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**OBJECTIVES:** To analyze whether there were clinical differences between genetically positive and negative patients fulfilling periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome criteria and to test the accuracy of the Gaslini diagnostic score for identifying patients with PFAPA syndrome with higher probabilities of carrying relevant mutations in genes associated with periodic fevers.

**METHODS:** Complete clinical and genetic information was available for 393 children

with periodic fever; 82 had positive genetic test results, 75 had incomplete genetic test results, and 236 had negative results for MVK, TNFRSF1A, and MEFV mutations. Current diagnostic criteria for PFAPA syndrome were applied.

RESULTS: Of 393 children, 210 satisfied PFAPA syndrome criteria; 43 carried diagnostic mutations (mevalonate kinase deficiency:  $n = 33$ ; tumor necrosis factor receptor-associated periodic syndrome:  $n = 3$ ; familial Mediterranean fever:  $n = 7$ ), 37 displayed low-penetrance mutations or incomplete genotypes, and 130 demonstrated negative genetic testing results. Genetically positive patients had higher frequencies of abdominal pain and diarrhea ( $P < .001$ ), vomiting ( $P = .006$ ), and cutaneous rash and arthralgia ( $P = .01$ ). Genetically negative patients had a higher frequency of exudative pharyngitis ( $P = .010$ ). Genetically undetermined patients showed the same pattern of symptom frequency as genetically negative patients. The Gaslini diagnostic score was able to identify 91% of genetically positive patients correctly, with a global accuracy of 66%.

CONCLUSION: The Gaslini diagnostic score represents a useful tool to identify patients meeting PFAPA syndrome criteria and at low risk of carrying relevant mutations in genes associated with periodic fevers.

DOI: 10.1542/peds.2009-0088

PMID: 19786432 [Indexed for MEDLINE]

3433. PLoS One. 2009 Sep 28;4(9):e7154. doi: 10.1371/journal.pone.0007154.

Genetic variation in the familial Mediterranean fever gene (MEFV) and risk for Crohn's disease and ulcerative colitis.

Villani AC(1), Lemire M, Louis E, Silverberg MS, Collette C, Fortin G, Nimmo ER, Renaud Y, Brunet S, Libioulle C, Belaiche J, Bitton A, Gaudet D, Cohen A, Langelier D, Rioux JD, Arnott ID, Wild GE, Rutgeerts P, Satsangi J, Vermeire S, Hudson TJ, Franchimont D.

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BACKGROUND AND AIMS: The familial Mediterranean fever (FMF) gene (MEFV) encodes pyrin, a major regulator of the inflammasome platform controlling caspase-1

activation and IL-1 $\beta$  processing. Pyrin has been shown to interact with the gene product of NLRP3, NALP3/cryopyrin, also an important active member of the inflammasome. The NLRP3 region was recently reported to be associated with Crohn's disease (CD) susceptibility. We therefore sought to evaluate MEFV as an inflammatory bowel disease (IBD) susceptibility gene.

**METHODOLOGY AND RESULTS:** MEFV colonic mucosal gene expression was significantly increased in experimental colitis mice models (TNBS  $p < 0.0003$ ; DSS  $p < 0.006$ ), in biopsies from CD ( $p < 0.02$ ) and severe ulcerative colitis (UC) patients ( $p < 0.008$ ). Comprehensive genetic screening of the MEFV region in the Belgian exploratory sample set (440 CD trios, 137 UC trios, 239 CD cases, 96 UC cases, and 107 healthy controls) identified SNPs located in the MEFV 5' haplotype block that were significantly associated with UC (rs224217;  $p = 0.003$ ; A allele frequency: 56% cases, 45% controls), while no CD associations were observed. Sequencing and subsequent genotyping of variants located in this associated haplotype block identified three synonymous variants (D102D/rs224225, G138G/rs224224, A165A/rs224223) and one non-synonymous variant (R202Q/rs224222) located in MEFV exon 2 that were significantly associated with UC (rs224222:  $p = 0.0005$ ; A allele frequency: 32% in cases, 23% in controls). No consistent associations were observed in additional Canadian (256 CD trios, 91 UC trios) and Scottish (495 UC, 370 controls) sample sets. We note that rs224222 showed marginal association ( $p = 0.012$ ; G allele frequency: 82% in cases, 70% in controls) in the Canadian sample, but with a different risk allele. None of the NLRP3 common variants were associated with UC in the Belgian-Canadian UC samples and no significant interactions were observed between NLRP3 and MEFV that could explain the observed flip-flop of the rs224222 risk allele.

**CONCLUSION:** The differences in association levels observed between the sample sets may be a consequence of distinct founder effects or of the relative small sample size of the cohorts evaluated in this study. However, the results suggest that common variants in the MEFV region do not contribute to CD and UC susceptibility.

DOI: 10.1371/journal.pone.0007154

PMCID: PMC2745755

PMID: 19784369 [Indexed for MEDLINE]

3434. Rheumatol Int. 2010 Nov;30(12):1661-3. doi: 10.1007/s00296-009-1130-1. Epub 2009 Sep 24.

Periodic fever responds to vitamin B12 treatment.

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Periodic fever of childhood is a group of diseases that cause repeated febrile illnesses with various associated symptoms. In our article, we present the case of a 6-year-old girl with unusual appearance of periodic fever syndrome. Our patient suffered from repeated episodes of high fever from the age of 2 years old. Each episode usually lasted 24-48 h, the interval between events was 1-3 weeks long. During high fever episodes the child usually felt well, without associated accompanying complaints. As a rule, the physical examination did not reveal any pathologic finding explaining the fever. During the 4 years of follow-up the patient sustained treatment attempts with prednisone for a number of months and half a year with colchicine without any response. We considered treatment with sublingual tablets of vitamin B12 (VIT B12). Beyond all expectation, we witnessed complete resolution of attacks during the first 2 months following treatment. After a long episode-free period, the parents withheld the treatment on their own accord, and in a short time the disease recurred. We advised to renew the treatment with VIT B12, and during approximately half year of follow-up there were no recurrences of periodic fever. CONCLUSION: we believe that our observation raises interest in systematic evaluation of the therapeutic role of VIT B12 as a treatment option for disorders of the periodic fever spectrum.

DOI: 10.1007/s00296-009-1130-1

PMID: 19777239 [Indexed for MEDLINE]

3435. Rheumatol Int. 2010 Aug;30(10):1293-8. doi: 10.1007/s00296-009-1140-z. Epub 2009 Sep 24.

MEFV mutations in Egyptian patients suffering from familial Mediterranean fever: analysis of 12 gene mutations.

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The objective of the study is to screen 12 MEFV gene mutations in Egyptian patients with familial Mediterranean fever (FMF) and to study the initial hypothesis that the phenotypic expression of the disease may be attributable to the existence of a particular mutation. We enrolled 136 Egyptian patients (74 males, and 62 females) with a clinical diagnosis of FMF. DNA was amplified by PCR and subjected to reverse hybridization for the detection of 12 MEFV gene mutations. The phenotypic expression of the disease was compared in two subgroups according to the presence of homozygote E148Q and M694V gene mutations. The most frequent gene mutations in the studied group were V726A, M694V, M680I, E148Q and M694I in 41.2, 32.4, 29.4, 25 and 20.6%, respectively. At least one of these main five founder mutations was present in 132 patients (97.1%). Thirty-two patients (23.5%) were homozygote for one of the main five founder mutations. The most common homozygote gene mutations were E148Q and M694V, each in 12 patients (8.8%). Significant increase in abdominal pain and arthritis was found in patients with homozygote M694V mutation compared to those with E148Q mutation. All patients with amyloidosis had M694V gene mutation. The increased frequency of V726A gene mutation and the rarity of amyloidosis in this study suggest that Egyptian patients may have a milder form of FMF compared to other populations. The five main founder mutations account for the vast majority of cases of FMF. M694V gene mutation may be associated with increased frequency of abdominal pain, arthritis and the presence of amyloidosis.

DOI: 10.1007/s00296-009-1140-z

PMID: 19777236 [Indexed for MEDLINE]

3436. Clin Rheumatol. 2010 Feb;29(2):209-10. doi: 10.1007/s10067-009-1279-8. Epub 2009 Sep 23.

Anti-IL-1 treatment for secondary amyloidosis in an adolescent with FMF and Behçet's disease.

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Familial Mediterranean fever (FMF) is associated with mutations in the gene coding for pyrin which lead to accentuated innate immune responses resulting in increased production of IL-1. We present a teenager who had severe FMF and Behçet's disease and developed moderate proteinuria. Renal biopsy showed secondary amyloidosis. Anakinra was started at 1 mg/kg/day subcutaneously along with colchicine treatment. The clinical response was excellent. Acute phase reactants decreased. The level of proteinuria and renal functions remained stable and the hypoalbuminemia returned to normal. Her clinical and laboratory symptoms returned when anakinra had to be stopped at 6 months. Thus, the drug was restarted and she is now clinically in excellent condition a year after the start of therapy. She has normal renal functions, normal serum proteins, and normal acute-phase reactants. However, recently, after 18 months of anakinra treatment, her proteinuria gradually increased and albumin levels decreased. We suggest that anti-IL-1 treatment is beneficial for the suppression of inflammation; however, long-term studies are needed to understand whether progressive renal disease will be prevented.

DOI: 10.1007/s10067-009-1279-8

PMID: 19774408 [Indexed for MEDLINE]

3437. Trans Am Clin Climatol Assoc. 2009;120:413-8.

The inherited autoinflammatory syndrome: a decade of discovery.

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The hereditary autoinflammatory diseases arise from mutations of genes regulating the innate immune system. These rare disorders are well characterized, both clinically and in terms of their molecular pathogenesis. The recurrent attacks of

febrile polyserositis of Familial Mediterranean Fever (FMF) are due to defective pyrin, a protein that down-regulates inflammation. The Hyperimmunoglobulinemia D Syndrome (HIDS), which mimics FMF, results from a genetically conferred deficiency of mevalonate kinase. TRAPS (TNF Receptor Associated Periodic Syndrome), formerly known as Familial Hibernian Fever, is caused by a defective membrane receptor for TNF. Three other hereditary disorders which overlap in their clinical expression - Familial Cold Autoinflammatory Syndrome, the Muckle Wells syndrome, and Neonatal Onset Multisystem Inflammatory Disease (NOMID) - are a consequence of gain-of-function mutations of the gene encoding cryopyrin, the scaffolding protein of the inflammasome. The PAPA syndrome (Pyogenic Arthritis, Pyoderma gangrenosum, Acne) results from mutations of a gene that increases the binding of its product (PSPSTPIP1) to pyrin, thereby blunting the inhibitory effect of pyrin on inflammasome activation.

PMCID: PMC2744542

PMID: 19768193 [Indexed for MEDLINE]

3438. Immunity. 2009 Sep 18;31(3):389-400. doi: 10.1016/j.immuni.2009.08.012.

Intestinal effector T cells in health and disease.

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Crohn's disease and ulcerative colitis are the two major forms of chronic relapsing inflammatory disorders of the human intestines collectively referred to as inflammatory bowel disease (IBD). Though a complex set of autoinflammatory disorders that can be precipitated by diverse genetic and environmental factors, a feature that appears common to IBD pathogenesis is a dysregulated effector T cell response to the commensal microbiota. Due to the heightened effector T cell activity in IBD, developmental and functional pathways that give rise to these cells are potential targets for therapeutic intervention. In this review, we highlight recent advances in our understanding of effector T cell biology in the context of intestinal immune regulation and speculate on their potential clinical

significance.

DOI: 10.1016/j.immuni.2009.08.012

PMCID: PMC3109492

PMID: 19766082 [Indexed for MEDLINE]

3439. Ann Rheum Dis. 2010 Apr;69(4):677-82. doi: 10.1136/ard.2009.114363. Epub 2009 Sep 17.

Neutrophil-derived S100A12 as novel biomarker of inflammation in familial Mediterranean fever.

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**OBJECTIVE:** Familial Mediterranean fever (FMF) is characterised by recurrent periodic febrile attacks and persistent subclinical inflammation. The damage-associated molecular pattern (DAMP) protein S100A12 has proven to be a sensitive marker for disease activity and inflammation in numerous inflammatory disorders. The aim of this study was to analyse the role of S100A12 in the detection of inflammation in patients with FMF.

**METHODS:** 52 children and adolescents with a clinical and/or genetic diagnosis of FMF were prospectively followed-up over 18 months (in total 196 visits). During clinical visits, erythrocyte sedimentation rate, C reactive protein, serum amyloid A and S100A12 serum concentrations were determined. Patients were categorised into four groups according to the clinical activity of FMF.

**RESULTS:** Serum concentrations of S100A12 were excessively increased in patients with a mean increase of about 290-fold in active FMF above normal controls. S100A12 decreased significantly after introduction of colchicine therapy. Serum concentrations of S100A12 were significantly higher in patients treated with colchicine with persistent symptoms (mean $\pm$ -SEM, 6260 $\pm$ -2120 ng/ml) than in those with clinically controlled disease (440 $\pm$ -80 ng/ml,  $p$ <0.001). In contrast to classical markers of inflammation, S100A12 was significantly elevated in clinically unaffected homozygous MEFV gene mutation carriers, indicating



subclinical inflammation.

CONCLUSIONS: S100A12 is a valuable biomarker for monitoring disease activity, inflammation and response to colchicine treatment in patients with FMF. It might even be more sensitive in detecting subclinical inflammation than other available indicators.

DOI: 10.1136/ard.2009.114363

PMID: 19762364 [Indexed for MEDLINE]

3440. Ann N Y Acad Sci. 2009 Sep;1173:766-73. doi: 10.1111/j.1749-6632.2009.04674.x.

Colchicine revisited.

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Purified from a Mediterranean plant nearly two centuries ago, colchicine has been discovered to inhibit many steps in the inflammatory process. The drug has good oral bioavailability and some enterohepatic recirculation, requiring dose adjustments for kidney disease and avoidance in liver disease. Toxicities are primarily gastrointestinal, hepatic, and hematologic. Colchicine is approved by the U.S. Federal Drug Administration for the treatment and prophylaxis of gout flares but has also been tried with varying success in the treatment of familial Mediterranean fever, primary biliary cirrhosis, psoriasis, Behçet's disease, aphthous stomatitis, linear IgA dermatosis, relapsing polychondritis, Sweet's syndrome, scleroderma, amyloidosis, leukocytoclastic vasculitis, epidermolysis bullosa, and dermatomyositis.

DOI: 10.1111/j.1749-6632.2009.04674.x

PMID: 19758227 [Indexed for MEDLINE]

3441. Curr Vasc Pharmacol. 2010 Jul;8(4):437-49.

The rationale for comparative studies of accelerated atherosclerosis in rheumatic

diseases.

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The inflammatory pathogenesis of atherosclerosis is now well-established, owing to in vitro and in vivo studies and the application of high sensitivity assays for C-reactive protein (CRP) in the general population and specific groups at risk for cardiovascular disease (CVD). In view of the complexity of inflammation-induced atherosclerosis, the rationale for comparative studies of atherogenesis in rheumatic diseases with diverse inflammatory pathogenesis seems obvious; they are human in vivo models to study inflammatory mechanisms involved in atherosclerosis and the impact of treatment. Factors implicated in atherogenesis in systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), familial Mediterranean fever (FMF) and Behçet's disease (BD) are discussed in this review. Evidence suggests that enhanced atherosclerosis causes premature cardiovascular events in the autoimmune disease, SLE, and the "high-grade" inflammatory rheumatic disease, RA. Preliminary data suggest that enhanced atherogenesis may accompany FMF in the absence of sufficient suppression of inflammation by colchicine. In the setting of BD, the role of atherosclerosis in the premature manifestation of coronary pathology has not been confirmed; coronary vasculitis and aneurysms appear to constitute the basis of myocardial infarction (MI) in BD. A variety of established and novel risk factors are believed to influence enhanced atherogenesis in rheumatic diseases. Antiphospholipid antibodies are thought to be intimately involved in atherogenesis in SLE and to a lesser extent in RA. CRP may play a more universal role in all rheumatic diseases. The application of high resolution ultrasound of peripheral arteries and other non-invasive techniques may allow targeted use of statins, ACE inhibitors, antiplatelet agents and other cardioprotective drugs in patients with rheumatic diseases, but this needs to be evaluated specifically in prospective studies.

PMID: 19758114 [Indexed for MEDLINE]

3442. Z Rheumatol. 2009 Nov;68(9):766-71. doi: 10.1007/s00393-009-0542-3.

[Recommendations on therapy using interleukin-1beta-blocking agents].

[Article in German]

Manger B(1), Gaubitz M, Michels H; Kommission Pharmakotherapie der DGRh; German Society of Rheumatology.

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In Germany, the only available interleukin-1beta (IL-1beta) blocking agent is anakinra (ANR) (as of August 2009) which is given subcutaneously at a dosage of 100 mg/day (adults) and 1-2 mg/kg body weight/day (maximum 100 mg/day) (children), respectively. Based on published data and clinical experience the German Society of Rheumatology (Deutsche Gesellschaft für Rheumatologie) recommends the following indications for ANR: (1) Rheumatoid arthritis, if treatment with two DMARDs (one of the two being methotrexate, MTX) for at least 6 months has failed. (2) Adult-onset and juvenile-onset Still's disease (systemic juvenile idiopathic arthritis) in the case of insufficient response to glucocorticoids or inadequate long-term dosage, as well as failure of a conventional DMARD, usually MTX. For both indications the treatment should be supervised and documented by a rheumatologist or paediatric rheumatologist. Cryopyrin-associated periodic syndromes (CAPS) are recommended as an additional treatment option for IL-1 blocking therapy. The efficacy of the fusion protein rilonacept (RIC) and the monoclonal antibody canakinumab in the treatment of CAPS has been proven by randomized, placebo-controlled trials. In the US, RIL was recently approved by the FDA for the treatment of CAPS under the "Orphan Drug Status".

DOI: 10.1007/s00393-009-0542-3

PMID: 19756659 [Indexed for MEDLINE]

3443. Hum Mol Genet. 2009 Dec 15;18(24):4746-55. doi: 10.1093/hmg/ddp437. Epub 2009 Sep 15.

Expression of the familial Mediterranean fever gene is regulated by nonsense-mediated decay.

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Mutations in the MEditerranean FeVer (MEFV) gene are responsible for familial Mediterranean fever (FMF), a recessively inherited auto-inflammatory disease. Cases of dominant inheritance and phenotype-genotype heterogeneity have been reported; however, the underlying molecular mechanism is not currently understood. The FMF protein named pyrin or marenostrin (P/M) is thought to be involved in regulating innate immunity but its function remains subject to controversy. Recent studies postulate that a defect in MEFV expression regulation may play a role in FMF physiopathology. Our group, along with others, has identified several alternatively spliced MEFV transcripts in leukocytes. Since alternative splicing and nonsense-mediated decay (NMD) pathways are usually coupled in the post-transcriptional regulation of gene expression, we hypothesized that NMD could contribute to the regulation of the MEFV gene. To address this issue, we examined the effect of indirect and direct inhibition of NMD on expression of the MEFV transcripts in THP1, monocyte and neutrophil cells. We showed that MEFV is the first auto-inflammatory gene regulated by NMD in both a cell- and transcript-specific manner. These results and preliminary western-blot analyses suggest the possible translation of alternatively spliced MEFV transcripts into several P/M variants according to cell type and inflammatory state. Our results introduce the novel hypothesis that variation of NMD efficiency could play an important role in FMF physiopathology as a potent phenotypic modifier.

DOI: 10.1093/hmg/ddp437

PMID: 19755381 [Indexed for MEDLINE]

3444. Rev Med Inst Mex Seguro Soc. 2009 Mar-Apr;47(2):211-4.

[Recurrent pericardial effusion due to familiar Mediterranean fever].

[Article in Spanish]

Halabe-Cherem J(1), Hamui-Sutton A, Cohen-Cohen S, Sacal-Dumani E, Shuchleib-Cung A, Nellen-Hummel H, Rábago-Arredondo J.

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Pericarditis is usually a complication of viral or bacterial infection. In addition, it can be associated to systemic diseases such as autoimmune disorders, rheumatic fever, cancer, tuberculosis and AIDS. It can also be related to familial Mediterranean fever, an autosomic recessive inflammatory disease, characterized by fever, abdominal pain, and pleuritis mainly seen in persons from the Mediterranean area. In this study, we described the evolution and treatment response to colchicine in three patients with pericarditis associated to familial Mediterranean fever. Two of the patients had a pericardiectomy showing in their biopsy nonspecified inflammatory changes. Later their diagnosis were confirmed by genetic markers, echocardiogram and EKG. They were treated with antiviral and antibiotics without any improvement; subsequently they had good results with colchicine.

PMID: 19744393 [Indexed for MEDLINE]

3445. Cell Immunol. 2009;260(1):6-13. doi: 10.1016/j.cellimm.2009.08.003. Epub 2009 Aug 14.

The role of inflammatory cytokines and NF-kappaB/MAPK signaling pathways in the evolution of familial Mediterranean fever: current clinical perspectives and potential therapeutic approaches.

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Familial Mediterranean fever (FMF) is one of the social and health care problems for several populations that is known as a historically endemic disease of inflammatory nature. FMF, albeit a rare disorder, is characterized by recurrent fevers and painful inflammation of various body parts, especially the abdomen, lungs, and joints. FMF is typically characterized by inflammation of the abdominal lining (peritonitis), inflammation of the lining surrounding the lungs (pleurisy), painful, swollen joints (arthralgia and occasionally arthritis), and a characteristic ankle rash, a condition that is referred to as recurrent polyserositis, or familial paroxysmal polyserositis. Moreover, FMF is an inherited inflammatory disorder usually occurring in people of Mediterranean origin - including Sephardic Jews, Arabs, Armenians, and Turks; but it may ostensibly affect any other ethnic group, however, rarely. While there's no cure for this disorder, FMF is typically diagnosed during childhood, and signs and symptoms are treatable - or even preventable - by specialized medical attrition. The inflammatory signaling pathways associated with the evolution of FMF are currently being unraveled has that has therapeutic repercussions. In this review, I recap major concepts associated with the cellular and molecular immunology of FMF, especially shedding light on the likely roles of inflammatory cytokines, the transcription factor nuclear factor (NF)-kappaB, and the superfamily of mitogen-activated protein kinases (MAPKs). Furthermore, I summarize current advances for the clinical treatments available for FMF.

DOI: 10.1016/j.cellimm.2009.08.003

PMID: 19733345 [Indexed for MEDLINE]

3446. J Mol Biol. 2009 Nov 27;394(2):226-36. doi: 10.1016/j.jmb.2009.08.059. Epub 2009 Aug 31.

The crystal structure of human pyrin b30.2 domain: implications for mutations associated with familial Mediterranean fever.

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The inherited autoinflammatory syndrome familial Mediterranean fever (FMF) is characterized by recurrent episodes of fever, which are independent of any bacterial or viral infections. This disease is associated with point mutations in the *mefv* gene product pyrin. Although the precise molecular functions of pyrin are unknown, it seems to be involved in the maturation and secretion of interleukin-1 $\beta$ . Approximately two thirds of all FMF-associated mutations cluster in the C-terminal B30.2 domain of pyrin. To investigate the molecular consequences of FMF-associated mutations, we determined the crystal structure of the pyrin B30.2 domain at 1.35-Å resolution. The comparison with other B30.2/ligand complex structures revealed a shallow cavity, which seems to be involved in binding the pyrin ligand. The bottom of this cavity is covered mainly with hydrophobic amino acids, suggesting that pyrin recognizes its ligand by hydrophobic contacts and surface complementarities. FMF-associated mutations cluster around two sites on the B30.2 surface. Approximately two thirds, including those mutations with the most severe disease outcomes, are observed in the vicinity of the predicted peptide binding site, suggesting that they will have a direct impact on ligand binding. A second mutational hot spot was observed on the opposite side of the B30.2 domain in the neighbourhood of its artificial N-terminus. Although most FMF-associated mutations are solvent exposed, several will modify the main-chain conformation of loops. The experimental crystal structure of the pyrin B30.2 domain serves as a basis for an accurate modelling of these mutations.

DOI: 10.1016/j.jmb.2009.08.059

PMID: 19729025 [Indexed for MEDLINE]

3447. Acta Reumatol Port. 2009 Apr-Jun;34(2B):442-3.

A coincidence of FMF and vitiligo: a case report.

Melikoglu MA, Melikoglu M.

PMID: 19727060 [Indexed for MEDLINE]

3448. J Allergy Clin Immunol. 2009 Sep;124(3 Suppl 2):R13-8. doi: 10.1016/j.jaci.2009.07.014.

Antimicrobial peptides and the skin immune defense system.

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Republished from

J Allergy Clin Immunol. 2008 Aug;122(2):261-6.

Our skin is constantly challenged by microbes but is rarely infected. Cutaneous production of antimicrobial peptides (AMPs) is a primary system for protection, and expression of some AMPs further increases in response to microbial invasion. Cathelicidins are unique AMPs that protect the skin through 2 distinct pathways: (1) direct antimicrobial activity and (2) initiation of a host response resulting in cytokine release, inflammation, angiogenesis, and reepithelialization. Cathelicidin dysfunction emerges as a central factor in the pathogenesis of several cutaneous diseases, including atopic dermatitis, in which cathelicidin is suppressed; rosacea, in which cathelicidin peptides are abnormally processed to forms that induce inflammation; and psoriasis, in which cathelicidin peptide converts self-DNA to a potent stimulus in an autoinflammatory cascade. Recent work identified vitamin D3 as a major factor involved in the regulation of cathelicidin. Therapies targeting control of cathelicidin and other AMPs might provide new approaches in the management of infectious and inflammatory skin diseases.

DOI: 10.1016/j.jaci.2009.07.014

PMID: 19720207

3449. Mol Biol Rep. 2010 Jan;37(1):355-8. doi: 10.1007/s11033-009-9779-9.

MEFV heterogeneity in Turkish Familial Mediterranean Fever patients.



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Turkey is one of the few countries in the world where Familial Mediterranean Fever (FMF), an autoinflammatory disease caused by mutations in MEFV, the gene encoding pyrin, is not rare. Many interesting studies regarding the genetics of Familial Mediterranean Fever in Turkey have been already published. Despite that different MEFV genetic profiles have been revealed for Turkish FMF patients, deriving from different regions of Turkey, a systematic population genetics analysis has not been carried out yet. The present study aims to investigate the population genetics of MEFV in Turkish FMF patients so as to additionally facilitate the clinical interpretation of individualized genetic data. All relevant studies have been recruited by searching PubMed with the terms "MEFV", "FMF", and "Turkey". Seven of them, including 3,061 FMF patients, contained all necessary data concerning allelic and genotypic frequencies of the 4 commonest MEFV mutations in Turkey (M694V, V726A, M680I, E148Q). From all 6,122 MEFV alleles analyzed, the M694V mutation was recognized in 15.6-52.2% (mean 29.3%), the V726A in 1.5-9.7% (mean 4.8%), the M680I in 1.5-15.5% (mean 7.6%), and the E148Q in 3.2-13.9% (mean 5.5%). Unidentified mutations ranged from 0-42.9% (mean 16.8%). No mutations were found in 0-54.5% (mean 36.0%) of the patients. The allelic and genotypic frequencies of the most frequent mutation (M694V) showed aberration of the Hardy-Weinberg law for all 7 populations studied. By application of the Arlequin 2.0 population genetics software, the Fixation index (F<sub>ST</sub>) was found to be 0.09994, thus demonstrating that the observed variability is mainly within (90.006%) and not among (9.994%) populations (P < 0.00001). Moreover, the global test of differentiation demonstrated that every population differs from each other (P < 0.00325). Finally, the Ewens-Watterson test of selective neutrality yielded to statistical significance in only 3 populations. In conclusion, Turkish FMF patients are characterized by an increased genetic heterogeneity, explained by the intrapopulation differentiation. Thus, the regional origin should be regarded as a determining factor in the diagnosis of FMF in Turkish patients.

DOI: 10.1007/s11033-009-9779-9

PMID: 19714479 [Indexed for MEDLINE]

3450. Eur J Intern Med. 2009 Sep;20(5):548-50. doi: 10.1016/j.ejim.2009.04.005. Epub 2009 May 15.

Esophageal motor function in Familial Mediterranean Fever: a prospective evaluation of motility in 31 patients.

Bektaş M(1), Doğanay B, Alkan M, Ustun Y, Soykan I.

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**BACKGROUND:** The aims of this study were to evaluate esophageal motor function in patients with Familial Mediterranean Fever (FMF) who had upper gastrointestinal symptoms and to compare esophageal motor function between FMF patients who developed amyloidosis and patients without amyloidosis.

**METHODS:** 31 FMF patients with dyspeptic symptoms and 31 healthy age-matched individuals were included in the study. Endoscopic examination and esophageal motility testing were performed.

**RESULTS:** Esophageal motor abnormalities were detected in 25.8% (8/31) of these patients [incomplete Lower esophageal sphincter (LES) relaxation: n=4, esophageal hypomotility: n=2, and hypotensive LES: n=2]. Median LES relaxation (%) (min-max) was significantly lower in patients with FMF compared to control group 94% (54-100) vs. 98% (80-100), p=0.019 respectively). However, mean LES pressure (mmHg) (19.5+/-8.9 vs. 19.7+/-5.6, p=0.813), duration of LES relaxation (s) (7.9+/-1.7 vs. 8.7+/-1.7, p=0.068), contraction amplitude of esophageal body (mmHg) (60.4+/-23.3 vs. 58.2+/-19.7, p=0.691) and median (min-max) peak velocity (s) [3.1(-1.43-50.3) vs. 3.1 (0.9-8.7), p=0.435] were similar in patients with FMF compared to control group. There were no significant differences with regard to LES pressure, LES relaxation, LES relaxation duration, contraction amplitude (mmHg) and peak velocity (sc) among patients with FMF and amyloidosis, amyloidosis negative FMF patients and healthy controls.

**CONCLUSIONS:** Abnormal esophageal manometric findings can be observed at least in a subgroup of patients with FMF regardless of amyloid status. Investigation of esophageal motor function in patients with FMF who exhibit unexplained upper gastrointestinal symptoms between attacks may be a helpful tool in order to delineate esophageal motor dysfunction.

2009 European Federation of Internal Medicine.

DOI: 10.1016/j.ejim.2009.04.005

PMID: 19712864 [Indexed for MEDLINE]

3451. Rheumatol Int. 2010 Nov;30(12):1647-9. doi: 10.1007/s00296-009-1115-0. Epub 2009 Aug 27.

Acute adrenal crisis mimicking familial Mediterranean fever attack in a renal transplant FMF patient with amyloid goiter.

Emeksiz H(1), Bakkaloglu S, Camurdan O, Boyraz M, Soylemezoglu O, Hasanoglu E, Buyan N.

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The most devastating complication of familial Mediterranean fever (FMF) is amyloidosis which is capable of resulting in chronic renal failure. Although amyloid deposits are frequent in adrenal glands based on the autopsies of FMF patients however; to our knowledge, symptomatic adrenal insufficiency has not been reported yet. We describe a 21-year-old-FMF amyloidosis case with a well-functioning allograft who presented to the emergency clinic with the complaints of abdominal pain, vomiting and diarrhea mimicking FMF attack. adrenocorticotrophic hormone stimulation test was performed due to resistant hyponatremia and disclosed Addison disease. In countries with a high prevalence of FMF, adrenal crisis should be borne in mind in long standing FMF patients.

DOI: 10.1007/s00296-009-1115-0

PMID: 19711078 [Indexed for MEDLINE]

3452. Biologics. 2008 Dec;2(4):733-42.

Long term management of patients with cryopyrin-associated periodic syndromes (CAPS): focus on rilonacept (IL-1 Trap).

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Cryopyrin-associated periodic syndromes (CAPS) are a group of inherited inflammatory disorders consisting of familial cold-induced autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID; also known as chronic infantile neurologic, cutaneous, articular [CINCA] syndrome). These rare disorders are associated with heterozygous mutations in the NLRP3 (CIAS1) gene, which encodes the protein NALP3 or cryopyrin, and inflammation driven by excessive production of the cytokine interleukin-1beta (IL-1beta). Amyloidosis is a serious complication with 25% of MWS patients developing amyloidosis, with occasional fatal consequences, whilst up to 20% of CINCA/NOMID patients die from various complications, before reaching the early adulthood. In some CINCA/NOMID adult survivors amyloidosis can also occur. Prior to the discovery of the CIAS1 gene mutations and the advent of IL-1 targeted therapy, treatment was aimed at suppressing inflammation, with limited success. The selective blockade of IL-1beta, with anakinra (IL-1 receptor antagonist), not only provided supportive evidence for the role of IL-1beta in CAPS, but also demonstrated the efficacy of targeting IL-1beta for treatment of these conditions. In February, 2008, 'Orphan Drug' approval from the Food and Drug Administration (FDA) for rilonacept (IL-1 Trap/Arcalyst(), Regeneron Pharmaceuticals, Inc) was given for the treatment of two CAPS disorders, FCAS and MWS in adults and children 12 years and older, making rilonacept the first therapy approved for the treatment of CAPS.

PMCID: PMC2727888

PMID: 19707454

3453. Clin Rheumatol. 2009 Dec;28(12):1389-93. doi: 10.1007/s10067-009-1254-4. Epub 2009 Aug 18.

Does breast-feeding affect severity of familial Mediterranean fever?

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Familial Mediterranean fever (FMF) is the most common inherited autoinflammatory disease, which is caused by an inborn error in innate immune system. It was shown that disease severity of patients of the same ethnic origin differed according to different country of residence, suggesting an influence of environment on phenotype of FMF. Different microbial milieus of the countries were accused. Breast-feeding has an important role on innate immunity and protects the infant from infections. The aim of this study is to investigate whether being breast-fed and duration of breast-feeding has an impact on disease severity of FMF. The mothers of patients were asked to fill a questionnaire about the feeding type in infancy. Mode of delivery, gestational age, and age at onset of FMF symptoms were also asked. The disease severity score of each patient was calculated according to the scoring system suggested by Pras et al. (Am J Med Genet 75:216-219, 1998). MEFV mutations were noted. The mothers of 81 FMF patients completed the questionnaire. Fifteen patients (18.5%) had mild, 49 (60.5%) had moderate, and 17 (21%) had severe disease. All the patients except four were breast-fed for some period. The duration of breast-feeding was similar between three severity groups. Time to introduce cow's milk and complementary foods also did not differ between groups. Longer duration of breast-feeding did not delay the onset of FMF symptoms. Mode of delivery and gestational age had no effect on disease severity. Patients homozygous for M694V had higher severity scores. This preliminary study suggests that breast-feeding is not an exogenous factor having an influence on phenotype of FMF. M694V genotype seems to cause more severe disease.

DOI: 10.1007/s10067-009-1254-4

PMID: 19688293 [Indexed for MEDLINE]

3454. J Eur Acad Dermatol Venereol. 2009 Sep;23 Suppl 1:9-13. doi: 10.1111/j.1468-3083.2009.03363.x.

Enthesitis: an autoinflammatory lesion linking nail and joint involvement in psoriatic disease.

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The traditional model for psoriasis and psoriatic arthritis (PsA) is that autoimmunity directed against a common skin and joint autoantigen leads to chronic autoreactive T cell driven inflammation. However, recent imaging, histological and genetic studies have challenged this view, especially with respect to joint and nail disease, and provide a broader insight into the pathogenesis of PsA and associated nail involvement. Clinically unrecognized enthesitis (inflammation at tendon and ligament attachments) is commonly seen in early PsA at all sites of the disease. Specifically, enthesitis is associated with adjacent osteitis or bone and synovial inflammation. Even in normal joints, normal insertions are associated with microdamage and inflammatory change, strongly suggesting that local tissue specific, or what has been described as autoinflammatory factors, may dictate disease expression. Distal interphalangeal (DIP) joint disease in PsA is associated with diffuse inflammation that envelops the nail root and adjacent bone. In fact, the nail is intimately linked to entheses, with the extension tendon of the DIP joint sending fibres from bone that envelop the nail root in an interdigitating fashion. Furthermore, the joint collateral ligament enthesis has fibres that merge with the lateral borders of the nail. Other anchorage mechanisms include fibres that directly tether the nail plate to the underlying periosteum, which itself is closely anchored to the extension tendon. The frequent microdamage and tissue repair at normal enthesis attachment sites in healthy joints has resulted in a proposed new model of PsA pathogenesis embracing the concept of autoinflammation, whereby tissue specific factors, including microtrauma, lead to regional innate immune activation and persistent inflammation, as an alternative to primary immunopathology driven by T and B cell abnormalities. Unlike the classical autoimmune diseases, which may attack a completely normal organ, autoimmunity in psoriatic disease is likely to involve tissues where there is intrinsic dysregulation of the target tissues. These tissue specific factors related to the enthesis appear to be key to the phenotypic expression of diseases hitherto regarded as autoimmune. The pathogenesis of PsA, nail disease and to a lesser extent psoriasis therefore appear to have an autoinflammatory (innate immune driven) rather than autoimmune basis. Taken together, these findings are important for better understanding PsA, nail disease and psoriasis, and for conceptualizing the immunopathogenic basis of

these diseases and further exploring the role of enthesitis in their pathophysiology.

DOI: 10.1111/j.1468-3083.2009.03363.x

PMID: 19686380 [Indexed for MEDLINE]

3455. Br J Dermatol. 2009 Nov;161(5):1081-8. doi: 10.1111/j.1365-2133.2009.09329.x. Epub 2009 Jun 5.

Cytokine imbalance with increased production of interferon-alpha in psoriasiform eruptions associated with antitumour necrosis factor-alpha treatments.

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**BACKGROUND:** Psoriasiform eruptions occur in association with antitumour necrosis factor (TNF)-alpha treatments in autoinflammatory diseases. The major reported clinical presentation is palmoplantar pustulosis, sometimes accompanied with plaque-like psoriasis. In some reports, histological findings suggest psoriasis whereas others favour a lichenoid drug reaction. We present a case series with a comprehensive clinical, histopathological and immunohistochemical study.

**OBJECTIVES:** To investigate the mechanism involved in psoriasiform eruptions in patients receiving anti-TNF-alpha inhibitors.

**METHODS:** Between July 2004 and May 2008, 13 patients with psoriasiform eruptions arising under anti-TNF-alpha treatment were enrolled in the study. Punch biopsy specimens of lesions were processed for standard and immunohistochemical analyses using antibodies against CD3, CD4, CD8, CD20, CD1a, KP1, CXCR3, CXCL9, Tia1 and MxA, which is specifically induced by type I interferons (IFNs). Additionally, we analysed biopsies from lesional skin of patients with cutaneous discoid lupus erythematosus, lichen planus and psoriasis. Control biopsies were taken from unaffected skin.

**RESULTS:** All patients developed psoriasiform plaques on the body accompanied with palmoplantar keratoderma or pustulosis in three patients. Histological and immunohistochemical findings showed a psoriasiform pattern with focal lichenoid and spongiotic features. We detected strong production of the MxA protein in

inflammatory cells, indicating involvement of type I IFNs, and the expression was higher than in control psoriasis samples. Expression of MxA was closely associated with the recruitment of CXCR3+ lymphocytes in the skin bearing markers of cytotoxic capacity.

CONCLUSIONS: Results support the hypothesis that psoriasiform eruptions are a new model of drug reaction characterized by an increased expression of type I IFNs induced by anti-TNF-alpha.

DOI: 10.1111/j.1365-2133.2009.09329.x

PMID: 19681863 [Indexed for MEDLINE]

3456. Acta Ophthalmol. 2010 Mar;88(2):e5; author reply e6. doi: 10.1111/j.1755-3768.2009.01652.x. Epub 2009 Jul 21.

Colchicine and ocular surface changes in familial Mediterranean fever.

Lazar M, Rothkoff L.

Comment on

Acta Ophthalmol. 2009 Feb;87(1):39-43.

DOI: 10.1111/j.1755-3768.2009.01652.x

PMID: 19681787 [Indexed for MEDLINE]

3457. J Pediatr Gastroenterol Nutr. 2009 Oct;49(4):481-4. doi: 10.1097/MPG.0b013e3181a8152e.

Is familial Mediterranean fever a possible cofactor for Budd-Chiari syndrome?

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DOI: 10.1097/MPG.0b013e3181a8152e

PMID: 19680153 [Indexed for MEDLINE]



3458. Genes Immun. 2009 Dec;10(8):678-86. doi: 10.1038/gene.2009.59. Epub 2009 Aug 13.

A population genetics study of the familial Mediterranean fever gene: evidence of balancing selection under an overdominance regime.

Fumagalli M(1), Cagliani R, Pozzoli U, Riva S, Comi GP, Menozzi G, Bresolin N, Sironi M.

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Familial Mediterranean Fever (FMF) is a recessively inherited systemic autoinflammatory disease caused by mutations in the MEFV gene. The frequency of different disease alleles is extremely high in multiple populations from the Mediterranean region, suggesting heterozygote advantage. Here, we characterize the sequence variation and haplotype structure of the MEFV 3' gene region (from exon 5 to the 3' UTR) in seven human populations. In non-African populations, we observed high levels of nucleotide variation, an excess of intermediate-frequency alleles, reduced population differentiation and a genealogy with two common haplotypes separated by deep branches. These features are suggestive of balancing selection having acted on this region to maintain one or more selected alleles. In line with this finding, an excess of heterozygotes was observed in Europeans and Asians, suggesting an overdominance regime. Our data, together with the earlier demonstration that the MEFV exon 10 has been subjected to episodic positive selection over primate evolution, provide evidence for an adaptive role of nucleotide variation in this gene region. Our data suggest that further studies aimed at clarifying the role of MEFV variants might benefit from the integration of molecular evolutionary and functional analyses.

DOI: 10.1038/gene.2009.59

PMID: 19675583 [Indexed for MEDLINE]

3459. Br J Dermatol. 2009 Oct;161(4):968-70. doi: 10.1111/j.1365-2133.2009.09409.x. Epub 2009 Aug 10.

A novel missense mutation in tumour necrosis factor receptor superfamily 1A (TNFRSF1A) gene found in tumour necrosis factor receptor-associated periodic syndrome (TRAPS) manifesting adult-onset Still disease-like skin eruptions: report of a case and review of the Japanese patients.

Nakamura M, Kobayashi M, Tokura Y.

DOI: 10.1111/j.1365-2133.2009.09409.x

PMID: 19673872 [Indexed for MEDLINE]

3460. Nefrologia. 2009;29(4):373-5. doi: 10.3265/Nefrologia.2009.29.4.5252.en.full.

[Renal amyloidosis in a female with familial Mediterranean fever: clinical response to treatment with colchicine and infliximab].

[Article in Spanish]

Heras M, Sánchez R, Saiz A, Fernández-Reyes MJ, Molina A, Alvarez-Ude F.

DOI: 10.3265/Nefrologia.2009.29.4.5252.en.full

PMID: 19668321 [Indexed for MEDLINE]

3461. Mol Biol Rep. 2010 Jan;37(1):273-6. doi: 10.1007/s11033-009-9677-1. Epub 2009 Aug 6.

Investigation of C5a receptor gene 450 C/T polymorphism in Turkish patients with familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is a genetic disorder with acute inflammatory serosal attacks due to MEFV gene mutations which resides in chromosome 16. Lack of a C5a inhibitor activity in the peritoneum has previously been proposed in

part to contribute in propagation of the serosal inflammation in FMF attacks. The aim of this study is to investigate C5a receptor (C5aR) gene polymorphism in patients with FMF and its relation to the main features of the disease. A polymorphism in the coding region of C5aR gene leading to C to T transition at nucleotide position 450 has been investigated in 85 non-related Turkish FMF patients and 160 non-related healthy controls by using PCR-RFLP. The frequencies of C5aR gene 450 CT genotype and T allele were not significantly different between Turkish FMF patients and healthy subjects (14.12 and 8.24% for FMF vs. 10 and 5% for controls, respectively). C5aR gene 450 CT genotype tended to associate with the presence Henoch-Schonlein purpura (OR: 1.25, 95% CI: 0.917-1.704, P = 0.017) but with no other clinical findings of the disease. C5aR polymorphism might be searched in populations having high prevalence of FMF.

DOI: 10.1007/s11033-009-9677-1

PMID: 19657723 [Indexed for MEDLINE]

3462. Drugs Today (Barc). 2009 Jun;45(6):423-30. doi: 10.1358/dot.2009.45.6.1378935.

Riloncept in the treatment of chronic inflammatory disorders.

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Riloncept (IL-1 Trap/Arcalyst) is a long-acting interleukin-1 (IL-1) blocker developed by Regeneron Pharmaceuticals. Initially, Regeneron entered into a joint development effort with Novartis to develop riloncept for the treatment of rheumatoid arthritis (RA) but this was discontinued following the review of phase II clinical data showing that IL-1 blockade appeared to have limited benefit in RA. In February 2008, Regeneron received Orphan Drug approval from the Food and Drug Administration for riloncept in the treatment of two cryopyrin-associated periodic syndromes (CAPS) disorders, namely, familial cold-induced autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS), for children and adults 12 years and older. CAPS is a group of inherited inflammatory disorders consisting of FCAS, MWS, neonatal-onset multisystem inflammatory

disease (NOMID), also known as chronic infantile neurologic, cutaneous and articular (CINCA) syndrome, all associated with heterozygous mutations in the NLRP3 (CIAS1) gene, which encodes the protein NLRP3 or cryopyrin. Prior to the discovery of the NLRP3 (CIAS1) mutations and the advent of IL-1-targeted therapy, treatment was aimed at suppressing inflammation but with limited success. The dramatic success of selective blockade of IL-1beta, initially with the IL-1 receptor antagonist (IL-1Ra; Kineret(R) or anakinra/ Amgen, Inc.), not only provided supportive evidence for the role of IL-1beta in CAPS but also demonstrated the efficacy of targeting IL-1beta for treatment of these conditions. A high-affinity protein called rilonacept has been produced by cytokine Trap technology and was developed by Regeneron. The desirable longer half-life of rilonacept offers potential alternatives to patients who do not tolerate daily injections very well or have difficulty with drug compliance. The initial evidence for the beneficial effects of rilonacept for MWS and FCAS suggests that it would also be a suitable treatment for CNICA/NOMID. It is yet to be determined whether rilonacept would be an effective treatment for other chronic inflammatory conditions such as gout, familial Mediterranean fever and systemic juvenile idiopathic arthritis.

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DOI: 10.1358/dot.2009.45.6.1378935

PMID: 19649332 [Indexed for MEDLINE]

3463. Nat Rev Drug Discov. 2009 Aug;8(8):605. doi: 10.1038/nrd2953.

IL-1beta-targeted antibody approved for rare autoinflammatory disorders.

[No authors listed]

DOI: 10.1038/nrd2953

PMID: 19644468 [Indexed for MEDLINE]

3464. Med Sci Monit. 2009 Aug;15(8):RA179-87.

Autoinflammatory syndromes behind the scenes of recurrent fevers in children.

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Many children experience recurrent fevers with no easily identifiable source and only a careful follow-up helps in the early identification of other presenting symptoms of other defined conditions which require medical intervention. Autoinflammatory syndromes are rare childhood-onset disorders of the innate immunity in which recurrent flares of fever and inflammation affecting skin, joints, the gastrointestinal tube, or serous membranes are the most striking signs, without any evidence of autoantibody production or underlying infections. Among the pediatric conditions belonging to this group we can consider hereditary recurrent fevers (familial Mediterranean fever, mevalonate kinase deficiency syndrome, tumor necrosis factor receptor-associated periodic syndrome, cryopyrin-associated periodic syndromes), pyogenic disorders (PAPA syndrome, CRMO syndrome, Majeed syndrome), immune-mediated granulomatous diseases (Blau syndrome, Crohn's disease), and idiopathic febrile syndromes (systemic-onset juvenile idiopathic arthritis, PFAPA syndrome, Behçet syndrome). Their genetic background has only been partially elucidated and advances in their molecular pathogenesis are shedding new light on the innate immune system, whilst more and more diseases are being reconsidered at a pathogenetic level and included in this new chapter of postgenomic medicine. The diagnosis of most autoinflammatory syndromes relies on clinical history, demonstration of an increased acute-phase response during inflammatory attacks, and, possibly, genetic confirmation, which is still elusive especially for idiopathic febrile syndromes. This astonishing progress in the awareness and knowledge of autoinflammatory syndromes has anticipated the actual possibilities of medical intervention and rationalized treatment with targeted biologic agents.

PMID: 19644432 [Indexed for MEDLINE]

3465. Curr Opin Rheumatol. 2009 Sep;21(5):552-7. doi: 10.1097/BOR.0b013e32832f142e.

Theoretical and practical basis for early aggressive therapy in paediatric autoimmune disorders.

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**PURPOSE OF REVIEW:** The clinical practice of introducing anti-inflammatory therapies in paediatric autoimmune disorders has changed substantially in the last two decades. This is partly due to the fact that we are able to put disease into remission with potent drugs, and so the issue of when to introduce these drugs is important. This review will seek to highlight the consequences of chronic inflammation and the change to outcomes if adequate or 'aggressive' treatment is given early to induce remission.

**RECENT FINDINGS:** The review not only highlights publications on this topic over the past 12-18 months but also refers to key publications before when appropriate. The disorders reviewed are juvenile idiopathic arthritis, systemic lupus erythematosus, Wegener's granulomatosis, juvenile dermatomyositis, juvenile scleroderma and autoinflammatory syndromes.

**SUMMARY:** Outcomes can be influenced by potent anti-inflammatory therapies. Their use early in the evolution of the disorder in question can limit damage and allow the possibility of normal life and function in the child.

DOI: 10.1097/BOR.0b013e32832f142e

PMID: 19644377 [Indexed for MEDLINE]

3466. Rheumatol Int. 2010 May;30(7):911-5. doi: 10.1007/s00296-009-1073-6. Epub 2009 Jul 30.

Demographic, clinical and mutational characteristics of Turkish familial Mediterranean fever patients: results of a single center in Central Anatolia.

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Clinical and genetic findings of familial Mediterranean fever (FMF) may be variable in different populations. Environmental factors may also affect phenotypic features of FMF. In this study, we investigated demographic, clinical and mutational features of FMF patients who were treated in a single reference hospital in Turkey. Two hundred and sixty patients (169 females, 91 males, mean age 30.44 +/- 10.29 years) were included in this study. All patients were evaluated regarding MEFV gene mutations. The mean age of disease onset was 17.21 +/- 8.66 years (range 2-40 years). The mean duration between the disease onset and diagnosis was 9.39 +/- 8.92 years. Seventy percent of patients had symptoms before 20 years of age (early onset FMF). Arthritis and erysipelas like erythema (ELE) were more common, and the mean duration between the disease onset and diagnosis was longer in early onset FMF patients. The frequency of attacks per year, and disease severity score (DSS) was higher in early onset patients. Homozygote mutation of M694V was detected in 37 (20.2%) and 4 (5.2%) patients in early onset FMF and adult onset FMF groups, respectively ( $p < 0.05$ ). Histological diagnosis of amyloidosis was established in 7 patients (2.7%). The age of disease onset was earlier, and arthritis and ELE were more frequent, and DSS was higher in patients with M694V/M694V mutation. In conclusion, mean delay to diagnosis in our FMF population is quite high. Early and adult onset forms may differ regarding some clinical, molecular and prognostic characteristics. Disease activity was higher in patients with homozygote mutation of M694V.

DOI: 10.1007/s00296-009-1073-6

PMID: 19641922 [Indexed for MEDLINE]

3467. Clin Rheumatol. 2009 Nov;28(11):1331-5. doi: 10.1007/s10067-009-1237-5. Epub 2009 Jul 29.

Evaluation of pathergy test positivity in familial Mediterranean fever patients and comparison of clinical manifestations of FMF with Behçet's disease.

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Familial Mediterranean fever (FMF) shares a number of features with Behçet's disease (BD), such as their common ethnic origin, etiopathogenetic mechanisms, symptoms, and treatment. Pathergy reaction is accepted as a major criterion in BD. We aimed to determine the frequency of pathergy positivity in FMF patients and compared clinical features between FMF and BD. Pathergy test was performed in patients with FMF, BD, and healthy controls. Diagnostic criteria for FMF and BD were screened in both groups. None of the FMF patients or healthy controls yielded positive pathergy test. Pathergy test was positive in 13 out of 31 (41.9%) of the patients with BD. None of the FMF patients fulfilled the International Study Group criteria for BD. None of the BD patients fulfilled the Livneh diagnostic criteria for FMF. BD and FMF are associated with neutrophilic dermatoses and neutrophil hyper-reactivity. Although pathergy test and erysipelas-like erythema share some histological findings, pathergy test was negative among FMF patients.

DOI: 10.1007/s10067-009-1237-5

PMID: 19639361 [Indexed for MEDLINE]

3468. Hum Vaccin. 2009 Aug;5(8):510-9. Epub 2009 Aug 30.

Manipulation of T(H)17 responses in pulmonary immunity and disease through vaccination.

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Since the discovery of a novel subset of CD4(+) T helper cells, T(H)17 cells have been implicated in a wide range of human diseases, including autoimmunity, allergic reactions and autoinflammatory diseases. Conversely, it has also been determined that T(H)17 cells are required to mount a protective immune response to a number of pathogens. It has therefore been of great interest to manipulate T(H)17 responses to either prevent disease or promote immunity. Vaccination is a particularly attractive approach for this manipulation. With a focus on the pulmonary mucosal environment, we herein review T(H)17 responses and potential methods for manipulation.



PMID: 19617711 [Indexed for MEDLINE]

3469. Blood. 2009 Sep 17;114(12):2497-505. doi: 10.1182/blood-2009-02-204925. Epub 2009 Jul 16.

Primed innate immunity leads to autoinflammatory disease in PSTPIP2-deficient cmo mice.

Chitu V(1), Ferguson PJ, de Bruijn R, Schlueter AJ, Ochoa LA, Waldschmidt TJ, Yeung YG, Stanley ER.

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The mouse Lupo (I282N) mutation in proline-serine-threonine phosphatase-interacting protein 2 (PSTPIP2) leads to reduced expression of PSTPIP2 that is associated with a macrophage-mediated autoinflammatory disease. Another mutation in PSTPIP2, L98P, termed chronic multifocal osteomyelitis (cmo), leads to a disease in mice that resembles chronic recurrent multifocal osteomyelitis in humans. The cellular basis of cmo disease was investigated. cmo disease develops independently of lymphocytes and is cured by bone marrow transplantation. Macrophages, mast cells, and osteoclasts from cmo mice fail to express detectable PSTPIP2 protein. Asymptomatic Pstpip2(cmo/cmo) mice have increased circulating levels of macrophage inflammatory protein 1-alpha and interleukin-6, and their macrophages exhibit increased production of these inflammatory mediators, which is normalized by retroviral expression of wild-type PSTPIP2. Spleens of asymptomatic cmo mice contain increased numbers of macrophage precursors, and cmo mice mobilize more macrophage precursors in response to a sterile inflammatory stimulus. Signal transducer and activator of transcription 1 is elevated in cmo splenic macrophages, which also exhibit increased colony-stimulating factor-1-stimulated proliferation and increased extracellular signal-regulated kinase 1/2 phosphorylation. PSTPIP2 overexpression in macrophages leads to the opposite phenotype. Thus, PSTPIP2 deficiency causes both an expansion of macrophage progenitors and increased responsiveness of mature macrophages to activating stimuli, which together prime the organism for

exaggerated and sustained responses leading to autoinflammatory disease.

DOI: 10.1182/blood-2009-02-204925

PMCID: PMC2746474

PMID: 19608749 [Indexed for MEDLINE]

3470. Radiographics. 2009 Jul-Aug;29(4):1159-77. doi: 10.1148/rg.294085244.

Imaging of chronic recurrent multifocal osteomyelitis.

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Chronic recurrent multifocal osteomyelitis (CRMO) is an autoinflammatory disorder of children and young adults that is characterized by nonbacterial osteomyelitis. Patients typically present with multifocal bone pain secondary to sterile osseous inflammation, and the disease has a relapsing and remitting course. The cause of CRMO remains unclear, although the results of several studies have suggested a genetic component. The typical imaging findings of CRMO include lytic and sclerotic lesions in the metaphyses of long bones and the medial clavicles. Other common sites of disease are the vertebral bodies, pelvis, ribs, and mandible. CRMO is often bilateral and multifocal at presentation. Owing to the lack of a diagnostic test, CRMO remains a diagnosis of exclusion. Although generally a self-limiting disease, CRMO can have a prolonged course and result in significant morbidity. Radiologists can be the first to suggest this diagnosis given its characteristic radiographic appearance and distribution of disease. Radiologists should be familiar with the typical imaging findings of CRMO to prevent unnecessary multiple biopsies and long-term antibiotic treatment in children with CRMO.

Copyright RSNA, 2009

DOI: 10.1148/rg.294085244

PMID: 19605663 [Indexed for MEDLINE]

3471. Med Hypotheses. 2009 Oct;73(4):630-1. doi: 10.1016/j.mehy.2009.06.019. Epub 2009 Jul 14.

Altered circadian rhythm: possible trigger of familial Mediterranean fever attacks.

Makay B, Unsal E.

DOI: 10.1016/j.mehy.2009.06.019

PMID: 19604647 [Indexed for MEDLINE]

3472. Protein Pept Lett. 2009;16(7):830-3.

Plasma ghrelin levels in patients with Familial Mediterranean Fever.

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Familial mediterranean fever (FMF) is a familial disease characterized by recurrent episodes of febrile serositis, peritonitis, arthritis and pleuritis. Many studies have been performed is an attempt to understand the basis of the inflammatory attacks in FMF. Ghrelin, a recently described orexigene peptide is predominantly produced by stomach. Ghrelin also exerts multiple regulatory effects on immune system. It has reported that grelin has anti-inflammatory effects. There is currently no published evidence demonstrating a role for anti-inflammatory effects of ghrelin in FMF. For this reason, we investigated the role of plasma ghrelin levels in patients with FMF. Thirty seven patients with FMF and 10 healthy controls (5 female, 5 male; mean age 35.4 +/- 5.6 years) were enrolled in this study. Twenty-one patients were in active stage (10 female, 11 male, mean age; 31.0 +/- 5.4 years, mean disease duration 7.2 +/- 3.3 years) and 16 patients were in inactive stage (7 female, 9 male, mean age; 33.0 +/- 6.0 years, mean disease duration; 8.7 +/- 3.2 years). Plasma ghrelin levels were determined by EIA. The mean plasma ghrelin levels were 158.4 +/- 52.9 pg/ml in patients with FMF and 56.7 +/- 7.5 pg/ml in healthy controls. The mean plasma ghrelin levels were 190.5 +/- 49.4 pg/ml in the active patients and 116.2 +/-

11.7 pg/ml in the inactive patients. Plasma ghrelin levels were significantly high in patients with FMF compared to healthy controls ( $p<0.001$ ). Plasma ghrelin levels were significantly high in the active patients compared to in the inactive patients and healthy controls ( $p<0.001$  and  $p<0.001$  respectively). There was significantly difference between in active and inactive patients with FMF ( $p<0.001$ ). As a results; Plasma ghrelin levels were high both in active and inactive patients with FMF. It is showed that ghrelin may play significant role of the pathogenesis of FMF.

PMID: 19601914 [Indexed for MEDLINE]

3473. Rheumatol Int. 2010 Mar;30(5):667-70. doi: 10.1007/s00296-009-1052-y. Epub 2009 Jul 12.

TLR-2 Arg753Gln, TLR-4 Asp299Gly, and TLR-4 Thr399Ile polymorphisms in Henoch Schonlein purpura with and without renal involvement.

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Infections may trigger or aggravate glomerulonephritidis and renal vasculitis like Henoch Schonlein purpura (HSP). HSP is seen more frequently in patients with familial Mediterranean fever in which TLR-2 Arg753Gln polymorphism frequency is increased. Although renal involvement is the most important factor affecting the prognosis in HSP, it is not known which patients will have renal disease or why some patients have severe renal involvement while some others have mild renal disease. We investigated the role of TLR-2 and TLR-4 polymorphisms on the incidence and severity of renal involvement in HSP patients. We studied HSP patients with and without nephritis ( $n = 15$  for each group) and healthy controls ( $n = 100$ ). TLR-2 Arg753Gln and TLR-4 Asp299Gly/Thr399Ile polymorphisms were analyzed with polymerase chain reaction-restriction fragment length polymorphism method. The frequency of TLR-2 Arg753Gln, TLR-4 Asp299Gly, and Thr399Ile polymorphisms in healthy controls were 1, 3, and 2%, respectively. The frequencies of these polymorphisms were not different in HSP patients with or

without nephritis compared to healthy controls. TLR-2 Arg753Gln, TLR-4 Asp299Gly, and Thr399Ile polymorphisms are not increased in HSP or HSP nephritis patients.

DOI: 10.1007/s00296-009-1052-y

PMID: 19597734 [Indexed for MEDLINE]

3474. Clin Rheumatol. 2009 Oct;28(10):1235-7. doi: 10.1007/s10067-009-1222-z. Epub 2009 Jul 11.

Syndrome of periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) in siblings.

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PFAPA syndrome is characterized by episodes of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis. PFAPA syndrome usually begins in children under 5 years old and normally has self-resolution. The etiology of PFAPA syndrome remains unknown. In this paper, we report the cases of two different families with siblings with PFAPA syndrome: two sisters and two brothers. To our knowledge, this is the first report of siblings with PFAPA syndrome.

DOI: 10.1007/s10067-009-1222-z

PMID: 19593600 [Indexed for MEDLINE]

3475. Rheumatol Int. 2010 Jun;30(8):1089-90. doi: 10.1007/s00296-009-1024-2. Epub 2009 Jul 10.

Uncommon clinical pattern of FMF: protracted febrile myalgia syndrome.

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Familial Mediterranean fever (FMF) is a genetic multisystem disorder of unknown etiology characterized by recurrent episodes of fever and pain due to acute inflammation of the peritoneum, synovia, or pleura. Up to 25% of patients with FMF report muscle pain. Myalgia may be a spontaneous pattern, exercise-induced pattern, or protracted febrile myalgia syndrome (PFMS). PFMS is characterized by severe paralyzing myalgia, high fever, abdominal pain, diarrhea, arthritis/arthritis, and transient vasculitic rashes mimicking Henoch-Schonlein purpura. The episodes last for 4-6 weeks, except in those patients treated with corticosteroids. The PFMS may recur even under colchicine prophylaxis. We describe a 30-year-old pregnant Turkish woman with known FMF and under colchicine prophylaxis, with severe myalgia for 8 weeks, emphasizing the importance of a different clinical pattern of PFMS even in the absence of other symptoms.

DOI: 10.1007/s00296-009-1024-2

PMID: 19590876 [Indexed for MEDLINE]

3476. J Cutan Pathol. 2009 Aug;36(8):901-5. doi: 10.1111/j.1600-0560.2008.01158.x.

Sweet's syndrome in familial Mediterranean fever: possible continuum of the neutrophilic reaction as a new cutaneous feature of FMF.

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Sweet's syndrome (SS) or acute febrile neutrophilic dermatosis is an uncommon disorder that often occurs in association with other systemic diseases. In its systemic manifestation, SS resembles familial Mediterranean fever (FMF) in many aspects. Although the exact pathogenesis of SS and FMF is not yet clear, their clinical similarities and simultaneous occurrence suggest a possible common underlying mechanism and may represent a continuum of a reactive neutrophilic condition.

DOI: 10.1111/j.1600-0560.2008.01158.x

PMID: 19586502 [Indexed for MEDLINE]

3477. PLoS One. 2009 Jul 7;4(7):e6147. doi: 10.1371/journal.pone.0006147.

Pyrin Modulates the Intracellular Distribution of PSTPIP1.

Waite AL(1), Schaner P, Richards N, Balci-Peynircioglu B, Masters SL, Brydges SD, Fox M, Hong A, Yilmaz E, Kastner DL, Reinherz EL, Gumucio DL.

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PSTPIP1 is a cytoskeleton-associated adaptor protein that links PEST-type phosphatases to their substrates. Mutations in PSTPIP1 cause PAPA syndrome (Pyogenic sterile Arthritis, Pyoderma gangrenosum, and Acne), an autoinflammatory disease. PSTPIP1 binds to pyrin and mutations in pyrin result in familial Mediterranean fever (FMF), a related autoinflammatory disorder. Since disease-associated mutations in PSTPIP1 enhance pyrin binding, PAPA syndrome and FMF are thought to share a common pathoetiology. The studies outlined here describe several new aspects of PSTPIP1 and pyrin biology. We document that PSTPIP1, which has homology to membrane-deforming BAR proteins, forms homodimers and generates membrane-associated filaments in native and transfected cells. An extended FCH (Fes-Cip4 homology) domain in PSTPIP1 is necessary and sufficient for its self-aggregation. We further show that the PSTPIP1 filament network is dependent upon an intact tubulin cytoskeleton and that the distribution of this network can be modulated by pyrin, indicating that this is a dynamic structure. Finally, we demonstrate that pyrin can recruit PSTPIP1 into aggregations (specks) of ASC, another pyrin binding protein. ASC specks are associated with inflammasome activity. PSTPIP1 molecules with PAPA-associated mutations are recruited by pyrin to ASC specks with particularly high efficiency, suggesting a unique mechanism underlying the robust inflammatory phenotype of PAPA syndrome.

DOI: 10.1371/journal.pone.0006147

PMCID: PMC2702820

PMID: 19584923 [Indexed for MEDLINE]

3478. Rheumatol Int. 2010 Mar;30(5):617-21. doi: 10.1007/s00296-009-1029-x. Epub 2009 Jul 5.

Association of chronic non-bacterial osteomyelitis with Crohn's disease but not with CARD15 gene variants.

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Chronic non-bacterial osteomyelitis (CNO) is an inflammatory, non-infectious disorder of the skeletal system with unknown etiology. Besides bone-inflammation, patients may present with inflammatory involvement of other tissues. Chronic recurrent multifocal osteomyelitis (CRMO) is the most severe form of CNO. We describe the occurrence of Crohn's disease (CD) in four patients, previously diagnosed with CRMO. Mutations in CARD15, encoding the NOD2 protein, have recently been found in patients with CD. Based on the occurrence of CNO and CD in these four and several reported patients, we hypothesized that CD and CRMO might share a common autoinflammatory process. Thus, we searched for CD associated CARD15 gene variants R702W, G908R and 1007fs in 29 CNO patients, 4 of them additionally diagnosed with CD. In the latter one out of the four showed compound heterozygosity for the gene variants R702W and 1007fs. The allele frequency in the 25 patients diagnosed with CNO but not CD was not different from that already reported in healthy people (R702W 4.0%, G908R 2.0%, 1007fs 2.0%). The occurrence of non-bacterial bone inflammation and granulomatous intestinal inflammation seems to represent an extended phenotype of CD, which partly might be explained by potential disease causing mutations in CARD15. However, CNO without intestinal inflammation is not associated with common CARD15 gene variants. Therefore, other variants of genes coding for proteins involved in innate immunity and inflammation might predispose for the occurrence of CNO.

DOI: 10.1007/s00296-009-1029-x

PMID: 19579029 [Indexed for MEDLINE]



3479. Rheumatol Int. 2010 Mar;30(5):633-6. doi: 10.1007/s00296-009-1037-x. Epub 2009 Jul 5.

MEFV, TNF1rA, CARD15 and NLRP3 mutation analysis in PFAPA.

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PFAPA is a periodic fever disease, of unknown etiology, characterized by aphthous stomatitis, pharyngitis and cervical adenitis. To inquire whether genes implicated in other auto-inflammatory diseases might be involved in its pathogenesis, predominant mutations in the genes causing familial Mediterranean fever, TNF receptor-associated periodic fever syndrome, Crohn's disease and Muckle-Wells syndrome were analyzed in PFAPA patients. Patients (n = 57) with PFAPA, according to previously published criteria were recruited, at the Meyer Children Hospital during 2006-2007. Clinical information was complemented during physicians-parents encounter. Predominant mutations in MEFV, TNF1rA, CARD15/NOD2 and NLRP3 genes were tested. Mean age at diagnosis was 30.64 +/- 16.4 months. Boys (n = 33; 58%) were diagnosed earlier than girls (n = 21; 42%) at 26.18 +/- 13.83 and 36.41 +/- 18.32 months, respectively (P = 0.05). Fifteen patients (27%) carried an MEFV mutation; two patients (3.6%) a CARD15 mutation, one patient (1.8%) a variance in TNF1rA and another had both an MEFV and a CARD15 mutation. Clinical symptoms were equally manifested in carriers and non-carriers. The high carrier rate of MEFV mutations in our PFAPA cases compares well with that of the general population in Israel. It is debated whether MEFV mutations, when mediated by the presence of additional modifiers, may expose a transient fever condition, namely PFAPA.

DOI: 10.1007/s00296-009-1037-x

PMID: 19579027 [Indexed for MEDLINE]

3480. Mod Rheumatol. 2009;19(5):550-5. doi: 10.1007/s10165-009-0196-7. Epub 2009 Jul 4.

QT dispersion and transmural dispersion of repolarization in patients with familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is a disease characterized by sporadic, paroxysmal attacks of fever and serosal inflammation. QT dispersion (QTd) and transmural dispersion of repolarization (TDR), simple noninvasive arrhythmogenic markers, that can be used to assess homogeneity of cardiac repolarization, have not been studied in FMF patients before. The aim of our study was to evaluate the QTd and TDR in FMF patients without overt cardiac involvement. A total of 50 patients with FMF (30 men, 20 women, 29.4 +/- 11.8 years) and 50 controls (30 men, 20 women; mean age 31.3 +/- 11.9 years) were included. QTd, corrected QTd (cQTd), maximum QT (QTmax), maximum corrected QT (cQTmax), minimum QT (QTmin), and minimum corrected QT intervals (cQTmin) and TDR were measured from standard 12-lead electrocardiography (ECG). We found that QTd, QTmax, and TDR were greater in FMF patients than in the control group (36.0 +/- 11.4 vs. 20 +/- 11.2,  $P < 0.001$  and 354.8 +/- 30.9 vs. 342.8 +/- 18.0,  $P = 0.02$ ; 62.0 +/- 16.0 vs. 49.0 +/- 9.5  $P < 0.001$ , respectively), as were cQTd and cQTmax (40.4 +/- 13.5 vs. 21.9 +/- 12.4,  $P < 0.001$  and 397.7 +/- 40.2 vs. 375.5 +/- 25.4  $P = 0.001$ ). A modest positive correlation was found between cQTd and C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) ( $r = 0.30$ ,  $P < 0.001$ ;  $r = 0.40$ ,  $P < 0.001$ ; respectively). QTd, which is an index of inhomogeneity of ventricular repolarization and an important predictor of cardiovascular mortality, and TDR, which is a better marker of cardiac repolarization, increased in FMF patients similarly as in other rheumatologic diseases.

DOI: 10.1007/s10165-009-0196-7

PMID: 19578931 [Indexed for MEDLINE]

3481. Lupus. 2009 Aug;18(9):845-7. doi: 10.1177/0961203309103057.

Childhood stroke in a child with familial Mediterranean fever carrying several prothrombotic risk factors.

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Familial Mediterranean fever (FMF) was recently associated with a hypercoagulable state. However, clinically overt thrombosis remains a rare event limited to patients with other predisposing factors. We herein present a child with FMF who experienced a stroke. An extensive thrombophilia work-up revealed multiple inherited and acquired risk factors. In areas with high prevalence of prothrombotic mutations and in children who are products of consanguineous marriages, early screening for concurrent thrombotic risk factors is warranted; as this may help design an optimal management plan and prevent unfavourable outcomes.

DOI: 10.1177/0961203309103057

PMID: 19578111 [Indexed for MEDLINE]

3482. Curr Opin Rheumatol. 2009 Sep;21(5):538-46. doi: 10.1097/BOR.0b013e32832f13f1.

Progress in pediatric vasculitis.

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**PURPOSE OF REVIEW:** To examine recent advances in the pathophysiology and therapy of pediatric vasculitis.

**RECENT FINDINGS:** The past 2 years have been marked by significant progress in extending novel techniques to the investigation of the two most common pediatric vasculitis syndromes, Henoch-Schonlein purpura and Kawasaki disease. Study of other vasculitides, such as Wegener granulomatosis, Churg-Strauss syndrome, and microscopic polyangiitis, is impeded by the small number of pediatric patients. Nonetheless, national and international registries are beginning to provide the foundation for generation of testable hypotheses regarding pathogenesis and optimal treatment. Thus, recent data from the study of children suggest that

disorders in the control of inflammation, such as those that underlie familial Mediterranean fever and other autoinflammatory diseases, may predispose to vasculitis. Improved knowledge of mechanisms of disease, in turn, should pave the way for more targeted, effective, and tolerable therapies for children with systemic vasculitis.

SUMMARY: International collaboration to study rare disorders such as pediatric vasculitis are demonstrating disorders of inflammatory regulation that predispose to these diseases and may point toward new treatment approaches.

DOI: 10.1097/BOR.0b013e32832f13f1

PMID: 19568171 [Indexed for MEDLINE]

3483. Dev Med Child Neurol. 2009 Jun;51(6):420-8. doi: 10.1111/j.1469-8749.2009.03336.x.

Neurological manifestations of the Mendelian-inherited autoinflammatory syndromes.

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Autoinflammatory syndromes include an expanding list of conditions characterized by unprovoked recurrent attacks of systemic inflammation with lack of auto-antibodies or autoreactive T cells. Many of these syndromes are genetic diseases with a Mendelian inheritance. Neurological manifestations may be one of the major clinical features and, in some cases, the presenting symptom of these syndromes. The purpose of this review is to increase the recognition among neurologists of the Mendelian-inherited autoinflammatory syndromes by highlighting the neurological manifestations in the context of other symptoms that should lead physicians to suspect these syndromes. Most important for neurologists are the cryopyrin-associated periodic syndromes that include familial cold autoinflammatory syndrome, Muckle-Wells syndrome and neonatal-onset multisystem inflammatory disease (called chronic infantile neurological cutaneous and articular syndrome in Europe). We also review other syndromes with less

common neurological involvement, including familial Mediterranean fever, tumor necrosis factor receptor-associated periodic syndrome, and hyperimmunoglobulinemia D syndrome. Because these syndromes are often treatable and irreversible damage is prevented if they are treated early, it is important to recognize the features that may result in these syndromes presenting to a neurologist, especially in early childhood.

DOI: 10.1111/j.1469-8749.2009.03336.x

PMID: 19563585 [Indexed for MEDLINE]

3484. Tissue Antigens. 2009 Sep;74(3):222-7. doi: 10.1111/j.1399-0039.2009.01303.x. Epub 2009 Jun 25.

CTLA4 gene polymorphisms and soluble CTLA4 protein in Behcet's disease.

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Cytotoxic T lymphocyte antigen 4 (CTLA4; CD152) is a costimulatory molecule expressed on activated T cells that plays a key inhibitory role during T lymphocyte activation. The gene encoding for CTLA4 has been suggested as a candidate for conferring susceptibility to autoinflammatory diseases. We investigated the polymorphisms of the CTLA4 gene [promoter region (-1722 T/C, -1661 A/G and -318 C/T) and exon 1 (+49 G/A)] and the differences of serum soluble sCTLA4 levels in 285 patients with Behcet's disease (BD) and 287 controls. The frequency of the CTLA4 -1661 GG genotype was significantly higher in BD patients than in controls [ $P = 0.019$ , odds ratio (OR) = 5.2, 95% confidence interval (CI) = 1.13-23.86]. Also, the genotype frequency for CTLA4 -1722 TC was significantly higher ( $P = 0.014$ , OR = 1.8, 95% CI = 1.13-2.99), while CTLA4 -1722 CC was significantly lower ( $P = 0.018$ , OR = 0.4, 95% CI = 0.20-0.87) in BD patients with ocular lesions compared with patients without this symptom. Serum sCTLA4 levels in BD patients were significantly lower, especially in BD patients with the CTLA4 +49 G allele, than those in healthy controls ( $P < 0.05$ ). Although our understanding of the role of the CTLA4 gene and its protein product in BD is incomplete, these results suggest that single nucleotide polymorphisms of the

promoter and exon regions in the CTLA4 gene are candidates that predispose to BD and that sCTLA4 may be related to the immunological abnormalities and disease expressions associated with BD.

DOI: 10.1111/j.1399-0039.2009.01303.x

PMID: 19563524 [Indexed for MEDLINE]

3485. Nat Immunol. 2009 Aug;10(8):889-98. doi: 10.1038/ni.1748. Epub 2009 Jun 28.

Immunoglobulin D enhances immune surveillance by activating antimicrobial, proinflammatory and B cell-stimulating programs in basophils.

Chen K(1), Xu W, Wilson M, He B, Miller NW, Bengtén E, Edholm ES, Santini PA, Rath P, Chiu A, Cattalini M, Litzman J, Bussell J, Huang B, Meini A, Riesbeck K, Cunningham-Rundles C, Plebani A, Cerutti A.

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Immunoglobulin D (IgD) is an enigmatic antibody isotype that mature B cells express together with IgM through alternative RNA splicing. Here we report active T cell-dependent and T cell-independent IgM-to-IgD class switching in B cells of the human upper respiratory mucosa. This process required activation-induced cytidine deaminase (AID) and generated local and circulating IgD-producing plasmablasts reactive to respiratory bacteria. Circulating IgD bound to basophils through a calcium-mobilizing receptor that induced antimicrobial, opsonizing, inflammatory and B cell-stimulating factors, including cathelicidin, interleukin 1 (IL-1), IL-4 and B cell-activating factor (BAFF), after IgD crosslinking. By showing dysregulation of IgD class-switched B cells and 'IgD-armed' basophils in autoinflammatory syndromes with periodic fever, our data indicate that IgD orchestrates an ancestral surveillance system at the interface between immunity and inflammation.

DOI: 10.1038/ni.1748

PMCID: PMC2785232

PMID: 19561614 [Indexed for MEDLINE]

3486. Rheumatol Int. 2010 Apr;30(6):805-9. doi: 10.1007/s00296-009-0996-2. Epub 2009 Jun 23.

A monoallelic double mutation as a cause for TNF receptor-associated periodic fever syndrome.

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Comment in

Rheumatol Int. 2010 Jul;30(9):1269-71.

Hereditary periodic fever syndromes (HPFSs) are a subset of human autoinflammatory diseases characterized by periodic episodes of fever and signs of inflammation with or without involvement of inner organs. In this paper, we report phenotypic features of an index patient and affected family members that present a previously not described mutation type in the TNFRSF1A gene. The phenotype of a HPFS of affected family members was shown to be associated with two monoallelic mutations in TNFRSF1A. Primarily, the index patient was clinically diagnosed as being affected by familial Mediterranean fever (FMF). However, with molecular genetic analyses, it could be shown that the patient was in fact affected by tumor necrosis factor receptor-associated periodic syndrome, which requires a different therapy when compared with FMF. Thus, molecular genetic analyses of currently known disease loci enable the most precise diagnosis presently available and are consequently the basis for the most effective therapeutic intervention.

DOI: 10.1007/s00296-009-0996-2

PMID: 19547977 [Indexed for MEDLINE]

3487. Br J Anaesth. 2009 Jul;103(1):139. doi: 10.1093/bja/aep158.

Familial Mediterranean fever abdominal pain during spinal anaesthesia.

Sert H, Muslu B, Usta B, Gözdemir M.

DOI: 10.1093/bja/aep158

PMID: 19546210 [Indexed for MEDLINE]

3488. Rheumatology (Oxford). 2009 Aug;48(8):987-91. doi: 10.1093/rheumatology/kep140. Epub 2009 Jun 18.

Incidence of TNFRSF1A mutations in German children: epidemiological, clinical and genetic characteristics.

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**OBJECTIVE:** TNF receptor 1-associated periodic syndrome (TRAPS) is a rare disease belonging to the heterogeneous group of hereditary periodic fever (HPF) syndromes. By their monogenic origins, the HPF syndromes are clearly differentiated from other periodic inflammatory episodes occurring in autoimmune, neoplastic and infectious diseases. We aim to determine the incidence of TRAPS and the spectrum of mutations in the TNFRSF1A gene, and to give a brief survey of clinical signs.

**METHODS:** A prospective surveillance of children with TRAPS was conducted in Germany during a time period of 3 years (2003-06). Monthly inquiries were sent to 370 children's hospitals by the German Pediatric Surveillance Unit (Clinic-ESPED, n1) and to 23 laboratories (Laboratory-ESPED, n2). Inclusion criteria were TNFRSF1A mutation-positive patients < or =16 years of age, more than three self-limiting episodes of fever >38.5 degrees C, and increased inflammation markers. Clinical, epidemiological and genetic data were evaluated via questionnaires.

**RESULTS:** Of the 23 cases included, 19 were identical in 20 clinical and 22 laboratory reports. The incidence of TRAPS in German children was estimated to be approximately 5.6 per 10(7) person-years. In 20 TRAPS patients of the Clinic-ESPED, median age of onset and duration of fever periods were 6 (range 1-16) years and 6.3 (range 2-24) days, respectively. Main symptoms were



arthralgia, abdominal pain, lymphadenopathy, headache and skin involvement. The R92Q substitution was found in 19 (83%) of 23 cases.

CONCLUSION: The incidence of TRAPS is low and corresponds to 6-10 newly diagnosed patients < or =16 years per year in Germany.

DOI: 10.1093/rheumatology/kep140

PMID: 19541728 [Indexed for MEDLINE]

3489. Immunity. 2009 Jun 19;30(6):761-3. doi: 10.1016/j.immuni.2009.06.001.

Knocking in the NLRP3 inflammasome.

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Comment on

Immunity. 2009 Jun 19;30(6):875-87.

Immunity. 2009 Jun 19;30(6):860-74.

Mutations in the human NLRP3 gene cause interleukin-1beta-related autoinflammatory syndromes. In this issue of Immunity, Brydges et al. (2009) and Meng et al. (2009) report the characterization of Nlrp3 gene-targeted mice harboring mutations mimicking those causing disease in humans.

DOI: 10.1016/j.immuni.2009.06.001

PMID: 19538926 [Indexed for MEDLINE]

3490. Ther Clin Risk Manag. 2009 Apr;5(2):385-90. Epub 2009 May 20.

Managing Behçet's disease: An update on current and emerging treatment options.

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Behçet's disease is an autoinflammatory vasculitis of unknown origin characterized by recurrent oral and genital ulcers, uveitis, arthritis and skin lesions. Additionally, involvement of the gastrointestinal tract, central nervous system and large vessels may occur. The disease is prevalent in countries along the ancient Silk Road from Eastern Asia to the Mediterranean Basin. Many treatment modalities are currently available. The choice of treatment depends on organ involvement and severity of disease. Topical treatment with corticosteroids is often sufficient for mucocutaneous involvement, however for more severe disease with vasculitis or neurological involvement a more aggressive approach is warranted. Newer drugs (biologicals) influencing cytokines and thereby T-cell function are promising with an acceptable side effect profile. Unfortunately, reimbursement of the costs of biologicals for rare disease is still a problem in various countries. In this report we discuss the current treatment modalities for Behçet's disease.

PMCID: PMC2697543

PMID: 19536320

3491. Rheumatol Int. 2010 Feb;30(4):467-71. doi: 10.1007/s00296-009-0993-5. Epub 2009 Jun 17.

Antibodies directed to cyclic citrullinated peptides in familial Mediterranean fever.

Uyanik A(1), Albayrak F, Uyanik MH, Dursun H, Keles M, Cetinkaya R.

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(1)Division of Nephrology, Department of Internal Medicine, School of Medicine, Ataturk University, Erzurum, Turkey.

The aim of this study was to find the prevalence of anti-cyclic citrullinated peptide (anti-CCP) in patients with familial Mediterranean fever (FMF) and to examine the relationship between anti-CCP and joint findings. We measured the serum levels of the anti-CCP antibodies in patients with FMF (n = 55) and healthy

controls (n = 43). Serum levels of rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen, ferritin, erythrocyte sedimentation rate (ESR), and white blood cell (WBC) were also measured in all the samples. Fibrinogen, ferritin, erythrocyte sedimentation rate (ESR), and RF levels were normal in the patient and the control groups ( $P > 0.05$ ). There was a significant difference in anti-CCP between the patient and the control groups ( $P = 0.008$ ). There was a positive correlation between arthritis and anti-CCP ( $P = 0.001$ ). In patients without arthritis, there was no significant relationship between abdominal pain or fever and anti-CCP ( $P > 0.05$ ). Anti-CCP levels increased in FMF patients with arthritis independent from acute phase reactants such as CRP, ESR, and fibrinogen. We conclude that in patients who are under investigation for arthritis, the ones with positive anti-CCP and negative RF, may be examined for FMF. In addition, we also conclude that it is very likely that FMF patients with anti-CCP antibodies will have signs of arthritis. On the other hand, it is possible that long-term follow-up of the FMF patients with anti-CCP antibodies may reveal the eventual development of inflammatory joint disease.

DOI: 10.1007/s00296-009-0993-5

PMID: 19533138 [Indexed for MEDLINE]

3492. J Rheumatol. 2009 Aug;36(8):1677-81. doi: 10.3899/jrheum.081313. Epub 2009 Jun 16.

A clinical criterion to exclude the hyperimmunoglobulin D syndrome (mild mevalonate kinase deficiency) in patients with recurrent fever.

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**OBJECTIVE:** The hyperimmunoglobulin D syndrome (HIDS) is an autosomal recessive autoinflammatory disease caused by mutations in the mevalonate kinase gene. Our objective was to define a clinical criterion able to exclude HIDS without the need of genetic testing.

**METHODS:** A recursive partitioning algorithm was applied to derive the clinical

criterion in 149 patients with genetic testing in a French laboratory, among whom 35 had HIDS. The criterion was validated in 93 patients with genetic testing in a Dutch laboratory, among whom 28 had HIDS.

RESULTS: The most discriminatory composite clinical criterion satisfied by all patients with HIDS in the derivation group was [onset age < 5 years old OR (joint pain during attacks AND length of attacks < 14 days)]. It had a sensitivity of 100% (95% confidence interval 88% to 100%) and a specificity of 28% (95% CI 17% to 40%) in the validation group. If genetic testing had been limited to patients fulfilling this criterion, 18 tests (19%) would have been avoided in this highly selected validation sample, without missing a single patient with HIDS.

CONCLUSION: Even among patients already selected by expert physicians, this criterion could help prevent unnecessary genetic testing, which is resource- and time-consuming.

DOI: 10.3899/jrheum.081313

PMID: 19531764 [Indexed for MEDLINE]

3493. J Rheumatol. 2009 Aug;36(8):1671-6. doi: 10.3899/jrheum.081278. Epub 2009 Jun 16.

Clinical and genetic features of familial Mediterranean fever in Japan.

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OBJECTIVE: Familial Mediterranean fever (FMF) is thought to be a rare disorder in Japan, and the clinical features of Japanese patients with FMF remain unclear. Our aim was to elucidate the clinical characteristics of FMF in Japanese patients.

METHODS: We analyzed clinical and genetic data of 80 patients based on the results of a nationwide questionnaire survey and review of the literature.

RESULTS: From clinical findings of 80 Japanese patients, high-grade fever was observed in 98.8%, chest attacks (pleuritis symptoms) in 61.2%, abdominal attacks (peritonitis symptoms) in 55.0%, and arthritis in 27.5%. Twenty-four percent of

patients experienced their first attacks before 10 years of age, 40% in their teens, and 36% after age 20 years. Colchicine was effective in many patients at a relatively low dose (< 1.0 mg/day). AA amyloidosis was seen in only 1 patient. Common MEFV mutation patterns were E148Q/M694I (25.0%), M694I alone (17.5%), and L110P/E148Q/M694I (17.5%), and no patient carried the M694V mutation, the most common mutation in Mediterranean patients with FMF.

CONCLUSION: A larger than expected number of patients with FMF exist in Japan, and the clinical presentation of Japanese FMF patients seems to be relatively milder than those of Mediterranean FMF patients. AA amyloidosis rarely occurs in Japanese patients, probably due to difference in patterns of the MEFV genotype between Japanese and Mediterranean patients.

DOI: 10.3899/jrheum.081278

PMID: 19531756 [Indexed for MEDLINE]

3494. Eur Rev Med Pharmacol Sci. 2009 Mar;13 Suppl 1:51-3.

Clinical features of familial Mediterranean fever: an Italian overview.

Manna R(1), Cerquaglia C, Curigliano V, Fonnesu C, Giovinale M, Verrecchia E, Montalto M, De Socio G, Soriano A, La Regina M, Gasbarrini G.

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Familial Mediterranean Fever (FMF) is the most frequent periodic febrile syndrome among the autoinflammatory syndromes (AS), nowadays considered as innate immunity disorders, characterized by absence of autoantibodies and autoreactive T lymphocytes. FMF is a hereditary autosomal recessive disorder, characterized by recurrent, self-limiting episodes of short duration (mean 24e72 h) of fever and serositis. In FMF, periodic attacks show inter- and intra-individual variability in terms of frequency and severity. Usually, they are triggered by apparently innocuous stimuli and may be preceded by a prodromal period. The Mediterranean FeVer gene (MEFV) responsible gene maps on chromosome 16 (16p13) encoding the Pyrine/Marenostrin protein. The precise pathologic mechanism is still to be definitively elucidated; however a new macromolecular complex, called inflammasome, seems to play a major role in the control of inflammation and it

might be involved in the pathogenesis of FMF. The most severe long-term complication is type AA amyloidosis, causing chronic renal failure. Two types of risk factors, genetic and non-genetic, have been identified for this complication. Currently, the only effective treatment of FMF is the colchicine. New drugs in a few colchicine resistant patients are under evaluation

PMID: 19530512 [Indexed for MEDLINE]

3495. Rheumatol Int. 2010 Apr;30(6):797-9. doi: 10.1007/s00296-009-0990-8. Epub 2009 Jun 9.

Efficacy of cyclosporine A treatment in relapsing febrile lobular panniculitis associated with small vessel vasculitis.

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Weber-Christian Disease (WCD), also known as relapsing febrile lobular non-suppurative panniculitis, is a rare condition characterized by recurrent subcutaneous inflammatory nodules in the adipose tissue in addition to fever, malaise and other systemic manifestations such as polyarthralgia and polymyalgia. The association with small vessel vasculitis has been rarely reported. We report here an unusual case of WCD associated with small vessels vasculitis also describing the efficacy of Cyclosporin A treatment.

DOI: 10.1007/s00296-009-0990-8

PMID: 19506878 [Indexed for MEDLINE]

3496. Int J Immunopathol Pharmacol. 2009 Apr-Jun;22(2):521-4.

Association between familial mediterranean fever and retroperitoneal fibrosis:

retroperitoneal fibrosis regression after colchicine therapy.

De Socio G, Cerquaglia C, Curigliano V, Fonnesu C, Giovinale M, Verrecchia E, Marino GM, Natale L, Gasbarrini GB, Manna R.

Retroperitoneal fibrosis (RPF) is a disease characterized by inflammatory fibrotic processes affecting the retroperitoneal structures. Familial Mediterranean Fever (FMF) is an autosomal recessive disorder, characterized by fever and attacks of sterile serositis. Colchicine is the only suitable drug for prevention of acute episodes. We describe a case of association between RPF and FMF in a 48-year-old male, in whom therapy with colchicine, besides preventing acute episodes, allowed RPF regression. To date the association between FMF and RPF and the use of colchicine therapy alone for RPF has not been described.

DOI: 10.1177/039463200902200229

PMID: 19505404 [Indexed for MEDLINE]

3497. Immunity. 2009 Jun 19;30(6):860-74. doi: 10.1016/j.immuni.2009.04.012. Epub 2009 Jun 4.

A mutation in the Nlrp3 gene causing inflammasome hyperactivation potentiates Th17 cell-dominant immune responses.

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(1)Mucosal Immunity Section, Laboratory of Host Defenses, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA.

Comment in

Immunity. 2009 Jun 19;30(6):761-3.

Missense mutations of the gene encoding NLRP3 are associated with autoinflammatory disorders characterized with excessive production of interleukin-1beta (IL-1beta). Here we analyzed the immune responses of gene-targeted mice carrying a mutation in the Nlrp3 gene equivalent to the human mutation associated with Muckle-Wells Syndrome. We found that antigen-presenting

cells (APCs) from such mice produced massive amounts of IL-1beta upon stimulation with microbial stimuli in the absence of ATP. This was likely due to a diminished inflammasome activation threshold that allowed a response to the small amount of agonist. Moreover, the Nlrp3 gene-targeted mice exhibited skin inflammation characterized by neutrophil infiltration and a Th17 cytokine-dominant response, which originated from hematopoietic cells. The inflammation of Nlrp3 gene-targeted mice resulted from excess IL-1beta production from APCs, which augmented Th17 cell differentiation. These results demonstrate that the NLRP3 mutation leads to inflammasome hyperactivation and consequently Th17 cell-dominant immunopathology in autoinflammation.

DOI: 10.1016/j.immuni.2009.04.012

PMCID: PMC2764254

PMID: 19501001 [Indexed for MEDLINE]

3498. Immunity. 2009 Jun 19;30(6):875-87. doi: 10.1016/j.immuni.2009.05.005. Epub 2009 Jun 4.

Inflammasome-mediated disease animal models reveal roles for innate but not adaptive immunity.

Brydges SD(1), Mueller JL, McGeough MD, Pena CA, Misaghi A, Gandhi C, Putnam CD, Boyle DL, Firestein GS, Horner AA, Soroosh P, Watford WT, O'Shea JJ, Kastner DL, Hoffman HM.

Author information:

(1)Genetics and Genomics Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD 20892, USA.

Comment in

Immunity. 2009 Jun 19;30(6):761-3.

NLRP3 nucleates the inflammasome, a protein complex responsible for cleavage of prointerleukin-1beta (IL-1beta) to its active form. Mutations in the NLRP3 gene cause the autoinflammatory disease spectrum cryopyrin-associated periodic syndromes (CAPS). The central role of IL-1beta in CAPS is supported by the response to IL-1-targeted therapy. We developed two Nlrp3 mutant knockin mouse



strains to model CAPS to examine the role of other inflammatory mediators and adaptive immune responses in an innate immune-driven disease. These mice had systemic inflammation and poor growth, similar to some human CAPS patients, and demonstrated early mortality, primarily mediated by myeloid cells. Mating these mutant mice to various gene mutant backgrounds showed that the mouse disease phenotype required an intact inflammasome, was only partially dependent on IL-1 $\beta$ , and was independent of T cells. These data suggest that CAPS are true inflammasome-mediated diseases and provide insight for more common inflammatory disorders.

DOI: 10.1016/j.immuni.2009.05.005

PMCID: PMC2759865

PMID: 19501000 [Indexed for MEDLINE]

3499. N Engl J Med. 2009 Jun 4;360(23):2467-70. doi: 10.1056/NEJMe0811014.

Interleukin-1 $\beta$  and the autoinflammatory diseases.

Dinarello CA.

Comment on

N Engl J Med. 2009 Jun 4;360(23):2438-44.

N Engl J Med. 2009 Jun 4;360(23):2426-37.

DOI: 10.1056/NEJMe0811014

PMID: 19494224 [Indexed for MEDLINE]

3500. N Engl J Med. 2009 Jun 4;360(23):2438-44. doi: 10.1056/NEJMoa0809568.

An autoinflammatory disease due to homozygous deletion of the IL1RN locus.

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Comment in

N Engl J Med. 2009 Jun 4;360(23):2467-70.

We describe a patient with an autoinflammatory disease in which the main clinical features are pustular rash, marked osteopenia, lytic bone lesions, respiratory insufficiency, and thrombosis. Genetic studies revealed a 175-kb homozygous deletion at chromosome 2q13, which encompasses several interleukin-1 family members, including the gene encoding the interleukin-1-receptor antagonist (IL1RN). Mononuclear cells, obtained from the patient and cultured, produced large amounts of inflammatory cytokines, with increasing amounts secreted after stimulation with lipopolysaccharide. A similar increase was not observed in peripheral-blood mononuclear cells from a patient with neonatal-onset multisystem inflammatory disorder (NOMID). Treatment with anakinra completely resolved the symptoms and lesions.

2009 Massachusetts Medical Society

DOI: 10.1056/NEJMoa0809568

PMCID: PMC2803085

PMID: 19494219 [Indexed for MEDLINE]

3501. N Engl J Med. 2009 Jun 4;360(23):2426-37. doi: 10.1056/NEJMoa0807865.

An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist.

Aksentijevich I(1), Masters SL, Ferguson PJ, Dancey P, Frenkel J, van Royen-Kerkhoff A, Laxer R, Tedgård U, Cowen EW, Pham TH, Booty M, Estes JD, Sandler NG, Plass N, Stone DL, Turner ML, Hill S, Butman JA, Schneider R, Babyn P, El-Shanti HI, Pope E, Barron K, Bing X, Laurence A, Lee CC, Chapelle D, Clarke GI, Ohson K, Nicholson M, Gadina M, Yang B, Korman BD, Gregersen PK, van Hagen PM, Hak AE, Huizing M, Rahman P, Douek DC, Remmers EF, Kastner DL, Goldbach-Mansky R.

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Comment in

N Engl J Med. 2009 Jun 4;360(23):2467-70.

**BACKGROUND:** Autoinflammatory diseases manifest inflammation without evidence of infection, high-titer autoantibodies, or autoreactive T cells. We report a disorder caused by mutations of IL1RN, which encodes the interleukin-1-receptor antagonist, with prominent involvement of skin and bone.

**METHODS:** We studied nine children from six families who had neonatal onset of sterile multifocal osteomyelitis, periostitis, and pustulosis. Response to empirical treatment with the recombinant interleukin-1-receptor antagonist anakinra in the first patient prompted us to test for the presence of mutations and changes in proteins and their function in interleukin-1-pathway genes including IL1RN.

**RESULTS:** We identified homozygous mutations of IL1RN in nine affected children, from one family from Newfoundland, Canada, three families from The Netherlands, and one consanguineous family from Lebanon. A nonconsanguineous patient from Puerto Rico was homozygous for a genomic deletion that includes IL1RN and five other interleukin-1-family members. At least three of the mutations are founder mutations; heterozygous carriers were asymptomatic, with no cytokine abnormalities in vitro. The IL1RN mutations resulted in a truncated protein that is not secreted, thereby rendering cells hyperresponsive to interleukin-1 $\beta$  stimulation. Patients treated with anakinra responded rapidly.

**CONCLUSIONS:** We propose the term deficiency of the interleukin-1-receptor antagonist, or DIRA, to denote this autosomal recessive autoinflammatory disease caused by mutations affecting IL1RN. The absence of interleukin-1-receptor antagonist allows unopposed action of interleukin-1, resulting in life-threatening systemic inflammation with skin and bone involvement.

(ClinicalTrials.gov number, NCT00059748.)

2009 Massachusetts Medical Society

DOI: 10.1056/NEJMoa0807865

PMCID: PMC2876877

PMID: 19494218 [Indexed for MEDLINE]

3502. N Engl J Med. 2009 Jun 4;360(23):2416-25. doi: 10.1056/NEJMoa0810787.

## Use of canakinumab in the cryopyrin-associated periodic syndrome.

Lachmann HJ(1), Kone-Paut I, Kuemmerle-Deschner JB, Leslie KS, Hachulla E, Quartier P, Gitton X, Widmer A, Patel N, Hawkins PN; Canakinumab in CAPS Study Group.

Collaborators: Madhoo S, Berthelot JM, Jorgensen C, Morell-Dubois S, Mouy R, Marie I, Lacassagne S, Chaturvedi R, Vargas C, Block JA, Smith J.

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**BACKGROUND:** The cryopyrin-associated periodic syndrome (CAPS) is a rare inherited inflammatory disease associated with overproduction of interleukin-1. Canakinumab is a human anti-interleukin-1beta monoclonal antibody.

**METHODS:** We performed a three-part, 48-week, double-blind, placebo-controlled, randomized withdrawal study of canakinumab in patients with CAPS. In part 1, 35 patients received 150 mg of canakinumab subcutaneously. Those with a complete response to treatment entered part 2 and were randomly assigned to receive either 150 mg of canakinumab or placebo every 8 weeks for up to 24 weeks. After the completion of part 2 or at the time of relapse, whichever occurred first, patients proceeded to part 3 and received at least two more doses of canakinumab. We evaluated therapeutic responses using disease-activity scores and analysis of levels of C-reactive protein (CRP) and serum amyloid A protein (SAA).

**RESULTS:** In part 1 of the study, 34 of the 35 patients (97%) had a complete response to canakinumab. Of these patients, 31 entered part 2, and all 15 patients receiving canakinumab remained in remission. Disease flares occurred in 13 of the 16 patients (81%) receiving placebo ( $P<0.001$ ). At the end of part 2, median CRP and SAA values were normal ( $<10$  mg per liter for both measures) in patients receiving canakinumab but were elevated in those receiving placebo ( $P<0.001$  and  $P=0.002$ , respectively). Of the 31 patients, 28 (90%) completed part 3 in remission. In part 2, the incidence of suspected infections was greater in the canakinumab group than in the placebo group ( $P=0.03$ ). Two serious adverse events occurred during treatment with canakinumab: one case of urosepsis and an episode of vertigo.

**CONCLUSIONS:** Treatment with subcutaneous canakinumab once every 8 weeks was associated with a rapid remission of symptoms in most patients with CAPS.

(ClinicalTrials.gov number, NCT00465985.)

2009 Massachusetts Medical Society

DOI: 10.1056/NEJMoa0810787

PMID: 19494217 [Indexed for MEDLINE]

3503. Rinsho Byori. 2009 Apr;57(4):371-81.

[Familial Mediterranean fever as representative autoinflammatory disease].

[Article in Japanese]

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Familial Mediterranean fever (FMF) is the most common of the hereditary periodic fevers. FMF is an autosomal recessive disease that affects populations among non-Ashkenazi Jews, Arabs, Turks, and Armenians. Yet, it is observed worldwide, and approximately 90 FMF patients have been reported in Japan. FMF is caused by mutations in the MEFV gene, which encodes the pyrin protein. Pyrin protein is associated with the interleukin (IL)-1-related inflammation cascade and involved in the regulation of apoptosis and inflammation. The clinical characteristics of FMF attacks are fever, abdominal pain, chest pain, and arthritis as symptoms of serositis. Reactive or secondary AA amyloidosis is the most devastating complication of FMF. As amyloid slowly accumulates in various organs and tissues, organ dysfunction ensues prominently in the kidneys. Colchicine has been used in the treatment of FMF, and has markedly changed the course of the disease. Although over 80 mutations in the MEFV gene have been reported, the majority of cases are caused by four mutations in exon 10: M694V, M694I, V726A, and M680I. The majority of Japanese FMF patients are compound heterozygous for M694I/E148Q. E148Q, which is found in populations of Japanese and Chinese, is considered to be a functional polymorphism. It is intriguing that about 10% of Japanese FMF patients have the L110P mutation in addition to E148Q in the same allele. Allelic frequencies of MEFV mutations and polymorphisms in 500 normal Japanese individuals were 0% for M694I and 23% for E148Q, respectively. In conclusion, FMF

is not a rare disease in Japan, and it is necessary to consider FMF when a patient experiences recurrent attacks of fever and serositis.

PMID: 19489440 [Indexed for MEDLINE]

3504. Semin Arthritis Rheum. 2010 Dec;40(3):e1-2. doi: 10.1016/j.semarthrit.2009.03.004. Epub 2009 May 28.

Steroid-resistant protracted febrile myalgia.

Bircan Z.

DOI: 10.1016/j.semarthrit.2009.03.004

PMID: 19481239 [Indexed for MEDLINE]

3505. Turk J Pediatr. 2009 Mar-Apr;51(2):183-6.

Type 1 diabetes mellitus associated with autoimmune thyroid disease, celiac disease and familial Mediterranean fever: case report.

Baş F(1), Kabataş-Eryilmaz S, Günöz H, Darendeliler F, Küçükemre B, Bundak R, Saka N.

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It is known that type 1 diabetes mellitus (type 1 DM) may be associated with other autoimmune diseases. Recently, a patient with an association of type 1 DM and familial Mediterranean fever (FMF) was reported in the medical literature. A 10.5-year-old boy was brought to our clinic with complaints of polydipsia, polyuria and weight loss and was diagnosed as diabetic ketoacidosis due to autoimmune type 1 DM. Insulin therapy was started. Elevated thyroid antibodies associated with diffuse goiter and hypothyroidism led to the diagnosis of autoimmune thyroid disease (ATD), and elevated antiendomysial antibodies and abnormal intestinal biopsy findings led to the diagnosis of celiac disease (CD).

L-thyroxine therapy and gluten-free diet were initiated accordingly. At the third-year of follow-up, acute attacks of fever, abdominal pain and chest pain developed. Laboratory investigations, which were normal between the attacks, revealed elevated erythrocyte sedimentation rate, fibrinogen, white blood cell count and pleural effusion on chest X-ray during the attacks. Molecular analysis for FMF revealed compound heterozygous M694I and V726A. The patient responded well to colchicine therapy started at a dose of 1.5 mg/day. We present the second patient with type 1 DM associated with FMF who also had ATD and CD.

PMID: 19480334 [Indexed for MEDLINE]

3506. Arthritis Rheum. 2009 Jun;60(6):1862-6. doi: 10.1002/art.24570.

Clinical disease among patients heterozygous for familial Mediterranean fever.

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Author information:

(1)Danek Gertner Institute of Human Genetics, Sheba Medical Center, Tel Hashomer, Israel, and Sackler School of Medicine, Tel Aviv University, Ramat Aviv, Israel.

Comment in

Arthritis Rheum. 2009 Jun;60(6):1575-7.

**OBJECTIVE:** To define the molecular basis of familial Mediterranean fever (FMF) in patients with only 1 mutation in the MEFV gene.

**METHODS:** Genetic analysis was performed in 20 FMF patients, including full sequencing of complementary DNA (cDNA) samples and multiplex ligation-dependent probe amplification analysis. In patients with first-degree relatives with FMF, haplotype analysis was also performed.

**RESULTS:** A second mutation was found in 2 patients. In the other 18 patients, we could not identify additional mutations, large genomic deletions, or duplications. Analysis of single-nucleotide polymorphisms along the cDNA ruled out a lack of expression of 1 of the alleles. In 2 of the 3 families in which more than 1 sibling had FMF, we showed that the affected siblings inherited a different MEFV allele from the parent who did not have the MEFV mutation.

**CONCLUSION:** These findings are highly consistent with the existence of a clinical phenotype among some patients who are heterozygous for FMF and could explain the vertical transmission in some families. A single mutation in the MEFV gene may be much more common than was previously thought and may include up to 25% of patients who are diagnosed as having FMF.

DOI: 10.1002/art.24570

PMID: 19479871 [Indexed for MEDLINE]

3507. Arthritis Rheum. 2009 Jun;60(6):1851-61. doi: 10.1002/art.24569.

Familial Mediterranean fever with a single MEFV mutation: where is the second hit?

Booty MG(1), Chae JJ, Masters SL, Remmers EF, Barham B, Le JM, Barron KS, Holland SM, Kastner DL, Aksentijevich I.

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Comment in

Arthritis Rheum. 2009 Jun;60(6):1575-7.

**OBJECTIVE:** Familial Mediterranean fever (FMF) has traditionally been considered an autosomal-recessive disease; however, it has been observed that a substantial number of patients with clinical FMF possess only 1 demonstrable MEFV mutation. The purpose of this study was to perform an extensive search for a second MEFV mutation in 46 patients diagnosed clinically as having FMF and carrying only 1 high-penetrance FMF mutation.

**METHODS:** MEFV and other candidate genes were sequenced by standard capillary electrophoresis. In 10 patients, the entire 15-kb MEFV genomic region was resequenced using hybridization-based chip technology. MEFV gene expression levels were determined by quantitative reverse transcription-polymerase chain reaction. Pyrin protein levels were examined by Western blotting.

**RESULTS:** A second MEFV mutation was not identified in any of the patients who were screened. Haplotype analysis did not identify a common haplotype that might be associated with the transmission of a second FMF allele. Western blots did not



demonstrate a significant difference in pyrin levels between patients with a single mutation and those with a double mutation; however, FMF patients of both types showed higher protein expression as compared with controls and with non-FMF patients with active inflammation. Screening of genes encoding pyrin-interacting proteins identified rare mutations in a small number of patients, suggesting the possibility of digenic inheritance.

CONCLUSION: Our data underscore the existence of a significant subset of FMF patients who are carriers of only 1 MEFV mutation and demonstrate that complete MEFV sequencing is not likely to yield a second mutation. Screening for the set of the most common mutations and detection of a single mutation appears to be sufficient in the presence of clinical symptoms for the diagnosis of FMF and the initiation of a trial of colchicine.

DOI: 10.1002/art.24569

PMCID: PMC2753538

PMID: 19479870 [Indexed for MEDLINE]

3508. Arthritis Rheum. 2009 Jun;60(6):1575-7. doi: 10.1002/art.24565.

Changing concepts in familial Mediterranean fever: is it possible to have an autosomal-recessive disease with only one mutation?

Ozen S.

Comment on

Arthritis Rheum. 2009 Jun;60(6):1862-6.

Arthritis Rheum. 2009 Jun;60(6):1851-61.

DOI: 10.1002/art.24565

PMID: 19479854 [Indexed for MEDLINE]

3509. Rheumatology (Oxford). 2009 Aug;48(8):911-5. doi: 10.1093/rheumatology/kep131. Epub 2009 May 28.

Intima-media thickening in patients with familial Mediterranean fever.

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**OBJECTIVE:** The aim of this study was to assess the frequency of atherosclerotic plaques and intima-media thickness (IMT) in patients with FMF and suitable controls.

**METHODS:** We studied 100 (46 males, 54 females; mean age: 40 +/- 6 years) patients with FMF. Also 94 (15 males, 79 females; mean age: 41 +/- 7 years) patients with SLE and 103 (44 males, 59 females; mean age: 40 +/- 5 years) apparently healthy volunteers were included as the control groups. Subclinical atherosclerosis was assessed by investigating atherosclerotic plaques and measuring IMT from carotid and common femoral arteries using B-mode ultrasonography (USG). Traditional atherosclerotic risk factors were also assessed.

**RESULTS:** Both FMF and SLE patients had significantly higher carotid (C-IMT) and femoral artery IMT (F-IMT) compared with healthy controls. This was also true after adjustment for atherosclerotic risk factors. Only patients with SLE were found to have higher frequency of atherosclerotic plaques in the carotid and in the carotid and/or femoral artery. When all atherosclerotic risk factors were adjusted, again only patients with SLE were found to have risk for atherosclerotic plaques. In FMF, whereas the presence of atherosclerotic plaques was only associated significantly with diabetes mellitus; C-IMT was correlated with age, BMI and fasting glucose; and F-IMT with age and BMI.

**CONCLUSIONS:** Increased atherosclerosis defined as the presence of plaques was not observed in patients with FMF. The significance of increased C- and F-IMT among patients with FMF must be further assessed.

DOI: 10.1093/rheumatology/kep131

PMID: 19478036 [Indexed for MEDLINE]

3510. Med Clin (Barc). 2010 May 15;134(14):661-2. doi: 10.1016/j.medcli.2009.03.004. Epub 2009 May 26.

[Familial Mediterranean fever].

[Article in Spanish]

Nicolás-Sánchez FJ, Aróstegui-Gorospe JI, Encinas Piñol A, Sarrat-Nuevo RM.

DOI: 10.1016/j.medcli.2009.03.004

PMID: 19473678 [Indexed for MEDLINE]

3511. Clin Exp Rheumatol. 2009 Mar-Apr;27(2):354-65.

An update on autoinflammatory diseases. New concepts for new and old diseases.

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The discovery of MEFV as the susceptibility gene for autosomal recessive Familial Mediterranean Fever (FMF) in 1997 represents the beginning of the new era of the monogenic autoinflammatory diseases. During the last decade, the increasing knowledge on the pathogenic mechanisms related to a number of diseases associated to mutations of genes associated to autoinflammatory diseases had a terrific impact on the understanding of pivotal mechanisms regulating the inflammatory response and therefore represents one of the major advance in the field of inflammation. The International Congress on Familial Mediterranean Fever and Systemic Autoinflammatory Diseases brings together the experts in the field every two and a half years and represents a unique opportunity for an update on the recent progress in this growing field. The fifth edition of the congress was held in Rome (Italy, 4-8 April 2008). Most of the contributions to this meeting have been published during the course of the present year. Thus, the aim of the present article is to report the main highlights from the above-mentioned meeting and to give a general update of the more recent advances in this field.

PMID: 19473583 [Indexed for MEDLINE]

3512. Tunis Med. 2008 Aug;86(8):764.

[Association between ankylosing spondylitis and familial Mediterranean fever].

[Article in French]

Chekili S, Laatar A, Ben Abdelghani K, Kassab S, Hajri R, Marhoul LR, Zakraoui L.

PMID: 19472765 [Indexed for MEDLINE]

3513. Br J Haematol. 2009 Sep;146(5):467-78. doi: 10.1111/j.1365-2141.2009.07733.x. Epub 2009 May 14.

Advances in the understanding of familial Mediterranean fever and possibilities for targeted therapy.

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Familial Mediterranean fever (FMF) is a systemic autoinflammatory disorder characterized by seemingly unprovoked recurrent episodes of fever and serosal, synovial, or cutaneous inflammation. FMF is caused by recessively inherited mutations in MEFV, which encodes pyrin, and most of the mutations are present in the C-terminal end of the protein encoding B30.2 domain. The FMF carrier frequencies are extremely high in several eastern Mediterranean populations. Pyrin is expressed in granulocytes, monocytes, dendritic cells, and synovial fibroblasts. Pyrin regulates caspase-1 activation and consequently interleukin-1 $\beta$  production through the interactions of its N-terminal PYRIN domain and C-terminal B30.2 domain with an adaptor protein, apoptosis-associated speck-like protein with a caspase-recruitment domain (ASC) and caspase-1 respectively. Pyrin is cleaved by caspase-1 and the cleaved N-terminal fragment translocates to nucleus and enhances ASC-independent nuclear factor (NF)- $\kappa$ B activation through interactions with p65 NF- $\kappa$ B and I $\kappa$ B- $\alpha$ . In addition to the regulatory role of pyrin for caspase-1, the cleavage of pyrin provides an important clue not only in understanding the molecular pathogenesis of FMF but also in developing new therapeutic targets for FMF.

DOI: 10.1111/j.1365-2141.2009.07733.x

PMCID: PMC2759843

PMID: 19466978 [Indexed for MEDLINE]

3514. *Int J Hematol*. 2009 Jul;90(1):91-93. doi: 10.1007/s12185-009-0336-z. Epub 2009 May 23.

Presentation of familial Mediterranean fever in a heterozygous MEFV mutation triggered by immunosuppressive therapy for myelodysplastic syndrome.

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Familial Mediterranean fever (FMF) is a recessively inherited disease characterized by recurrent episodes of systemic inflammation. The cause of this disease is the mutations affecting both the alleles of MEFV gene. We describe here a case in a heterozygous MEFV mutation complicated with myelodysplastic syndrome (MDS). Clinical symptoms and the effectiveness of colchicines in this patient are typical for FMF. The first attack of FMF in this patient was observed during immunosuppressive therapy for MDS. This case suggests the possibility that certain immunosuppressants may trigger FMF attack in asymptomatic cases carrying MEFV heterozygous mutation.

DOI: 10.1007/s12185-009-0336-z

PMID: 19466506 [Indexed for MEDLINE]

3515. *Rheumatol Int*. 2010 Feb;30(4):531-4. doi: 10.1007/s00296-009-0957-9. Epub 2009 May 23.

A rare cause of refractory ascites in a child: familial Mediterranean fever.

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Comment in

Rheumatol Int. 2011 Jul;31(7):979-80.

Familial Mediterranean fever (FMF) is hereditary episodic febrile syndrome characterized by acute attacks of fever and serosal inflammation, generally lasting 1-3 days and resolves spontaneously. Apart from abdominal pain, patients may present with variety of abdominal manifestations such as acute peritonitis, mechanical intestinal obstruction, diarrhea, bowel infarction, amyloidosis and small amounts of peritoneal fluid during the acute attacks. A 6-year-old boy was admitted with massive ascites. After extensive laboratory investigations, no causative agent could be identified. On subsequent days, he developed fever and skin eruptions. Acute-phase reactants were increased. A second tomography revealed cystic fluid collection near the anterior side of spleen that invades the stomach. An exploratory was performed and histopathological examination of the all resected specimens revealed mix inflammatory cell infiltrate associated with severe myofibroblast proliferation suggesting chronic inflammatory process on the mesenteric region. A diagnosis of FMF was suspected based on the clinical, laboratory and histopathological findings, and a trial of colchicine therapy initiated. Ascites and other serosal inflammations improved within 1 week without any recurrence during the next 12-month period on colchicine treatment. Atypical presentations of FMF have been increasingly reported. Pediatricians should keep FMF in mind in the differential diagnosis of massive ascites especially in regions where hereditary inflammatory disease are common.

DOI: 10.1007/s00296-009-0957-9

PMID: 19466424 [Indexed for MEDLINE]

3516. Rheumatology (Oxford). 2009 Jul;48(7):840-2. doi: 10.1093/rheumatology/kep121. Epub 2009 May 22.

The clinical spectrum of 94 patients carrying a single mutated MEFV allele.

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**OBJECTIVE:** To assess the clinical characteristics of patients living in France and carrying a single MEFV mutation.

**METHOD:** A retrospective chart review of patients referred to us for recurrent fevers. Genetic testing: systematic screening of exons 2 and 10 was performed in the MEFV gene. A subset of patients was also investigated for other auto-inflammatory genes.

**RESULTS:** We analysed 94 patients (sex ratio:1). Forty-two percent of them were Jews and 17% were Arabs. The median age of onset was 2 years (3 months-47 years). Fever was >39 degrees C in 80% of them, while the duration and frequency of an attack varied (<24 h: 8%; 1-3 days: 56%; >3 days: 36%; >2 months: 15%; 1-2 months: 48%; and <1 month: 37%, respectively). Peritonitis occurred in 97%, pleuritis in 25%, arthralgia in 53%; skin rashes in 20%, aphthosis in 18% and lymphadenopathy in 9%. MEFV mutations were M694V (60%) and M694I (7%). The R92Q TRAPS mutation was retrieved in 3/21 patients tested and the V377I MKD mutation in 1/6. Associated diseases in these patients were periodic fever, aphthosis pharyngitis and adenitis syndrome (4), AS (5), Crohn's disease (2) and Castleman's disease (1).

**CONCLUSION:** The clinical picture of French heterozygote patients with recurrent fevers resembles that of homozygote patients. Most of them required colchicine treatment.

DOI: 10.1093/rheumatology/kep121

PMID: 19465590 [Indexed for MEDLINE]

3517. Mol Biol Rep. 2010 Jan;37(1):93-8. doi: 10.1007/s11033-009-9543-1. Epub 2009 May 17.

MEFV mutations in patients with Familial Mediterranean Fever from the Aegean region of Turkey.

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Familial Mediterranean Fever (FMF) which is frequently present in Mediterranean populations is caused by mutations in the MEFV gene. According to recent data, MEFV mutations are not the only cause of FMF, but these are major genetic determinants which cause FMF. It has also been suggested that there may be a number of other genes causing FMF. The MEFV gene is located at 16p13.3 and encodes a protein, pyrin/marenostrin. More than 70 disease associated mutations and totally 186 mutations and polymorphisms have been defined in affected individuals. We have retrospectively evaluated the molecular test results of 1,201 patients identified as having FMF clinical symptoms referred to the Molecular Genetics Laboratory of the Department of Medical Genetics, Faculty of Medicine, Ege University, Izmir/Turkey over the last 4 years. Patients were tested for 12 common mutations in the MEFV gene using a strip assay method (Innogenetics, Belgium). Out of the 1,201 patients tested (2,402 chromosomes) in the Aegean region in Turkey, 654 (54.45%) did not carry any mutations, among the 547 (45.55%) patients with mutations 246 patients were either homozygous (101) or compound heterozygous (145), 296 carried only one detected mutation, and five patients had three mutations. Allelic frequencies for the four most common mutations in the mutation positive groups were 47.60% (M694V), 16.75% (E148Q), 12.95% (V726A), 11.94% (M680I G/C). The remaining alleles (10.76%) showed rare mutations which were R761H, P369S, A744S, K695R, F479L, M694I. When the frequencies of mutations detected in our group were compared to the frequencies reported in the other regions of Turkey, an increase in V726A mutation frequency was observed. No patient showed a I692del mutation which is sometimes evident in other Mediterranean populations.

DOI: 10.1007/s11033-009-9543-1

PMID: 19449169 [Indexed for MEDLINE]



May 16.

Bone mineral density in patients with familial Mediterranean fever.

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This study was carried out to determine lumbar and femoral bone mineral density (BMD) in patients with familial Mediterranean fever (FMF), an autosomal-recessive disease characterized by recurrent episodes of peritonitis, pleuritis, and arthritis, which are usually associated with fever. In patients with FMF and control subjects, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were measured. BMD was determined at the lumbar spine (L1-4) and the femoral regions (neck and total) using dual energy X-ray absorptiometry. Twenty-eight FMF patients and 30 control subjects without a history of inflammatory disease participated in our study. The demographic variables, such as age, sex and body mass index were similar between patients and controls ( $P > 0.05$ ). We found statistically significant difference in ESR and CRP between FMF patients and controls ( $P < 0.01$ ,  $P < 0.05$  respectively). There was statistically significant difference in lumbar spine, femoral neck, and total femur BMD between FMF patients and control groups ( $P < 0.001$ ,  $P < 0.01$ ,  $P < 0.01$  respectively). Our study indicates that lumbar spine and femoral neck and total femur BMD in patients with FMF may be lower than in healthy subjects.

DOI: 10.1007/s00296-009-0950-3

PMID: 19449009 [Indexed for MEDLINE]

3519. Nat Med. 2009 Jun;15(6):623-5. doi: 10.1038/nm.1959.

Netting neutrophils in autoimmune small-vessel vasculitis.

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Comment in

J Am Soc Nephrol. 2009 Aug;20(8):1654-6.

Small-vessel vasculitis (SVV) is a chronic autoinflammatory condition linked to antineutrophil cytoplasm autoantibodies (ANCA). Here we show that chromatin fibers, so-called neutrophil extracellular traps (NETs), are released by ANCA-stimulated neutrophils and contain the targeted autoantigens proteinase-3 (PR3) and myeloperoxidase (MPO). Deposition of NETs in inflamed kidneys and circulating MPO-DNA complexes suggest that NET formation triggers vasculitis and promotes the autoimmune response against neutrophil components in individuals with SVV.

DOI: 10.1038/nm.1959

PMCID: PMC2760083

PMID: 19448636 [Indexed for MEDLINE]

3520. Hum Immunol. 2009 Sep;70(9):750-3. doi: 10.1016/j.humimm.2009.05.004. Epub 2009 May 13.

TLR2 and TLR4 polymorphisms in familial Mediterranean fever.

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It has been suggested that MEVF mutations offer advantage against infections, including tuberculosis. Bearing in mind the central role of TLR-2 and TLR-4 in the recognition of pathogens, we conducted this study to examine whether the TLR2-R753Q, TLR4-D299G, TLR4-T399I common polymorphisms are associated with susceptibility to familial Mediterranean fever (FMF) or affect the course of the disease. A cohort of 169 FMF patients and 245 healthy bone marrow donors were enrolled in the study. FMF patients appeared with a significantly lower frequency

of the TLR4-D299G mutated allele (3.2% vs 6.9%,  $p = 0.032$ ). No association was observed with the other analyzed polymorphisms. Moreover, we found no association between polymorphisms and the frequency of attacks or the development of amyloidosis. Our results may reinforce the hypothesis that FMF patients display a better defense against pathogens, providing an additional mechanism and suggesting a positive selection advantage in the area of the Mediterranean basin.

DOI: 10.1016/j.humimm.2009.05.004

PMID: 19445990 [Indexed for MEDLINE]

3521. World J Gastroenterol. 2009 May 14;15(18):2293-5.

Successful use of adalimumab for treating fistulizing Crohn's disease with pyoderma gangrenosum: Two birds with one stone.

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Crohn's disease (CD) is a chronic relapsing and remitting autoinflammatory disorder of the gastrointestinal tract that has many intestinal and extraintestinal complications. The purpose of treatment is long-term remission, reduction of complications, and improvement of patients' quality of life. In many cases, this can be quite challenging and it is necessary to have a well thought out management strategy. We present the case of a 38-year-old woman with fistulizing CD that manifested as diffuse abdominal pain and bloody diarrhea accompanied by arthralgia. In addition, there were ulcerative lesions surrounded by cutaneous inflammation and erythema on her extremities, indicative of pyoderma gangrenosum. The patient was treated with high doses of parenteral methylprednisolone without any improvement and was started on adalimumab. A positive response to adalimumab therapy was observed: after 2 mo of therapy, the ulcerative skin lesion healed completely and the enterogastric fistula was closed after 5 mo adalimumab treatment. Adalimumab might be a suitable initial as well as maintenance therapy in patients with complicated CD.

PMCID: PMC2682250

PMID: 19437575 [Indexed for MEDLINE]

3522. Internist (Berl). 2009 Jun;50(6):676-84. doi: 10.1007/s00108-009-2302-5.

[Autoinflammatory syndromes].

[Article in German]

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In its strict sense, the term "autoinflammatory syndromes" comprises the hereditary periodic fever syndromes (HPF), which are caused by mutations of pattern-recognition receptors (PRR) and perturbations of the cytokine balance. These include the cryopyrinopathies, familial Mediterranean fever, TNF-receptor associated periodic fever syndrome (TRAPS), hyper-IgD and periodic syndrome (HIDS), pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA) syndrome, NALP12-HPF, and the Blau syndrome. The diseases are characterized by spontaneous activation of cells of the innate immunity in the absence of ligands. Autoantibodies are usually not found. HPF clinically present with recurrent fever episodes and inflammation, especially of serosal and synovial interfaces and the skin. Intriguingly, PRR-mediated autoinflammatory mechanisms also play a role in a number of chronic inflammatory and autoimmune diseases.

DOI: 10.1007/s00108-009-2302-5

PMID: 19434382 [Indexed for MEDLINE]

3523. J Biosoc Sci. 2009 Sep;41(5):575-81. doi: 10.1017/S0021932009003393. Epub 2009 May 12.

Consanguineous marriages in Morocco and the consequence for the incidence of autosomal recessive disorders.

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Consanguineous marriage is traditionally common throughout Arab countries. This leads to an increased birth prevalence of infants with recessive disorders, congenital malformations, morbidity and mortality. The aim of this study was to evaluate the rate of consanguineous marriage in families with autosomal recessive diseases, and to compare it with the average rate of consanguinity in the Moroccan population. The study was conducted in the Department of Medical Genetics in Rabat on 176 families with autosomal recessive diseases diagnosed and confirmed by clinical, radiological, enzymatic or molecular investigations. The rate of consanguinity was also studied in 852 families who had infants with trisomy 21 confirmed by karyotyping. These families were chosen because: (i) there is no association between trisomy 21 and consanguinity, (ii) these cases are referred from different regions of Morocco and (iii) they concern all social statuses. Among 176 families with autosomal recessive disorders, consanguineous marriages comprised 59.09% of all marriages. The prevalence of consanguinity in Morocco was found to be 15.25% with a mean inbreeding coefficient of 0.0065. The differences in the rates of consanguineous marriages were highly significant when comparing the general population and couples with offspring affected by autosomal recessive conditions. These results place Morocco among the countries in the world with high rates of consanguinity. Autosomal recessive disorders are strongly associated with consanguinity. This study better defines the health risks associated with consanguinity for the development of genetic educational guidelines targeted at the public and the health sector.

DOI: 10.1017/S0021932009003393

PMID: 19433002 [Indexed for MEDLINE]

3524. *Pediatr Rheumatol Online J.* 2009 May 7;7:8. doi: 10.1186/1546-0096-7-8.

Rapidly progressive glomerulonephritis in a child with Henoch-Schönlein Vasculitis and familial Mediterranean fever.

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Henoch-Schonlein Vasculitis (HSV) is systemic small vessel vasculitis involving the skin, kidney, joints, and gastrointestinal tract. The proportion of patients reported to have renal involvement varies between 20% and 80%. Rapidly progressive glomerulonephritis (RPGN) is rare syndrome in children, characterized by clinical features of glomerulonephritis (GN) and rapid loss of renal function. We present a severe kidney involvement in a 14 year old boy with HSV in who is carrying MEFV mutation. A 14 year old boy had developed sudden onset of palpable purpuric rash on his extensor surfaces of lower extremities. He had elevated an erythrocyte sedimentation rate (ESR) (45 mm/h), C-reactive protein (3.74 mg/dl), serum urea 66 mg/dl, serum creatinine 1.8 mg/dl. Also, he had hypocomplementemia. Antinuclear antibody, anti ds DNA, antineutrophil cytoplasmic antibody, anticardiolipine antibodies were negative. Urinalysis revealed macroscopic hematuria and proteinuria with a 24-h urinary protein excretion of 55 mg/m<sup>2</sup>/h. The renal biopsy specimen showed crescentic and necrotizing glomerulonephritis. He had also M694V/E148Q compound heterozygote mutation. Clinical symptoms and renal failure resolved with intermittent hemodialysis and medical therapy.

DOI: 10.1186/1546-0096-7-8

PMCID: PMC2685790

PMID: 19422708

3525. Nat Rev Rheumatol. 2009 May;5(5):249-56. doi: 10.1038/nrrheum.2009.40.

Recurrent febrile syndromes: what a rheumatologist needs to know.

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Rheumatologists are likely to be asked to evaluate patients with recurrent febrile syndromes, so it is important that they are familiar with the clinical

and diagnostic features, pathophysiology and therapeutic options for these rare autoinflammatory disorders. These syndromes are all characterized by recurrent episodes of fever and systemic inflammation; however, some syndromes have unique historical and physical features that can help with making a diagnosis. The primary associated morbidity is systemic amyloidosis, usually with renal involvement. Diagnostic testing is mostly limited to genetic testing. NSAIDs, colchicine and corticosteroids have roles in the treatment of some of these disorders, but biologic drugs that target interleukin-1beta are emerging as consistently effective therapies.

DOI: 10.1038/nrrheum.2009.40

PMID: 19412191 [Indexed for MEDLINE]

3526. *Pediatr Rev.* 2009 May;30(5):e34-41. doi: 10.1542/pir.30-5-e34.

Periodic fever syndromes.

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DOI: 10.1542/pir.30-5-e34

PMID: 19411331 [Indexed for MEDLINE]

3527. *Genet Test Mol Biomarkers.* 2009 Jun;13(3):291-3. doi: 10.1089/gtmb.2008.0101.

Screening for Familial Mediterranean Fever M694V and V726A mutations in the Greek population.

Gkretsi V, Deltas C, Yapijakis C, Lamnissou K.

Familial Mediterranean Fever (FMF) is an autosomal recessive genetic disease that primarily affects populations surrounding the Mediterranean basin. FMF patients suffer from recurrent episodes of fever accompanied by abdominal pain, pleuritis, and arthritis. Missense mutations in the gene for FMF (MEFV) have been shown to

be responsible for the disease, while more than 70 mutations have been identified to date. The aim of the present study was to determine the carrier rates of two of the most common MEFV mutations, M694V and V726A, in the general Greek population. A cohort of 220 healthy and unrelated individuals of Greek descent was screened for the two MEFV mutations using the Amplification Refractory Mutation System. Our results showed that none of the healthy individuals tested were carriers of any of the two mutations. In conclusion, our study independently confirms that the carrier rate for the MEFV mutations M694V and V726A is extremely low in the general Greek population.

DOI: 10.1089/gtmb.2008.0101

PMID: 19397405 [Indexed for MEDLINE]

3528. Duodecim. 2009;125(5):542-5.

[Fever from the cold--familial cold autoinflammatory syndrome].

[Article in Finnish]

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Familial cold autoinflammatory syndrome (FCAS) is a dominantly inherited syndrome caused by mutations of the CIAS1 gene. It is characterized by recurrent episodes involving fever, urticaria, articular symptoms and conjunctivitis. The episodes may be associated with exposure to cold. In some families, association with reactive AA amyloidosis has been described for the syndrome. We describe a Finnish family, in which at least 16 persons were affected with FCAS, and one person had been diagnosed with renal amyloidosis.

PMID: 19385344 [Indexed for MEDLINE]

3529. Rheumatol Int. 2009 Dec;30(2):207-12. doi: 10.1007/s00296-009-0937-0.



Tumor necrosis factor receptor 1-associated periodic syndrome without fever: cytokine profile before and during etanercept treatment.

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The objectives of this study are autoinflammatory syndromes which are usually characterized by repeated attacks of fever, especially in children. The presentation of these diseases, however, varies between entities and between patients of a particular syndrome. We report a 16-year-old female patient, who suffered from periodic erythema and myositis/fasciitis. She experienced at least nine attacks of dermatitis and myositis, while no fever episodes were noted over a 3-year period. A delay of puberty with amenorrhea and a short stature were also present. Laboratory investigations consistently showed markedly increased inflammatory parameters (especially a high serum amyloid A) and dysproteinemia. Because the patient's mother complained about chronic and periodic abdominal pain with also persistently elevated inflammatory parameters, the differential diagnosis included hereditary disorders resulting in chronic inflammation. The diagnosis of an inherited tumor necrosis factor receptor (TNFR) 1-associated periodic syndrome (TRAPS) was confirmed by genetic analyses. Long-term anti-inflammatory treatment with etanercept resulted in a significant clinical improvement and reduction of the inflammatory parameters ESR, CRP, interleukin-6, TNF- $\alpha$ , and soluble TNF- $\alpha$  receptor 1, but not of interleukin-12. Monitoring of the cytokine profile suggested partial effectiveness of etanercept in the treatment of TRAPS. Hereditary fever syndromes have to be considered in case of chronic unexplained inflammation even if fever is no presenting symptom.

DOI: 10.1007/s00296-009-0937-0

PMID: 19381634 [Indexed for MEDLINE]

3530. J Hum Genet. 2009 Jun;54(6):369-71. doi: 10.1038/jhg.2009.33. Epub 2009 Apr 17.

MEFV mutation carriage in Israeli Jewish individuals from ethnicities with low risk for familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is a disease caused by mutations in the MEditerranean FeVer gene (MEFV), and in Israel it most commonly affects Jews of North African extraction, in whom the mutation carrier rate is as high as 1 in 5. To assess the protective as well as the modulating affect of MEFV mutation carriage on various inflammatory disease states, we sought to define the frequency of MEFV mutations in Israeli Jewish individuals of various ethnicities, including those with low frequency of FMF, which were not in the focus of our attention hitherto. A total of 163 adults of Bucharian, Turkish, Georgian, Yemenite and Bulgarian origin comprised the study group. The prevalence of the most frequent MEFV mutations in the Israeli Jewish population, namely: M694V, V726A and E148Q, was assessed. The association of mutation carriage with a personal history of FMF-like phenomena, as well as various inflammatory and non-inflammatory diseases, was evaluated. A high MEFV mutation frequency was found among Jews of Bucharian, Georgian and Bulgarian origin (20%), whereas intermediate and low rates were detected in Jews of Turkish and Yemenite extraction (14 and 8%, respectively). FMF-like manifestations and related diseases were observed more often in MEFV mutation carriers than in their counterparts. MEFV mutation frequency, directly assessed by DNA analysis, exceeds the rate calculated from disease prevalence in Israeli Jewish individuals originated from ethnicities with a low prevalence of FMF. MEFV mutation carriage in this subgroup is associated with various inflammatory disorders.

DOI: 10.1038/jhg.2009.33

PMID: 19373257 [Indexed for MEDLINE]

3531. Acta Reumatol Port. 2009 Jan-Mar;34(1):117-9.

Familial mediterranean fever and multiple sclerosis--a case report.

Ugurlu S(1), Bolayir E, Candan F, Gumus C.

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A 30-year old man diagnosed with Familial Mediterranean fever (FMF) 2.5 years ago presented with numbness in his left lower extremity and ataxia. Multiple sclerosis (MS) plaques were founded in his spinal and cranial MRI. The diagnosis of MS was established and steroid treatment was started. FMF and MS coexistence is rare, but should not be missed.

PMID: 19365307 [Indexed for MEDLINE]

3532. J Exp Med. 2009 May 11;206(5):1037-46. doi: 10.1084/jem.20082179. Epub 2009 Apr 13.

Mast cells mediate neutrophil recruitment and vascular leakage through the NLRP3 inflammasome in histamine-independent urticaria.

Nakamura Y(1), Kambe N, Saito M, Nishikomori R, Kim YG, Murakami M, Núñez G, Matsue H.

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Erratum in

J Exp Med. 2009 May 11;206(5):1205. Nishikomori, Ryuta [corrected to Nishikomori, Ryuta].

Urticarial rash observed in cryopyrin-associated periodic syndrome (CAPS) caused by nucleotide-binding oligomerization domain-leucine-rich repeats containing pyrin domain 3 (NLRP3) mutations is effectively suppressed by anti-interleukin (IL)-1 treatment, suggesting a pathophysiological role of IL-1beta in the skin. However, the cellular mechanisms regulating IL-1beta production in the skin of CAPS patients remain unclear. We identified mast cells (MCs) as the main cell population responsible for IL-1beta production in the skin of CAPS patients. Unlike normal MCs that required stimulation with proinflammatory stimuli for

IL-1 $\beta$  production, resident MCs from CAPS patients constitutively produced IL-1 $\beta$ . Primary MCs expressed inflammasome components and secreted IL-1 $\beta$  via NLRP3 and apoptosis-associated speck-like protein containing a caspase recruitment domain when stimulated with microbial stimuli known to activate caspase-1. Furthermore, MCs expressing disease-associated but not wild-type NLRP3 secreted IL-1 $\beta$  and induced neutrophil migration and vascular leakage, the histological hallmarks of urticarial rash, when transplanted into mouse skin. Our findings implicate MCs as IL-1 $\beta$  producers in the skin and mediators of histamine-independent urticaria through the NLRP3 inflammasome.

DOI: 10.1084/jem.20082179

PMCID: PMC2715029

PMID: 19364881 [Indexed for MEDLINE]

3533. J Exp Med. 2009 May 11;206(5):1029-36. doi: 10.1084/jem.20082481. Epub 2009 Apr 13.

In vivo regulation of interleukin 1 $\beta$  in patients with cryopyrin-associated periodic syndromes.

Lachmann HJ(1), Lowe P, Felix SD, Rordorf C, Leslie K, Madhoo S, Wittkowski H, Bek S, Hartmann N, Bosset S, Hawkins PN, Jung T.

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The investigation of interleukin 1 $\beta$  (IL-1 $\beta$ ) in human inflammatory diseases is hampered by the fact that it is virtually undetectable in human plasma. We demonstrate that by administering the anti-human IL-1 $\beta$  antibody canakinumab (ACZ885) to humans, the resulting formation of IL-1 $\beta$ -antibody complexes allowed the detection of in vivo-produced IL-1 $\beta$ . A two-compartment mathematical model was generated that predicted a constitutive production rate of 6 ng/d IL-1 $\beta$  in healthy subjects. In contrast, patients with cryopyrin-associated periodic syndromes (CAPS), a rare monogenetic disease driven by uncontrolled caspase-1 activity and IL-1 production, produced a mean of 31 ng/d. Treatment with canakinumab not only induced long-lasting complete clinical response but also reduced the production rate of IL-1 $\beta$  to normal levels within

8 wk of treatment, suggesting that IL-1beta production in these patients was mainly IL-1beta driven. The model further indicated that IL-1beta is the only cytokine driving disease severity and duration of response to canakinumab. A correction for natural IL-1 antagonists was not required to fit the data. Together, the study allowed new insights into the production and regulation of IL-1beta in man. It also indicated that CAPS is entirely mediated by IL-1beta and that canakinumab treatment restores physiological IL-1beta production.

DOI: 10.1084/jem.20082481

PMCID: PMC2715040

PMID: 19364880 [Indexed for MEDLINE]

3534. Anadolu Kardiyol Derg. 2009 Apr;9(2):148-9; author reply 149-50.

Assessment of aortic stiffness and ventricular functions in familial Mediterranean fever.

Ulusoy RE.

Comment on

Anadolu Kardiyol Derg. 2008 Aug;8(4):271-8.

PMID: 19357062 [Indexed for MEDLINE]

3535. Mil Med. 2009 Mar;174(3):311-4.

Common rheumatic diseases of the Middle East.

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OBJECTIVE: The objective of this article is to educate military physicians and providers about rare, endemic rheumatic diseases that may be encountered in

deployments to the Middle East region, specifically Familial Mediterranean Fever (FMF), Behcet's disease (BD), and tumor necrosis factor-associated periodic syndrome (TRAPS).

METHODS: We found review articles using MDConsult and Ovid.

RESULTS: Suitable articles were employed to describe the characteristics of each disease.

CONCLUSIONS: Although these diseases are considered rare, they can be endemic to current areas of deployment. Awareness of these conditions may prevent unnecessary and invasive treatment as well as make the clinician aware of possible disease complications.

PMID: 19354098 [Indexed for MEDLINE]

3536. Singapore Med J. 2009 Mar;50(3):e116-9.

Familial Mediterranean fever-related spondyloarthropathy.

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Familial Mediterranean fever (FMF) is an autosomal recessively-transmitted disease characterised by attacks of fever and serositis. Articular involvement is the second most common manifestation following abdominal pain. Patients with FMF are considered to have an increased risk of sacroiliitis, while the association of such abnormalities with FMF has not been accepted uniformly. We report two cases of FMF with accompanying seronegative spondyloarthropathy, a 18-year-old boy and a 29-year-old man, and review the literature for FMF-related seronegative spondyloarthropathy.

PMID: 19352557 [Indexed for MEDLINE]

3537. Medicine (Baltimore). 2009 Jan;88(1):23-31. doi: 10.1097/MD.0b013e3181943f5e.

Neutrophilic urticarial dermatosis: a variant of neutrophilic urticaria strongly associated with systemic disease. Report of 9 new cases and review of the literature.

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Comment in

JAMA Dermatol. 2013 Oct;149(10):1245.

JAMA Dermatol. 2013 Oct;149(10):1244-5.

We conducted the current study to define within the spectrum of the neutrophilic dermatoses a group of patients with an urticarial rash clinically and a neutrophilic dermatosis histopathologically. We reviewed the literature on neutrophilic urticaria and we report here a series of patients with this unique presentation. We reviewed all cutaneous biopsies submitted to our department between 2000 and 2006 in which histopathologic evaluation was compatible with this entity. We then retrieved the patient medical records and obtained information about follow-up and associated diseases. This allowed us to identify 9 patients with an urticarial eruption that was characterized histopathologically by a perivascular and interstitial neutrophilic infiltrate with intense leukocytoclasia but without vasculitis and without dermal edema. Four patients also had small foci of necrobiotic collagen bundles. The eruption consisted of pale, flat or only slightly raised, nonpruritic macules, papules, or plaques. Elementary lesions resolved within 24 hours. Purpura, angioedema, and facial swelling were not seen, but dermographism was present in 1 patient. Six patients had fever, 7 had polyarthritis, and 6 had leukocytosis. Seven patients had associated systemic diseases: adult-onset Still disease (3 patients), systemic lupus erythematosus (3 patients), and Schnitzler syndrome (1 patient). A similar rash has been reported previously in the literature, mostly in patients with systemic inflammatory diseases, but the majority of patients reported under the undefined designation of "neutrophilic urticaria" did have a different clinicopathologic presentation. Thus, we suggest naming this eruption "neutrophilic urticarial dermatosis," to emphasize that this entity expands the broad group of cutaneous manifestations of neutrophilic aseptic disease. This entity bears important medical significance as it is strongly indicative of an

associated systemic disease, mainly Schnitzler syndrome, adult-onset Still disease, lupus erythematosus, and the hereditary autoinflammatory fever syndromes.

DOI: 10.1097/MD.0b013e3181943f5e

PMID: 19352297 [Indexed for MEDLINE]

3538. Immunol Res. 2009 Dec;45(2-3):144-58. doi: 10.1007/s12026-009-8096-7. Epub 2009 Apr 7.

Insights into the heterogeneity of human B cells: diverse functions, roles in autoimmunity, and use as therapeutic targets.

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B cells are critical players in the orchestration of properly regulated immune responses, providing protection against infectious agents without inflicting autoinflammatory damage. A balanced B cell compartment is also essential to create protective immunity in response to vaccines. This difficult compromise is achieved through the finely regulated participation of multiple B cell populations with different antibody-dependent and independent functions. Both types of functions allow B cells to powerfully modulate other components of the innate and adaptive immune system. For the most part, however, the necessary division of labor among different B cell populations is poorly understood. B cell dysfunction has been implicated in multiple autoimmune conditions. The physiological importance and complexity of B cell functions has been brought to the fore in recent years by the success of rituximab-based B cell depletion therapy (BCDT) in multiple autoimmune diseases including rheumatoid arthritis (RA) and multiple sclerosis (MS) which are conventionally viewed as T-cell mediated conditions. Given the widespread utilization of BCDT in malignant and autoimmune diseases and the key role of B cells in both protective immunity and pathogenic autoimmunity, a better understanding of B cell functions is of the essence and a focus of the research in our division. We are investigating these issues through a variety of approaches, including the study of the phenotype and



function of human B cell populations in health, their perturbation in autoimmune disease states, the effects of targeted biologic therapies, and the study of relevant murine models.

DOI: 10.1007/s12026-009-8096-7

PMCID: PMC2891332

PMID: 19350211 [Indexed for MEDLINE]

3539. Tohoku J Exp Med. 2009 Apr;217(4):321-7.

Increased serum osteoprotegerin levels associated with decreased bone mineral density in familial Mediterranean fever.

Yuksel S(1), Samli H, Colbay M, Dundar U, Acarturk G, Demir S, Koken T, Aktepe OC, Kavuncu V, Solak M.

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Familial Mediterranean fever (FMF) has episodic or subclinical inflammation that may lead to a decrease in bone mineral density (BMD). The aim of this study was to evaluate the effect of FMF on bone metabolism and to investigate the factors that can influence bone metabolism, such as body mass index (BMI), mutations in Mediterranean fever (MEFV) gene, osteoprotegerin (OPG), leptin and inflammatory cytokines, including interleukin (IL)-1beta, IL-6 and tumor necrosis factor-alpha (TNF-alpha). OPG, a soluble protein produced by osteoblasts, favors increased bone mass. Leptin may influence bone metabolism by acting on differentiated osteoblasts, having anabolic effects on bone. Thirty-one FMF patients in attack-free period (12 females and 19 males; mean age 31.4 +/- 9.3 years) and 18 healthy controls (11 females and 7 males; mean age 34.6 +/- 9.5 years) were compared according to the above parameters. BMD (g/cm(2)) and standard deviation scores (Z-score) were measured at the lumbar spine L(1)-L(4) (BMD-L(1-4)) and proximal femur by dual X-ray absorptiometry. Osteopenia is defined as a Z-score between -1 and -2.5 and osteoporosis is equal or below -2.5. FMF patients showed statistically significant reduction in BMD-L(1-4) and Z-score-L(1-4). Moreover, serum OPG concentration was significantly elevated in FMF patients. In contrast, MEFV gene mutations, leptin and the inflammatory cytokines did not differ between

the patient and control groups. In conclusion, BMD was decreased and OPG was increased in our FMF patients. The high OPG levels may reflect a preventive mechanism against bone loss; namely, OPG might protect the FMF patients from excessive osteoporosis.

PMID: 19346738 [Indexed for MEDLINE]

3540. Expert Opin Biol Ther. 2009 Apr;9(4):519-31. doi: 10.1517/14712590902875518 .

Rilonacept for the treatment of cryopyrin-associated periodic syndromes (CAPS).

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**BACKGROUND:** Cryopyrin-associated periodic syndromes (CAPS) encompass a group of rare inherited, autoinflammatory disorders that represent a spectrum of one disease with varying degrees of severity. Until recently, there was no effective treatment for CAPS, but identification of the genetic basis of CAPS highlighted the pathogenic role of IL-1beta.

**OBJECTIVES:** Rilonacept is a recently FDA approved biologic therapy for CAPS with high affinity for IL-1beta. Limited pharmacological data has been reported to date.

**METHODS:** A review of the pharmacokinetics and pharmacodynamics data as well as the results of a pilot study and Phase III placebo-controlled trials of rilonacept in CAPS. Unpublished data on an open-label extension study in adult and pediatric subjects is also reviewed.

**RESULTS:** Rilonacept produced rapid and profound improvements in symptoms and also reduced high-sensitivity C-reactive protein levels and normalized elevated serum amyloid A concentrations, an important risk factor for amyloidosis. The primary adverse events were injection- site reactions and upper respiratory tract infections.

**CONCLUSION:** Rilonacept, the only IL-1 Trap, is the first of many novel IL-1-targeted therapies being developed. In a very short time it has changed the

lives of CAPS patients.

DOI: 10.1517/14712590902875518

PMID: 19344287 [Indexed for MEDLINE]

3541. Curr Opin Infect Dis. 2009 Jun;22(3):309-15. doi: 10.1097/QCO.0b013e328329d15e.

Current perspectives on familial Mediterranean fever.

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**PURPOSE OF REVIEW:** The gene responsible for familial Mediterranean Fever (FMF), MEditerranean FeVer (MEFV), was identified two decades ago; however, only recent studies have shed light on its pathogenesis. This review focuses on recent studies that have led us to more fully understand FMF pathogenesis.

**RECENT FINDINGS:** The vast majority of FMF-associated mutations are located in the B30.2 (SPRY) domain, which functions as a ligand binding or a signal transduction domain, at the carboxy terminus of the protein. As a result, B30.2 mutations may lead to postponed apoptosis and inflammation due to the reduced ability of pyrin to control interleukin-1beta (IL-1beta) activation. Development of AA amyloidosis is rare in FMF patients without amyloidogenic single nucleotide polymorphisms (SNPs) (713T allele) of the SAA1 gene. High macrophage inflammatory protein-1alpha levels during FMF attacks might be responsible for the enhancement of T-cell mediated immunity in FMF. IL-1beta-511 (C/T), IL-1beta+3953 (C/T) and IL-1Ra VNTR polymorphisms were not associated with the development of amyloid in FMF patients.

**SUMMARY:** Future studies should focus on defining the impact of MEFV and other mutations on the pathological course of FMF, and to understand the exact pathophysiology of those patients who are unresponsive to colchicine, which may help to develop novel therapeutic options for the management and improvement of prognosis.

DOI: 10.1097/QCO.0b013e328329d15e

PMID: 19339884 [Indexed for MEDLINE]

3542. J Gastrointestin Liver Dis. 2009 Mar;18(1):119-20.

Familial Mediterranean Fever coexisting with celiac disease: is there a link with long-term colchicine treatment?

Yilmaz Y, Baran B, Seniz NB, Dolar E.

PMID: 19337649 [Indexed for MEDLINE]

3543. Intern Med. 2009;48(7):523-6. Epub 2009 Apr 1.

Frequency of abdominal surgery in patients with familial Mediterranean fever.

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**OBJECTIVE:** Familial Mediterranean fever (FMF) is characterized by recurrent episodes of peritonitis. Abdominal FMF attacks can be indistinguishable from those of an acute abdominal emergency, and patients may undergo one or more laparotomies before the true nature of their disease is documented. The objectives of this study were to investigate the frequency and reasons for abdominal surgeries performed on patients with FMF.

**METHODS:** We retrospectively reviewed the files of 254 patients with FMF (127 males, 127 females, mean age 27.2+/-6.3 years). We also included 182 healthy individuals for this study (89 males, 93 females, mean age 27.6+/-5 years; range 11-43) to make a comparison between FMF and healthy controls (HC) with respect to frequency of abdominal operations.

**RESULTS:** The number of patients with abdominal surgery in FMF group was 74 (29.1%). The number of surgeries performed in 74 patients with FMF was 92. The first abdominal surgery before the diagnosis of FMF was appendectomy in 68 patients (26.6%). In HC group, the number of abdominal operations was found to be 16 (8.7%). Of these abdominal operations, 9 (4.9%) were due to appendectomy. The

rate of total abdominal operations and appendectomy were significantly higher in FMF group than in HC group ( $p=0.0001$ ).

CONCLUSION: Abdominal attacks of FMF patients may cause an unnecessary laparotomy prior to the diagnosis of FMF. FMF patients can present with abdominal emergency while they are receiving colchicine. Therefore, each abdominal pain should be carefully determined according to clinical findings. The purpose of this study was to emphasize the misdiagnosis of appendicitis.

PMID: 19336953 [Indexed for MEDLINE]

3544. J Bone Miner Res. 2009 Aug;24(8):1493-505. doi: 10.1359/jbmr.090308.

Chronic recurrent multifocal osteomyelitis mimicked in childhood hypophosphatasia.

Whyte MP(1), Wenkert D, McAlister WH, Mughal MZ, Freemont AJ, Whitehouse R, Baildam EM, Coburn SP, Ryan LM, Mumm S.

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Hypophosphatasia (HPP) is the inborn error of metabolism characterized by low serum alkaline phosphatase (ALP) activity caused by inactivating mutations within TNSALP, the gene that encodes the "tissue-nonspecific" isoenzyme of ALP (TNSALP). In HPP, extracellular accumulation of inorganic pyrophosphate, a TNSALP substrate, inhibits hydroxyapatite crystal growth leading to rickets or osteomalacia. Chronic recurrent multifocal osteomyelitis (CRMO) is the pediatric syndrome of periarticular pain and radiographic changes resembling infectious osteomyelitis but without lesional pathogens. Some consider CRMO to be an autoinflammatory disease. An unrelated boy and girl with the childhood form of HPP suffered chronic, multifocal, periarticular pain, and soft tissue swelling. To investigate this unusual complication, we evaluated their cumulative clinical, biochemical, radiological, and histopathological findings and performed mutation analysis of their TNSALP alleles. The earliest radiographic disturbances were typical of childhood HPP. Subsequently, changes consistent with CRMO developed at sites where there was pain, including lucencies, osteosclerosis, and marked

expansion of the underlying metaphyses. Bone marrow edema was shown by MRI. Biopsies of affected bone showed nonspecific histopathological findings and no pathogens. The boy was heterozygous (c.1133A>T, p.D378V) and the girl compound heterozygous (c.350A>G, p.Y117C, c.400\_401AC>CA, p.T134H) for different TNSALP missense mutations. Nonsteroidal anti-inflammatory drugs diminished their pain, which improved or resolved at maturity. HPP should be considered when CRMO is a diagnostic possibility. Metaphyseal radiographic changes and marrow edema associated with periarticular bone pain and soft tissue swelling suggestive of osteomyelitis can complicate childhood HPP.

DOI: 10.1359/jbmr.090308

PMID: 19335222 [Indexed for MEDLINE]

3545. Pathologe. 2009 May;30(3):219-25. doi: 10.1007/s00292-009-1140-5.

[Diagnostics and therapy of AA amyloidosis].

[Article in German]

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AA amyloidosis can be the consequence of any chronic inflammatory disorder. It is most commonly associated with chronic inflammatory rheumatic, pulmonary or gastrointestinal diseases, familial Mediterranean fever or other rare periodic syndromes. AA amyloidosis often affects the kidneys, gastrointestinal tract and the heart. Effective therapy of the underlying disease can normalize the inflammatory reaction and can slow or inhibit the deterioration of organ function if the diagnosis is made at an early stage of the disease. In rheumatoid diseases and in some periodic syndromes the use of antibodies against TNFalpha or IL-1 beta might be helpful. Patients with familial Mediterranean fever should regularly take colchicine to prevent attacks and to reduce the risk for development or progression of AA amyloidosis. Eprodisate is currently being investigated for AA amyloidosis and renal involvement.

DOI: 10.1007/s00292-009-1140-5  
PMID: 19333604 [Indexed for MEDLINE]

3546. Eur J Intern Med. 2009 Mar;20(2):e25-6. doi: 10.1016/j.ejim.2008.07.028. Epub 2008 Sep 4.

Acute myocarditis and Tumor Necrosis Factor Receptor-Associated Periodic (TRAP) syndrome: first case described and discussion.

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DOI: 10.1016/j.ejim.2008.07.028  
PMID: 19327590 [Indexed for MEDLINE]

3547. Fiziol Cheloveka. 2009 Jan-Feb;35(1):107-20.

[Transition from physiological to pathophysiological indices as exemplified by amyloidosis in periodic disease, non-insulin-dependent diabetes mellitus, and Alzheimer's disease].

[Article in Russian]

Piruzian LA, Leksina LA.

PMID: 19323434 [Indexed for MEDLINE]

3548. Ann Saudi Med. 2009 Mar-Apr;29(2):138-41.

Amyloid goiter: two cases and a review of the literature.

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Although involvement of the thyroid gland by amyloid is a relatively common phenomenon, clinically significant enlargement of the thyroid owing to amyloid deposition is an extremely rare occurrence. We describe two cases of amyloid goiter and review the relevant literature. The first case was systemic amyloidosis secondary to familial Mediterranean fever. The second case was a chronic renal failure patient who presented with an enlarged thyroid and upper airway obstructive symptoms. To date, true amyloid goiter secondary to amyloidosis associated with familial Mediterranean fever has only been reported in twelve patients.

PMCID: PMC2813626

PMID: 19318742 [Indexed for MEDLINE]

3549. Clin Pediatr (Phila). 2009 Jun;48(5):561-3. doi: 10.1177/0009922808330775. Epub 2009 Mar 24.

Intermittent fevers, abdominal pain, and elevated inflammatory markers.

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DOI: 10.1177/0009922808330775

PMID: 19318707 [Indexed for MEDLINE]

3550. Genet Test Mol Biomarkers. 2009 Feb;13(1):91-5. doi: 10.1089/gtmb.2008.0081.

Distribution of killer cell immunoglobulin-like receptor (KIR) genotypes in patients with familial Mediterranean fever.



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Genotypic profiles of the natural killer cell immunoglobulin-like receptors (KIR) have been reported to vary among different ethnic groups and variable clinical entities. This study represents the first report on its distribution among patients with familial Mediterranean fever (FMF). We studied 56 unrelated Lebanese FMF patients, had their DNA typed using sequence-specific primer (SSP) technique for the presence of 16 KIR gene and pseudogene loci, and compared them to the general Lebanese population. The AA1 genotype was the most frequent in both the FMF and control groups. Six new KIR profiles were identified. The FMF group showed a higher prevalence of KIR 3DP1\*003 ( $p < 0.05$ ) and an increase in the BB genotype compared with controls. The results lead to an interesting future research question of whether or not KIR genotype is involved in the predisposition to or pathogenesis of FMF. This is the first report that describes the KIR genotypic profile in this important clinical disease.

DOI: 10.1089/gtmb.2008.0081

PMID: 19309280 [Indexed for MEDLINE]

3551. Genet Test Mol Biomarkers. 2009 Feb;13(1):87-90. doi: 10.1089/gtmb.2008.0094.

Detection of MEFV gene mutations in patients with inflammatory bowel disease.

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Inflammatory bowel disease (IBD) with ulcerative colitis (UC) and Crohn's disease (CD) as the most common forms is an inflammation of the gastrointestinal tract. Familial Mediterranean fever (FMF) is another inflammatory disease as well. In

the current study we studied FMF gene mutations in 47 patients with IBD and 25 healthy individuals to investigate the effects of these mutations on the clinical status of IBD. Twelve mutations were analyzed by reverse hybridization after multiplex PCR amplification of DNA samples. We did not find an association between FMF gene mutations and IBD phenotypic characteristics. However, in patients without Mediterranean fever (MEFV) mutations, extraintestinal disease frequencies were higher ( $p < 0.05$ ). IBD has a genetic basis with multiple genes probably playing a role via several pathways during disease progression. Studying other genes interacting with FMF gene in a larger group of patients will add to the knowledge of disease pathogenesis.

DOI: 10.1089/gtmb.2008.0094

PMID: 19309279 [Indexed for MEDLINE]

3552. Orthopade. 2009 Mar;38(3):283-94. doi: 10.1007/s00132-008-1402-6.

[Pediatric osteomyelitis].

[Article in German]

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Bacterial osteomyelitis in children must be diagnosed quickly and requires immediate and adequate antibiotic treatment. Surgical interventions may be necessary. Infants as well as immunodeficient patients suffer more often from hematogenic bone infections than immunocompetent patients. According to recent findings, autoinflammatory nonbacterial osteitis is more probable in immunocompetent patients in good general condition and should always be considered as a differential diagnosis. Diagnostic and therapeutic approaches are presented when childhood osteomyelitis is suspected.

DOI: 10.1007/s00132-008-1402-6

PMID: 19305968 [Indexed for MEDLINE]

3553. Annu Rev Immunol. 2009;27:621-68. doi: 10.1146/annurev.immunol.25.022106.141627.

Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease (\*).

Masters SL(1), Simon A, Aksentijevich I, Kastner DL.

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The autoinflammatory diseases are characterized by seemingly unprovoked episodes of inflammation, without high-titer autoantibodies or antigen-specific T cells. The concept was proposed ten years ago with the identification of the genes underlying hereditary periodic fever syndromes. This nosology has taken root because of the dramatic advances in our knowledge of the genetic basis of both mendelian and complex autoinflammatory diseases, and with the recognition that these illnesses derive from genetic variants of the innate immune system. Herein we propose an updated classification scheme based on the molecular insights garnered over the past decade, supplanting a clinical classification that has served well but is opaque to the genetic, immunologic, and therapeutic interrelationships now before us. We define six categories of autoinflammatory disease: IL-1beta activation disorders (inflammasomopathies), NF-kappaB activation syndromes, protein misfolding disorders, complement regulatory diseases, disturbances in cytokine signaling, and macrophage activation syndromes. A system based on molecular pathophysiology will bring greater clarity to our discourse while catalyzing new hypotheses both at the bench and at the bedside.

DOI: 10.1146/annurev.immunol.25.022106.141627

PMCID: PMC2996236

PMID: 19302049 [Indexed for MEDLINE]

3554. Annu Rev Immunol. 2009;27:519-50. doi: 10.1146/annurev.immunol.021908.132612.

Immunological and inflammatory functions of the interleukin-1 family.

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More than any other cytokine family, the interleukin (IL)-1 family is closely linked to the innate immune response. This linkage became evident upon the discovery that the cytoplasmic domain of the IL-1 receptor type I is highly homologous to the cytoplasmic domains of all Toll-like receptors (TLRs). Thus, fundamental inflammatory responses such as the induction of cyclooxygenase type 2, increased expression of adhesion molecules, or synthesis of nitric oxide are indistinguishable responses of both IL-1 and TLR ligands. Both families nonspecifically affect antigen recognition and lymphocyte function. IL-1 $\beta$  is the most studied member of the IL-1 family because of its role in mediating autoinflammatory diseases. Although the TLR and IL-1 families evolved to assist in host defense against infection, unlike the TLR family, the IL-1 family also includes members that suppress inflammation, both specifically within the IL-1 family but also nonspecifically for TLR ligands and the innate immune response.

DOI: 10.1146/annurev.immunol.021908.132612

PMID: 19302047 [Indexed for MEDLINE]

3555. Annu Rev Immunol. 2009;27:229-65. doi: 10.1146/annurev.immunol.021908.132715.

The inflammasomes: guardians of the body.

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The innate immune system relies on its capacity to rapidly detect invading pathogenic microbes as foreign and to eliminate them. The discovery of Toll-like receptors (TLRs) provided a class of membrane receptors that sense extracellular microbes and trigger antipathogen signaling cascades. More recently,

intracellular microbial sensors have been identified, including NOD-like receptors (NLRs). Some of the NLRs also sense nonmicrobial danger signals and form large cytoplasmic complexes called inflammasomes that link the sensing of microbial products and metabolic stress to the proteolytic activation of the proinflammatory cytokines IL-1 $\beta$  and IL-18. The NALP3 inflammasome has been associated with several autoinflammatory conditions including gout. Likewise, the NALP3 inflammasome is a crucial element in the adjuvant effect of aluminum and can direct a humoral adaptive immune response. In this review, we discuss the role of NLRs, and in particular the inflammasomes, in the recognition of microbial and danger components and the role they play in health and disease.

DOI: 10.1146/annurev.immunol.021908.132715

PMID: 19302040 [Indexed for MEDLINE]

3556. Amyloid. 2009 Mar;16(1):54-9. doi: 10.1080/13506120802676740.

Concomitant amyloidosis, renal papillary carcinoma and ipsilateral pelvicalyceal urothelial carcinoma in a patient with familial Mediterranean fever.

Kirkpantur A, Baydar DE, Altun B, Karcaaltincaba M, Aki T, Yuksel S, Turgan C.

We report a case of a 58-year-old man with a history of long standing familial Mediterranean fever (FMF) and AA amyloidosis, who developed renal papillary carcinoma and renal pelvic urothelial carcinoma simultaneously. Although the association between chronic inflammatory states like FMF and AA amyloidosis has been well established, the relationship between amyloidosis and solid tumors is not defined as clearly. Furthermore, to the best of our knowledge, co-existence of two different types of kidney malignancy with amyloidosis in a patient with FMF has not been reported. Our patient was admitted to hospital with gross hematuria and renal insufficiency. Imaging studies revealed mass lesions in the middle portion of the right kidney. Right radical nephrectomy showed extensive amyloid deposition, co-existing with renal papillary carcinoma and poorly differentiated invasive urothelial carcinoma.

DOI: 10.1080/13506120802676740

PMID: 19291516 [Indexed for MEDLINE]

3557. Arthritis Res Ther. 2009;11(1):216. doi: 10.1186/ar2619. Epub 2009 Feb 23.

Recent developments in anti-rheumatic drugs in pediatrics: treatment of juvenile idiopathic arthritis.

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Juvenile idiopathic arthritis (JIA) is the most common autoimmune-autoinflammatory disease in childhood and affects approximately 1 in 1,000 children. Despite advances in diagnosis and treatment options, JIA remains a chronic condition for most affected children. Recent evidence suggests that disease control at onset may determine the tempo of subsequent disease course and long-term outcomes, and raises the concept of a therapeutic window of opportunity in patients with JIA. This underscores the importance of early aggressive treatment in patients with JIA. With the advent of novel biologic therapeutics, the repertoire of agents available for treatment of children with JIA has greatly increased. The present article will summarize recent developments in the medical treatment of children with JIA and will offer insights into emerging therapies.

DOI: 10.1186/ar2619

PMCID: PMC2688259

PMID: 19291269 [Indexed for MEDLINE]

3558. Immunol Rev. 2009 Mar;228(1):312-24. doi: 10.1111/j.1600-065X.2008.00747.x.

PEST family phosphatases in immunity, autoimmunity, and autoinflammatory disorders.

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The proline-, glutamic acid-, serine- and threonine-rich (PEST) family of protein tyrosine phosphatases (PTPs) includes proline-enriched phosphatase (PEP)/lymphoid tyrosine phosphatase (LYP), PTP-PEST, and PTP-hematopoietic stem cell fraction (HSCF). PEP/LYP is a potent inhibitor of T-cell activation, principally by suppressing the activity of Src family protein tyrosine kinases (PTKs). This function seems to be dependent, at least in part, on the ability of PEP to bind C-terminal Src kinase (Csk), a PTK also involved in inactivating Src kinases. Interestingly, a polymorphism of LYP in humans (R620W) is a significant risk factor for autoimmune diseases including type 1 diabetes, rheumatoid arthritis, and lupus. The R620W mutation may be a 'gain-of-function' mutation. In non-hematopoietic cells, PTP-PEST is a critical regulator of adhesion and migration. This effect correlates with the aptitude of PTP-PEST to dephosphorylate cytoskeletal proteins such as Cas, focal adhesion associated-kinase (FAK), Pyk2, and PSTPIP. While not established, a similar function may also exist in immune cells. Additionally, overexpression studies provided an indication that PTP-PEST may be a negative regulator of lymphocyte activation. Interestingly, mutations in a PTP-PEST- and PTP-HSCF-interacting protein, PSTPIP1, were identified in humans with pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome and familial recurrent arthritis, two autoinflammatory diseases. These mutations abrogate the ability of PSTPIP1 to bind PTP-PEST and PTP-HSCF, suggesting that these two PTPs may be negative regulators of inflammation.

DOI: 10.1111/j.1600-065X.2008.00747.x

PMID: 19290936 [Indexed for MEDLINE]

3559. Clin Rheumatol. 2009 Aug;28(8):975-8. doi: 10.1007/s10067-009-1148-5. Epub 2009 Mar 13.

Mean platelet volume in children with familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is the most common inherited periodic fever syndrome characterized by recurrent episodes of serositis. Recently, a few studies have suggested that FMF is related to increased risk of atherosclerosis. Mean platelet volume (MPV) is a marker of platelet activation. Larger platelets are associated with increased atherosclerosis risk. The aim of the study is to evaluate levels of MPV in pediatric FMF patients during and between attacks. The study consisted of 48 patients during an attack (group 1), 63 patients in attack-free period (at least 2 weeks after an attack, group 2), and 49 healthy controls (group 3). Erythrocyte sedimentation rate, C-reactive protein, white blood cell count, platelet count (PLT), and MPV levels were retrospectively recorded from the computerized patient database. Mean platelet volume was significantly lower in FMF patients during attack than in attack-free period ( $p = 0.00$ ); however, there was no difference among attack-free patients and healthy controls ( $p = 0.38$ ). The mean platelet counts of FMF patients during attack were higher than the healthy controls ( $p = 0.02$ ). There was an inverse correlation between MPV and mean PLT in the attack-free period ( $r = -0.446$ ,  $p = 0.01$ ). This study suggests that an early atherosclerosis marker, MPV, is not elevated in pediatric FMF patients on colchicine treatment.

DOI: 10.1007/s10067-009-1148-5

PMID: 19283330 [Indexed for MEDLINE]

3560. Nihon Rinsho. 2009 Mar;67(3):626-36.

[Autoinflammatory syndrome].

[Article in Japanese]

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The autoinflammatory syndromes include a group of inherited diseases that are characterized by 1) seemingly unprovoked episodes of systemic inflammations, 2) absence of high titer of autoantibody or auto-reactive T cell, and 3) inborn



error of innate immunity. In this article, we will focus on the clinical features, the pathogenesis related the genetic defects, and the therapeutic strategies in the representative disorders including familial Mediterranean fever (FMF), TNF receptor associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndrome (CAPS), hyper-IgD with periodic fever syndrome (HIDS), syndrome of pyogenic arthritis with pyoderma gangrenosum and acne (PAPA), and Blau syndrome. Recent advances in genetics and molecular biology have proceeded our understanding of the pathogenesis of autoinflammatory syndromes.

PMID: 19280943 [Indexed for MEDLINE]

3561. Pacing Clin Electrophysiol. 2009 Mar;32(3):308-13. doi: 10.1111/j.1540-8159.2008.02237.x.

Assessment of atrial conduction time in patients with familial Mediterranean fever.

Acar G(1), Akcay A, Sayarlioglu M, Sokmen A, Sokmen G, Koroglu S, Gunduz M, Ispiroglu M, Tuncer C.

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**BACKGROUND:** Increased inflammatory activity is known to be a pathophysiologic characteristic of atrial fibrillation. Familial Mediterranean fever (FMF) is a disease characterized by recurrent and sustained increased inflammatory activity. Atrial conduction abnormalities in these patients have not been investigated in terms of P-wave duration, P-wave dispersion (Pd), and atrial electromechanical delay measured by tissue Doppler echocardiography (TDE). We aimed to assess atrial conduction time in patients with FMF.

**METHODS:** A total of 33 patients with FMF (13 males/20 females, 28.4 +/- 12.5 years), and 33 controls (13 males/20 females, 28.5 +/- 12.1 years) were included. Atrial electromechanical coupling (PA) and intra- and interatrial electromechanical delay were measured with TDE. From the 12-lead electrocardiogram Pd was calculated.

**RESULTS:** Atrial electromechanical coupling at the left lateral mitral annulus (PA

lateral) was significantly higher in FMF patients (58.0 +/- 9.0 vs 51.0 +/- 5.8,  $P < 0.001$ ). Interatrial (PA lateral-PA tricuspid) and intraatrial electromechanical delay (PA septum-PA tricuspid) were significantly longer in FMF patients (21.3 +/- 7.4 vs 12.9 +/- 4.6,  $P < 0.001$  and 4.7 +/- 5.5 vs 2.1 +/- 1.7,  $P = 0.01$ , respectively). Also, Pd and maximum P-wave duration were significantly higher in FMF patients (42.8 +/- 7.9 vs 35.3 +/- 6.1,  $P < 0.001$  and 98.6 +/- 9.0 vs 93.1 +/- 8.5,  $P = 0.01$ , respectively). A positive correlation was detected between interatrial electromechanical delay and Pd ( $r = 0.622$ ,  $P < 0.001$ ). Plasma level of C-reactive protein (CRP) correlated with interatrial electromechanical delay and Pd ( $r = 0.733$ ,  $P < 0.001$ ; and  $r = 0.427$ ,  $P < 0.001$ , respectively).  
CONCLUSION: This study shows that atrial electromechanical delay and Pd are prolonged in FMF patients. Atrial electromechanical delay is closely associated with Pd and plasma level of CRP.

DOI: 10.1111/j.1540-8159.2008.02237.x

PMID: 19272059 [Indexed for MEDLINE]

3562. J Am Soc Echocardiogr. 2009 May;22(5):542.e5-7. doi: 10.1016/j.echo.2009.01.022. Epub 2009 Mar 9.

A case of systemic amyloidosis following ankylosing spondylitis associated with congestive heart failure.

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Secondary (amyloid A [AA]) amyloidosis is a systemic disease characterized by amyloid deposition in many organs, leading to impaired function. Although cardiac involvement may occur with AA amyloidosis, significant deposition of amyloid in the heart is considered an infrequent observation and is rarely the cause of death. It occurs in 5% of patients with poorly controlled chronic inflammatory disease, mainly rheumatoid arthritis, ankylosing spondylitis, and familial Mediterranean fever. The authors report a case of AA amyloidosis diagnosed by rectal and skin biopsies, with cardiac involvement demonstrated by typical echocardiographic features in the presence of low voltage on electrocardiography.

DOI: 10.1016/j.echo.2009.01.022

PMID: 19269784 [Indexed for MEDLINE]

3563. Clin Pediatr (Phila). 2009 Jul;48(6):679-82. doi: 10.1177/0009922809333090. Epub 2009 Mar 4.

Recurrent fever and rash.

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Periodic fever is uncommon in children. The differential diagnosis is large, even though associated symptoms such as rash may help narrow the differential diagnosis. Atypical presentations require thoughtful evaluation. This article describes a case of a 4-year-old boy who presented to the emergency department with recurrent fever, vomiting, abdominal pain, myalgias, and rash. His hospital course is described along with a review on the background, evaluation, management, and complications of tumor necrosis receptor-1 alpha periodic syndrome.

DOI: 10.1177/0009922809333090

PMID: 19264716 [Indexed for MEDLINE]

3564. Genes Immun. 2009 Apr;10(3):273-9. doi: 10.1038/gene.2009.8. Epub 2009 Mar 5.

Characterization of new mutations in the 5'-flanking region of the familial Mediterranean fever gene.

Notarnicola C(1), Boizet-Bonhoure B, de Santa Barbara P, Osta MA, Cattani D, Touitou I.

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Familial Mediterranean fever (FMF) is a recessive autoinflammatory disease commonly found in the Mediterranean populations. Genetic diagnosis has developed since the discovery of the causative gene MEFV in 1997. As many patients could not be confirmed genetically by routine exon screening, we searched for mutations in the 5'-flanking region of this gene. Using denaturing gradient gel electrophoresis, we screened DNA from 108 patients with clinical FMF and 91 asymptomatic individuals. We found six novel sequence variants in a region extending -825 bp upstream of the first translated codon. To investigate the potential role of these variants in altering MEFV gene expression, we first characterized the MEFV promoter. Promoter mapping assays revealed that the region located between nucleotides -949 and -152 of the initiation codon was important for regulating expression of the gene. We identified a putative enhancer element between -571 and -414. Investigation of the sequence variants found in two patients demonstrated that c.-614C>G resulted in a 70% decrease in promoter activity, whereas c.-382C>T induced a 100% increase in activity, when compared to the wild type. We observed specific DNA-protein binding to both wild-type sites, suggesting that transcription factors may bind to these sequences to modulate MEFV expression.

DOI: 10.1038/gene.2009.8

PMID: 19262573 [Indexed for MEDLINE]

3565. Med Clin (Barc). 2009 Nov 28;133(20):804-5. doi: 10.1016/j.medcli.2008.11.011. Epub 2009 Mar 3.

[Familial mediterranean fever].

[Article in Spanish]

Carceller Lechón F, Alvarez-Coca González J, Martínez Pérez J, Aróstegui Gorospe JI.

DOI: 10.1016/j.medcli.2008.11.011

PMID: 19261306 [Indexed for MEDLINE]

3566. Z Rheumatol. 2009 Mar;68(2):137-48; quiz 149. doi: 10.1007/s00393-009-0449-z.

[Periodic fever syndrome/autoinflammatory syndrome].

[Article in German]

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Hereditary periodic fever syndromes (autoinflammatory syndromes) are characterised by relapsing fevers and additional manifestations such as skin rashes, mucosal manifestations, and joint pain. Some of these disorders only present with organ manifestations and serological signs of inflammation without obvious fever (e.g. PAPA and Blau syndrome). There is a strong serological inflammatory response with an elevation of serum amyloid A (risk of secondary amyloidosis). There are monogenic disorders for which the mode of inheritance and gene mutation are known, but probably also polygenic diseases which present with similar symptoms to the classic autoinflammatory syndromes. Gene mutations have been described for the monogenic disorders (FMF, HIDS, CAPS, PAPA and Blau syndrome), which lead to an induction of the production of IL-1ss.

Therapeutically, the IL-1-receptor antagonist anakinra is mainly used. In the case of TRAPS and Blau syndrome, TNF antagonists may also be used. PFAPA syndrome, the Schnitzler syndrome, Still's disease of adult and pediatric onset, Behçet's disease and Crohn's disease also are mentioned as additional possible autoinflammatory syndromes.

DOI: 10.1007/s00393-009-0449-z

PMID: 19255765 [Indexed for MEDLINE]

3567. Mol Biol Rep. 2010 Jan;37(1):1-5. doi: 10.1007/s11033-009-9475-9. Epub 2009 Mar 1.

Familial Mediterranean fever in Syrian patients: MEFV gene mutations and genotype-phenotype correlation.

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Familial Mediterranean fever is an autosomal recessive disorder characterized by recurrent attacks of abdominal pain, synovitis and pleuritis. MEFV gene mutations are responsible for the disease. The objective of this study was to identify the frequency and distribution of 12 MEFV mutations in 153 Syrian patients and perform a genotype-phenotype correlation in the patients' cohort. Of the 153 unrelated patients investigated, 97 (63.4%) had at least one mutation. The most frequent mutation was M694V (36.5%), followed by V726A (15.2%), E148Q (14.5%), M680I (G/C) (13.2%), and M694I (10.2%) mutations. Rare mutations (R761H, A744S, M680I (G/A), K695R, P369S, F479L and I692del) were also detected in the patients. M694V was associated with the severe form of the disease. The identification of a significant number of FMF patients with no mutations or only one known mutation identified indicates the presence of new mutations in the MEFV gene which will be investigated in the future.

DOI: 10.1007/s11033-009-9475-9

PMID: 19253030 [Indexed for MEDLINE]

3568. Clin Exp Immunol. 2009 May;156(2):373-6. doi: 10.1111/j.1365-2249.2009.03891.x. Epub 2009 Feb 19.

Co-existence of Hashimoto's thyroiditis with familial Mediterranean fever: is there a pathophysiological association between the two diseases?

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Familial Mediterranean fever is an autosomal recessive disease characterized by periodic attacks of fever and polyserositis, while Hashimoto's thyroiditis is the most common cause of hypothyroidism. We suggest that common autoimmune mechanisms

may underlie both disorders, describe their clinical co-existence in a patient, and discuss a possible causal link between them.

DOI: 10.1111/j.1365-2249.2009.03891.x

PMCID: PMC2759487

PMID: 19250274 [Indexed for MEDLINE]

3569. Semin Arthritis Rheum. 2010 Aug;40(1):53-72. doi: 10.1016/j.semarthrit.2008.12.001. Epub 2009 Feb 26.

Laboratory tests in the diagnosis and follow-up of pediatric rheumatic diseases: an update.

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**OBJECTIVES:** We reviewed the literature to evaluate the role of common laboratory tests and to examine the recent progress in the laboratory diagnosis of pediatric rheumatic diseases.

**METHODS:** We used the PubMed database (1950-2008) to search for the keywords "laboratory," "erythrocyte sedimentation rate" (ESR), "C-reactive protein" (CRP), "blood cytology," "procalcitonin" (PCT), "complement system," "ferritin," "antistreptolysin O titer" (ASO), "autoantibodies," "genetic studies," in conjunction with "rheumatic disease in children" and "pediatric autoimmune diseases." All relevant original and review articles in English were reviewed as well as textbooks of pediatric rheumatology.

**RESULTS:** Laboratory tests (ESR, CRP, blood cytology, complement system, ferritin, ASO titer) play an important role in confirming a diagnosis and in the follow-up of rheumatic diseases in the pediatric age group. The ESR is probably the most widely measured index of the acute phase response. Measurement of CRP is very useful in the rapid diagnosis of infection as a progressive increase can be shown in the first 48 hours. Also, the subsequent fall in serum CRP concentration on resolution of inflammation is useful for monitoring the efficacy of treatment. In chronic diseases, a combination of CRP and ESR may provide the most useful information. Cytopenia and different forms of anemia can be encountered in many

rheumatic diseases: they can be related to disease activity or to therapeutic side effects. Determination of complement levels (C3 and/or C4) is useful in the follow-up of systemic lupus erythematosus (SLE) and membranoproliferative glomerulonephritis. Ferritin is a laboratory hallmark of primary and secondary hemophagocytic lymphohistiocytosis. ASO titer should be obtained to confirm a diagnosis of acute rheumatic fever; other important antibody markers of streptococcal infection include antihyaluronidase, antideoxyribonuclease B, and antistreptokinase antibodies. We also found that, in the pediatric age, the main indication for synovial fluid analysis is suspected joint infection. Antinuclear antibodies, anti-Smith antigen, and anti-double-stranded DNA antibodies are important in the diagnosis of SLE, are useful prognostic markers, and facilitate clinical and treatment follow-up. Anti-SSA/Ro and anti-SSB/La antibodies are associated with Sjögren's syndrome and congenital heart block, while the anti-U1 small nuclear ribonucleoprotein antibodies show high specificity for mixed connective tissue disease. Repetitive spontaneous abortions, thrombocytopenia, and many types of venous or arterial thrombosis are associated with antiphospholipid antibodies. The presence of cytoplasmic antineutrophil antibodies is essential in the diagnosis of Wegener granulomatosis. The discovery of underlying single causative gene defects led to the identification of several autoinflammatory diseases, a group of genetic disorders characterized by recurrent attacks of inflammation (hereditary periodic fever syndromes). These include familial Mediterranean fever due to mutations in the Mediterranean fever (MEFV) gene, hyperimmunoglobulinemia D syndrome due to mutations in the MK gene for mevalonate kinase, cryopyrinopathies such as Muckle-Wells syndrome or neonatal-onset multisystemic inflammatory disease (neonatal-onset multisystemic inflammatory disease or chronic infantile neurological cutaneous and articular (CINCA)) associated with cold-induced autoinflammatory syndrome 1 gene mutations, and tumor necrosis factor receptor-associated periodic syndrome due to mutation of TNF receptor I gene.

**CONCLUSIONS:** Laboratory investigations play an important role in the diagnosis and follow-up of inflammatory rheumatic diseases in children. A good history and a complete physical examination are the best screening tests. Routine laboratory tests are useful to confirm a suspected diagnosis, to assess disease activity, and to measure the response and toxicity to treatment. Only a few tests represent diagnostic criteria such as antinuclear antibodies and anti-double-stranded DNA in SLE or cytoplasmic antineutrophil cytoplasmic autoantibodies in Wegener's granulomatosis. Recent advances in molecular genetics have impacted diagnosis, pathogenesis, and treatment in genetic fever syndromes.



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DOI: 10.1016/j.semarthrit.2008.12.001

PMID: 19246077 [Indexed for MEDLINE]

3570. Clin Rheumatol. 2009 Jul;28(7):857-60. doi: 10.1007/s10067-009-1138-7. Epub 2009 Feb 25.

Skin and muscle involvement as presenting symptoms in four children with familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent attacks of fever and polyserositis. It is the most frequent periodic fever syndrome. In FMF, sterile peritonitis, pleuritis and arthritis are frequently seen in addition to recurrent febrile attacks. Skin and muscle involvement is less common. Here, we report four patients presented with skin lesions or myalgia. Most striking findings in those patients are the absence of other major criteria for FMF and dominance of skin lesions or myalgia. All four patients had MEFV gene mutations on both alleles. In patients with erysipelas-like lesions or erythema nodosum along with arthritis/arthritis or recurrent myalgia, FMF should be kept in mind.

DOI: 10.1007/s10067-009-1138-7

PMID: 19240979 [Indexed for MEDLINE]

3571. Eur J Intern Med. 2009 Jan;20(1):44-7. doi: 10.1016/j.ejim.2008.04.020. Epub 2008 Jun 20.

Serum adenosine deaminase activities during acute attacks and attack-free periods of familial Mediterranean fever.

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**BACKGROUND:** Familial Mediterranean Fever (FMF) is a systemic relapsing autoinflammatory disorder. Adenosine deaminase (ADA) is an enzyme widely distribute in tissues and body fluids. Circulating levels of ADA have been shown to increase in several inflammatory conditions. This study was designed to evaluate the serum ADA in patients with FMF during acute attacks and attack-free periods.

**METHODS:** The study groups comprised 23 FMF patients in attack-free period (male/female: 11/12), 30 FMF patients in attack period (male/female: 11/19) and 20 healthy control (male/female:10/10). The groups were similar for age, gender and disease duration.

**RESULTS:** The mean age of FMF patients in attack-free period, patient with acute attack were 34.3+/-11.7 and 29.4+/-11.1 respectively. The disease durations were 13.1+/-10.2 and 8.2+/-7.6 years for patients in attack-free periods and patients with acute FMF attack, respectively. Patients with acute attack had significantly higher ADA levels than both patients with attack-free periods and healthy controls (for each,  $p<0.001$ ).

**CONCLUSION:** In this study we demonstrated that FMF patients with acute attacks had higher serum ADA levels than attack-free periods and healthy controls. It is likely that ADA may have a role in the cytokine network of the inflammatory cascade of FMF. Also, elevated ADA levels may be a part of the activated Th1 response in the disease. ADA may be used as a supportive marker to differentiate FMF attacks from attack-free periods. Further larger-scale studies are needed to support this result.

DOI: 10.1016/j.ejim.2008.04.020

PMID: 19237091 [Indexed for MEDLINE]

3572. Med Clin (Barc). 2009 Feb 21;132(6):237-8. doi: 10.1016/j.medcli.2008.05.012. Epub 2009 Feb 12.

[Anakinra in familial Mediterranean fever].

[Article in Spanish]

Fernández García MI, Albornoz López R, Cuevas Asencio I.

DOI: 10.1016/j.medcli.2008.05.012

PMID: 19237010 [Indexed for MEDLINE]

3573. Arthritis Res Ther. 2009;11(1):212. doi: 10.1186/ar2579. Epub 2009 Jan 30.

Developments in the scientific and clinical understanding of autoinflammatory disorders.

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The autoinflammatory diseases, also known as periodic fever syndromes, are disorders of innate immunity which can be inherited or acquired and which cause recurrent, self-limiting, seemingly spontaneous episodes of systemic inflammation and fever in the absence of autoantibody production or infection. There has been much recent progress in elucidating their aetiologies and treatment. With the exception of familial Mediterranean fever, which is common in certain populations, autoinflammatory diseases are mostly rare but should not be overlooked in the differential diagnosis of recurrent fevers since DNA diagnosis and effective therapies are available for many of them.

DOI: 10.1186/ar2579

PMCID: PMC2688228

PMID: 19232070 [Indexed for MEDLINE]

3574. Clin Rheumatol. 2009 Jun;28(6):623-30. doi: 10.1007/s10067-009-1117-z. Epub 2009 Feb 18.

Rare monogenetic syndromes in rheumatology practice.

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The EULAR Executive Committee defined eight overall objectives for EULAR to achieve by 2012. The first of these objectives is to strengthen activities in areas that are currently less prioritized, such as non-inflammatory and orphan diseases. This study aims to increase awareness of rheumatologists towards rare hereditary musculoskeletal disorders, by describing their genetics, pathogenesis, and typical clinical and radiological features. We analyzed patient charts from the recent 5 years from the Rheumatology Outpatient Department of the University Erlangen-Nuremberg and of two rheumatologic practices, all joined in a regional network ("Rheumazentrum Erlangen") retrospectively for hereditary musculoskeletal disorders other than hemochromatosis, autoinflammatory syndromes, lysosomal storage diseases, and hypermobility syndromes. We were able to identify four patients with trichorhinophalangeal syndrome type I, multiple exostoses, Kirner's deformity, and osteopoikilosis. In addition, a PubMed and OMIM ("Online Mendelian Inheritance in Man") database search was carried out using these as key words and all relevant articles were reviewed for each of these diseases. Our findings show that rare hereditary musculoskeletal disorders occur in a routine rheumatological setting and that rheumatologists should know the clinical and radiological features of these diseases in order to adequately counsel the patient.

DOI: 10.1007/s10067-009-1117-z

PMID: 19224127 [Indexed for MEDLINE]

3575. Curr Opin Immunol. 2009 Feb;21(1):10-6. doi: 10.1016/j.coi.2009.01.006. Epub 2009 Feb 14.

Sensing pathogens and danger signals by the inflammasome.

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Comment in

Curr Opin Immunol. 2009 Feb;21(1):1-2.

The NLR (nucleotide-binding domain leucine-rich repeat containing) family of intracellular sensors is a crucial component of the innate immune system. A number of NLR family members can form multiprotein complexes, called inflammasomes, and are capable of activating the cysteine protease caspase-1 in response to a wide range of stimuli including both microbial and self-molecules. Caspase-1 activation leads to processing and secretion of the proinflammatory cytokines interleukin-1beta (IL-1beta) and IL-18, which play crucial roles in host defense to infectious insults. Dysregulation of the inflammasome has also been linked to a number of autoinflammatory and autoimmune disorders. Recent advances in the inflammasome field will be discussed in this review.

DOI: 10.1016/j.coi.2009.01.006

PMCID: PMC2701640

PMID: 19223160 [Indexed for MEDLINE]

3576. Clin Exp Rheumatol. 2008 Nov-Dec;26(6):1091-4.

MEFV mutations in Japanese rheumatoid arthritis patients.

Migita K(1), Nakamura T, Maeda Y, Miyashita T, Koga T, Tanaka M, Nakamura M, Komori A, Ishibashi H, Origuchi T, Ida H, Kawasaki E, Yasunami M, Eguchi K.

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**OBJECTIVE:** Familial Mediterranean Fever (FMF) is common among Mediterranean populations, while other populations are rarely affected. The aim of this study was to assess the involvement of MEFV gene mutations among Japanese rheumatoid arthritis patients with or without amyloid A (AA) amyloidosis.

**METHODS:** The frequency of the MEFV mutations, which were identified in Japanese FMF patients, was determined in 126 Japanese RA patients and 76 Japanese healthy subjects.

**RESULTS:** The M694I mutation was not observed among RA patients and healthy

subjects. Allele frequency of R408Q, P369S, E148Q, L110P mutations account respectively for 3.3%, 3.9%, 23.7%, 9.2% in healthy subjects and 5.6%, 6.7%, 24.2%, 9.5% in RA patients. The overall mutation rate was comparable between the RA patients and healthy subjects, as well as between the RA patients with and without amyloidosis.

**CONCLUSION:** This study shows the high prevalence of mutations of the MEFV genes in Japanese RA patients. However, our data suggest that the MEFV gene mutations may not be a genetic factor affecting the susceptibility of RA or the development of amyloidosis in a Japanese population.

PMID: 19210876 [Indexed for MEDLINE]

3577. Nihon Naika Gakkai Zasshi. 2008 Dec 10;97(12):3046-8.

[Systemic AA amyloidosis caused by familial Mediterranean fever and response to colchicine].

[Article in Japanese]

Fukui N(1), Mukoyama M, Saito Y, Mori K, Kasahara M, Yokoi H, Ogawa Y, Kuwabara T, Sugawara A, Nakao K.

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PMID: 19209520 [Indexed for MEDLINE]

3578. Rheumatology (Oxford). 2009 Apr;48(4):395-8. doi: 10.1093/rheumatology/ken509. Epub 2009 Feb 4.

A new set of criteria for the diagnosis of familial Mediterranean fever in childhood.

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**OBJECTIVES:** Several sets of criteria mainly for adults have been proposed for the diagnosis of FMF. The aim of the present study is to validate the most widely used diagnostic 'Tel Hashomer' criteria in children and to establish a new set of criteria for use in childhood.

**METHODS:** The study group consisted of 170 recently diagnosed FMF patients who had mutations at both alleles. They were interviewed about the presence of 35 features and manifestations of FMF at the time of diagnosis. Controls were consecutive patients without FMF (n = 141) who had episodes of fever and clinical features mimicking that of FMF. The diagnostic performance of the candidate features was assessed by multiple logistic regression analysis.

**RESULTS:** The sensitivity and specificity of Tel Hashomer criteria in our study group were 98.8 and 54.6%, respectively. The multiple logistic regression analysis showed that 5 (fever, abdominal pain, chest pain, arthritis and family history of FMF) of the 35 candidate criteria discriminate FMF from controls with a sensitivity and specificity of 88.8 and 92.2%, respectively. The presence of two or more of these five criteria diagnosed FMF with a sensitivity of 86.5% and a specificity of 93.6%.

**CONCLUSION:** It was demonstrated that although the Tel Hashomer criteria were successful in diagnosing the FMF patients in childhood, its specificity was definitely low in children. The new set of criteria has a high sensitivity and specificity for the diagnosis of FMF and is practical to use on an everyday basis.

DOI: 10.1093/rheumatology/ken509

PMID: 19193696 [Indexed for MEDLINE]

3579. Oral Dis. 2008 Nov;14(8):690-9. doi: 10.1111/j.1601-0825.2008.01484.x.

Auto-inflammatory syndromes and oral health.

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Auto-inflammatory diseases (periodic syndromes) are rare childhood-onset disorders which are characterized by fluctuating or recurrent episodes of fever and inflammation affecting serosal surfaces, joints, eyes and/or skin without significant autoantibody production or an identifiable underlying infection. They are disorders of innate immunity and the underlying genetic defect has been identified in most of the syndromes. Diagnosis relies on clinical symptoms and evidence of an elevated acute phase response during attacks, supported by finding mutations in the relevant genes. Several syndromes can lead to systemic AA amyloidosis. Aphthous-like oral ulceration has been reported as one manifestation in several of the syndromes, including periodic fever, aphthous-stomatitis, pharyngitis, adenitis (PFAPA) familial Mediterranean fever (FMF), hyperimmunoglobulinaemia D and periodic fever syndrome, tumour necrosis factor receptor associated periodic syndrome and pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA). Chronic jaw recurrent osteomyelitis has been recorded in chronic recurrent multifocal osteomyelitis. Advances in the molecular pathogenesis of these syndromes and the regulation of innate immunity have enhanced diagnosis, and rationalized therapies. This article reviews the periodic fever syndromes relevant to oral health and the suggested association of FMF with Behçet's disease.

DOI: 10.1111/j.1601-0825.2008.01484.x

PMID: 19193198 [Indexed for MEDLINE]

3580. *Pediatr Res*. 2009 May;65(5 Pt 2):38R-45R. doi: 10.1203/PDR.0b013e31819dbd0a.

An integrated classification of pediatric inflammatory diseases, based on the concepts of autoinflammation and the immunological disease continuum.

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Historically, pediatric inflammatory diseases were viewed as autoimmune but



developments in genetics of monogenic disease have supported our proposal that "inflammation against self" be viewed as an immunologic disease continuum (IDC), with genetic disorders of adaptive and innate immunity at either end. Innate immune-mediated diseases may be associated with significant tissue destruction without evident adaptive immune responses and are designated as autoinflammatory due to distinct immunopathologic features. However, the majority of pediatric inflammatory disorders are situated along this IDC. Innate immunity has been demonstrated in polygenic disorders, particularly Crohn's disease (CD). A genetic overlap exists between CD and some major histocompatibility complex (MHC) class I-associated diseases, including psoriasis; these diseases seem to represent a true intermediate between autoinflammation and autoimmunity. Conversely, classical autoimmune diseases, with autoantibody and MHC class II associations, including celiac disease and rheumatoid arthritis (RA), have adaptive immune genetic associations, including Cytotoxic T-Lymphocyte Antigen-4 (CTLA4) and PTPN22. This proposed classification is clinically relevant, because innate immune-mediated disorders may respond to cytokine antagonism whereas autoimmune-mediated diseases respond better to anti-T and B cell therapies. Furthermore, the etiopathogenesis of poorly defined "autoimmune" diseases, such as juvenile idiopathic arthritis, may be inferred to have substantial innate immune involvement, based on response to IL-1 antagonism.

DOI: 10.1203/PDR.0b013e31819dbd0a

PMID: 19190531 [Indexed for MEDLINE]

3581. Eur Heart J. 2009 Mar;30(5):532-9. doi: 10.1093/eurheartj/ehn608. Epub 2009 Feb 3.

Colchicine for pericarditis: hype or hope?

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Colchicine has been effectively used in the treatment of several inflammatory conditions, such as gouty attacks, serositis related to familial Mediterranean fever, Behçet syndrome, and more recently also in acute and recurrent

pericarditis. Growing evidence has shown that the drug may be useful to treat an acute attack and may be a way to cope with the prevention of pericarditis in acute and recurrent cases and after cardiac surgery. Nevertheless, clinicians are often sceptical about the efficacy of the drug, and concerns have risen on possible side effects and tolerability. In this review, we analyse current evidence to support the use of the drug, as well as possible harms and risks related to drug interactions, reaching the conclusion that colchicine is safe and useful in recurrent pericarditis, if specific precautions are followed, although less evidence supports its use for the treatment of acute pericarditis, where colchicine remains optional and there is a need for further multicentre confirmatory studies. This paper also reviews specific dosing and precautions for the clinical use.

DOI: 10.1093/eurheartj/ehn608

PMID: 19190012 [Indexed for MEDLINE]

3582. Clin Exp Dermatol. 2009 Mar;34(2):216-8. doi: 10.1111/j.1365-2230.2008.02884.x.

Recurrent bullous lesions associated with familial Mediterranean fever: a case report.

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Familial Mediterranean fever (FMF) is an inherited, recurrent, inflammatory disease. Of its various cutaneous features, erysipelas-like erythema is the best known and most common skin lesion. We present a new case of FMF with recurrent bullous lesions. A 41-year-old woman was admitted to our clinic with tense bullae, 20 x 20 mm in diameter on the left shin. The patient had a history of fever, abdominal pain, peritonitis attacks and infertility. A lesional skin biopsy revealed subepidermal bullae and neutrophilic infiltration around dermal vessels. Direct immunofluorescence analysis was negative. Over the period of investigation, the lesion regressed spontaneously; 1 month later, a similar lesion appeared on the right wrist. Diagnosis of FMF was made according to the Tel-Hashomer criteria. Recognition of this peculiar skin lesion may lead to an

earlier diagnosis of the disease.

DOI: 10.1111/j.1365-2230.2008.02884.x

PMID: 19187302 [Indexed for MEDLINE]

3583. Arthritis Rheum. 2009 Feb;60(2):611-8. doi: 10.1002/art.24222.

The NOD2 defect in Blau syndrome does not result in excess interleukin-1 activity.

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Comment in

Arthritis Rheum. 2009 Aug;60(8):2544-5.

**OBJECTIVE:** Blau syndrome is a rare, autosomal-dominant, autoinflammatory disorder characterized by granulomatous arthritis, uveitis, and dermatitis. Genetics studies have shown that the disease is caused by single nonsynonymous substitutions in NOD-2, a member of the NOD-like receptor or NACHT-leucine-rich repeat (NLR) family of intracellular proteins. Several NLRs function in the innate immune system as sensors of pathogen components and participate in immune-mediated cellular responses via the caspase 1 inflammasome. Mutations in a gene related to NOD-2, NLRP3, are responsible for excess caspase 1-dependent interleukin-1beta (IL-1beta) in cryopyrinopathies such as Muckle-Wells syndrome. Furthermore, functional studies demonstrate that caspase 1-mediated release of IL-1beta also involves NOD-2. The aim of this study was to test the hypothesis that IL-1beta may mediate the inflammation seen in patients with Blau syndrome. **METHODS:** IL-1beta release was measured in peripheral blood mononuclear cells cultured in vitro, obtained from 5 Blau syndrome individuals with a NOD2 (CARD15) mutation.

**RESULTS:** We observed no evidence for increased IL-1beta production in cells obtained from subjects with Blau syndrome compared with healthy control subjects. Furthermore, we presented 2 cases of Blau syndrome in which recombinant human IL-1 receptor antagonist (anakinra) was ineffective treatment.

**CONCLUSION:** Taken together, these data suggest that in contrast to related IL-1beta-dependent autoinflammatory cryopyrinopathies, Blau syndrome is not mediated by excess IL-1beta or other IL-1 activity.

DOI: 10.1002/art.24222

PMCID: PMC2654171

PMID: 19180500 [Indexed for MEDLINE]

3584. Arthritis Rheum. 2009 Feb;60(2):619-25. doi: 10.1002/art.24294.

Proinflammatory action of the antiinflammatory drug infliximab in tumor necrosis factor receptor-associated periodic syndrome.

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**OBJECTIVE:** Tumor necrosis factor receptor (TNFR)-associated periodic syndrome (TRAPS) is an autosomal-dominant autoinflammatory condition caused by mutations in the TNFRSF1A gene. Unlike other autoinflammatory diseases in which anti-TNF therapy is largely a successful treatment option, therapy with the anti-TNF drug infliximab is often ineffective in patients with TRAPS. Moreover, in certain cases, infliximab actually triggers severe episodes of inflammation. The aim of this study was to elucidate the mechanisms underlying such a reaction.

**METHODS:** Peripheral blood mononuclear cells (PBMCs) were obtained from patients with TRAPS. Both caspase 3 activity and NF-kappaB subunit activity were determined by enzyme-linked immunosorbent assay. Cytokine secretion was assessed using a specific customized human multiplex bead immunoassay kit.

**RESULTS:** Unlike findings in controls, cells from a family of 9 patients, all of whom carried the T50M mutation in TNFRSF1A, failed to respond to infliximab through proapoptotic induction of caspase 3 activity. Instead, we observed enhanced antiapoptotic c-Rel subunit activity, accompanied by a significant increase in secretion of the proinflammatory cytokines interleukin- 1beta (IL-1beta), IL-1 receptor, IL-6, IL-8, and IL-12.

**CONCLUSION:** Altered extracellular conformation of TNFR1, resulting from the T50M

mutation in TNFRSF1A, results in failure of PBMCs to induce an apoptotic response to infliximab. We hypothesize that failure to shed infliximab-bound TNF/TNFR1 from the cell surface of cells from patients with the T50M mutation triggers c-Rel activation, and that this leads to a marked increase in cytokine secretion and an increased proinflammatory response. In light of these findings, we strongly advise caution when prescribing infliximab as anti-TNF therapy to patients with TRAPS.

DOI: 10.1002/art.24294

PMID: 19180495 [Indexed for MEDLINE]

3585. Mol Vis. 2009;15:208-12. Epub 2009 Jan 26.

Genotype analysis of polymorphisms in autoimmune susceptibility genes, CTLA-4 and PTPN22, in an acute anterior uveitis cohort.

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**PURPOSE:** Acute anterior uveitis (AAU) is the most common form of uveitis and is thought to be autoimmune in nature. Recent studies have described genes that act as master controllers of autoimmunity. Protein tyrosine phosphatase type 22 (PTPN22) and Cytotoxic T lymphocyte antigen-4 (CTLA-4) are two of these genes, and single nucleotide polymorphisms (SNPs) in the genes encoding these molecules have been associated with several autoimmune diseases. In this study we have analyzed SNPs in PTPN22 and CTLA-4 in patients with AAU.

**METHODS:** The functional protein tyrosine phosphatase type 22 (PTPN22) SNP (R620W rs2476601, 1858C/T), and two CTLA-4 SNPs (rs5742909, -318C/T and rs231775, 49A/G) were analyzed in 140 patients with AAU and 92 healthy controls by sequence-specific primer -polymerase chain reaction (SSP-PCR). Data was analyzed by chi(2) analysis and Fisher's exact test.

**RESULTS:** There was no significant association between PTPN22 620W, CTLA-4 -318C/T, or CTLA-4 49A/G and AAU. Similarly, there was no association with the three SNPs when patients were classified by race or gender. Finally, there was no association with the presence of ankylosing spondylitis in the patient cohort.

**CONCLUSIONS:** The data do not support an association between SNPs in PTPN22 and CTLA-4, genes regarded as genetic master switches of autoimmunity. This raises the issue of the etiology of AAU and the possibility that it should be regarded as an autoinflammatory rather than an autoimmune condition.

PMCID: PMC2632733

PMID: 19180256 [Indexed for MEDLINE]

3586. An Pediatr (Barc). 2009 Jan;70(1):53-6. doi: 10.1016/j.anpedi.2008.09.012. Epub 2008 Nov 29.

[Thyroid disorders and childhood rheumatic diseases].

[Article in Spanish]

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**INTRODUCTION:** The relationship between thyroid dysfunction and autoimmune diseases has mainly been described in adults. The aim of this study was to analyse the prevalence and characteristics of thyroid abnormalities in children with rheumatic diseases.

**PATIENTS AND METHOD:** One hundred and forty-five patients (109 girls and 36 boys) from a rheumatology paediatric unit were studied for two years. The diagnoses were: juvenile idiopathic arthritis (JIA) (n=115), lupus (n=17), juvenile dermatomyositis (n=5), scleroderma (n=4), and one case each of the following: mixed connective mixed disease, CINCA syndrome (chronic infantile neurological, cutaneous and articular), TRAPS (tumour necrosis factor receptor-associated periodic syndrome), and familial mediterranean fever. T4 and TSH levels were carried out, and if these showed abnormalities, antithyroid antibodies (ATA) were determined.

**RESULTS:** Six girls aged between 2 and 17 years old had thyroid abnormalities. Three had JIA and three had lupus. Five were diagnosed with autoimmune

hypothyroidism, with high ATA levels, and there was one case of hyperthyroidism. All of the patients with thyroid dysfunction had positive antinuclear antibodies (ANA), compared to 34.5% of the rest of the patients ( $p=0.003$ ).

CONCLUSIONS: The prevalence of thyroid abnormalities in children with rheumatic disease was 4.14% to 7.9% in JIA patients with positive ANA, and up to 17.6% with lupus. The majority of patients were asymptomatic. Thyroid hormones should be determined when rheumatic disease is diagnosed and periodically afterwards.

DOI: 10.1016/j.anpedi.2008.09.012

PMID: 19174120 [Indexed for MEDLINE]

3587. J Virol. 2009 Apr;83(7):3365-73. doi: 10.1128/JVI.00432-08. Epub 2009 Jan 19.

An invariant surface patch on the TRIM5alpha PRYSPRY domain is required for retroviral restriction but dispensable for capsid binding.

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TRIM5alpha is a retrovirus restriction factor in the host cell cytoplasm that blocks infection before provirus establishment. Restriction activity requires capsid (CA)-specific recognition by the PRYSPRY domain of TRIM5alpha. To better understand the restriction mechanism, nine charge-cluster-to-triple-alanine mutants in the TRIM5alpha PRYSPRY domain were assessed for CA-specific restriction activity. Five mutants distributed along the TRIM5alpha PRYSPRY primary sequence disrupted restriction activity against N-tropic murine leukemia virus and equine infectious anemia virus. Modeling of the TRIM5alpha PRYSPRY domain based on the crystal structures of PRYSPRY-19q13.4.1, GUSTAVUS, and TRIM21 identified a surface patch where disruptive mutants clustered. All mutants in this patch retained CA-binding activity, a reticular distribution in the cytoplasm, and steady-state protein levels comparable to those of the wild type. Residues in the essential patch are conserved in TRIM5alpha orthologues and in closely related paralogues. The same surface patch in the TRIM18 and TRIM20 PRYSPRY domains is the site of mutants causing Opitz syndrome and familial

Mediterranean fever. These results indicate that, in addition to CA-specific binding, the PRYSPRY domain possesses a second function, possibly binding of a cofactor, that is essential for retroviral restriction activity by TRIM5alpha.

DOI: 10.1128/JVI.00432-08

PMCID: PMC2655600

PMID: 19153241 [Indexed for MEDLINE]

3588. Rheumatol Int. 2009 Sep;29(11):1307-9. doi: 10.1007/s00296-009-0849-z. Epub 2009 Jan 20.

Increased frequency of familial Mediterranean fever in northern Turkey: a population-based study.

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Familial Mediterranean fever (FMF) is a systemic relapsing autoinflammatory disorder occurring in populations originating from the Mediterranean basin, mainly Turks, Levantine Arabs, Sephardic Jews, Druze, and Armenians. The prevalence of FMF shows considerable geographical variation. In Turkey, the prevalence rates were reported as 0.0027-0.25%. This field survey was conducted in different regions to investigate the frequency of FMF in a northern province of Turkey. This study was conducted in 70 areas (12 urban and 58 rural) in the province of Tokat, which is in northern Turkey. The population of Tokat was reported to be 828,000 at the last census in Turkey in 2000, about 530,000 for individuals aged >18 years ( <http://www.die.gov.tr> ). Mean age of 1,095 (541 male and 554 female; urban 555 and rural 540) subjects was 41 +/- 17 (range 18-95 years). FMF frequency in this study was 1/123 (0.82%, 95 CI: 0.40-1.61). Mean age of patients were 27 years (20-41) and mean age of symptoms were 16.3 years (11-23). In conclusion, the frequency of FMF in this study was 1/123 (0.82%) which was higher than expected. This rate is the highest frequency of FMF reported from Turkey. Further large sample studies are needed to define to true prevalence of FMF in Turkey.



DOI: 10.1007/s00296-009-0849-z  
PMID: 19152093 [Indexed for MEDLINE]

3589. Rheumatol Int. 2009 Oct;29(12):1477-80. doi: 10.1007/s00296-009-0842-6. Epub 2009 Jan 17.

Familial Mediterranean fever with chronic ascites: a case report and a review of literature.

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Familial Mediterranean fever (FMF) is an autosomal recessive inflammatory disease especially seen in Turks, Sephardic Jews, Armenians, and Arabs. Peritoneal and pleural inflammation, arthritis, erysipelas-like erythema, and arthralgia are well-known features of FMF. A small amount of peritoneal fluid collection can be seen during peritoneal attacks in FMF patients, but chronic ascites is a rather rare complication. We herein report a female FMF patient who developed chronic ascites. She was compound heterozygote for M694V/M680I mutation of the MEFV gene. Aspiration of the ascites fluid revealed a small amount of erythrocytes and mesothelial cells. After dose adjustment of colchicine the amount of ascites decreased. In conclusion, FMF should be considered in the differential diagnosis of chronic ascites in populations where the disease is endemic.

DOI: 10.1007/s00296-009-0842-6  
PMID: 19151977 [Indexed for MEDLINE]

3590. Ren Fail. 2009;31(1):13-7. doi: 10.1080/08860220802546305.

Is the urinary protein excretion pattern compatible with renal morphological findings in renal amyloidosis?

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The aims of this study are to compare urinary protein excretion pattern with renal morphological findings and to find out whether urinary protein excretion pattern is a prognostic indicator of renal amyloidosis. Fifteen children with renal amyloidosis secondary to familial Mediterranean fever were included in the study. The patients were classified into three groups according to the degree of tubulointerstitial injury in renal biopsy (group 1, <25%; group 2, 25-50%; and group 3, >50%). In all patients, urinary protein electrophoresis were performed. Levels of urinary beta(2)-microglobulin, retinol binding protein, and beta.N-acetyl-D glucosaminidase were measured as markers for tubular injury, and urinary excretions of protein and albumin and plasma albumin levels were measured as markers of glomerular injury. While urinary excretions of protein and albumin and plasma albumin levels were not different between groups, higher urinary beta(2)-microglobulin and retinol binding protein values and lower creatinine clearance values were found in group 3 than in groups 1 and 2 ( $p < 0.05$ ). We concluded that analysis of urinary protein excretion pattern is a non-invasive and reliable method to detect the degree of tubulointerstitial injury as the most important prognostic factor in renal amyloidosis and may be used to determine the changes during the follow-up period of the patients.

DOI: 10.1080/08860220802546305

PMID: 19142804 [Indexed for MEDLINE]

3591. J Clin Pathol. 2009 May;62(5):442-7. doi: 10.1136/jcp.2008.060616. Epub 2009 Jan 12.

Eosinophilia-associated muscle disorders: an immunohistological study with tissue localisation of major basic protein in distinct clinicopathological forms.

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AIMS: (a) To evaluate tissue eosinophil density, location of eosinophil cytotoxic products, histopathological muscle changes and inflammatory cell types in different eosinophilia-associated myopathies that are clinicopathologically heterogeneous. (b) To determine the immunohistological range of tissue eosinophil density in non-eosinophilic inflammatory myopathies.

METHODS: Muscle biopsy specimens from seven patients with blood and/or tissue eosinophilia and clinicolaboratory myopathic signs (five chronic course myopathies, one subacute onset fasciitis/myositis, one acute myositis), and from 18 non-eosinophilic inflammatory myopathies, underwent routine staining, inflammatory infiltrate immunophenotyping, immunostaining for eosinophil major basic protein (MBP) and transmission electron microscopy examination. Eosinophil and total inflammatory cell counts were statistically analysed.

RESULTS: Histological examination showed occasional or no infiltrating eosinophils in all cases. MBP staining showed that tissue eosinophil density and percentages in eosinophilia-associated myopathies were significantly higher than in idiopathic myositides. Extracellular MBP diffusion, the hallmark of eosinophil cytotoxicity, was recurrent on sarcolemma and endothelium. Electron microscopy showed eosinophils close to sarcolemma, abundant mast cells, and capillary endothelial swelling. Immunostaining detected a higher mean eosinophil density in idiopathic myositides than previously assessed histologically.

CONCLUSIONS: MBP immunohistology on skeletal muscle, previously performed only for acute eosinophilic polymyositis, suggests that eosinophil-mediated injury of muscle cells may occur in a wider spectrum of less aggressive eosinophilia-associated myopathies than previously thought. As conventional histology is likely to underestimate this leucocyte subset, MBP staining may be a useful tool in the analysis of tissue infiltration of eosinophils as a possible treatment target.

DOI: 10.1136/jcp.2008.060616

PMID: 19139036 [Indexed for MEDLINE]

3592. Immunol Rev. 2009 Jan;227(1):248-63. doi: 10.1111/j.1600-065X.2008.00733.x.

Microbe sensing, positive feedback loops, and the pathogenesis of inflammatory

diseases.

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The molecular apparatus that protects us against infection can also injure us by causing autoimmune or autoinflammatory disease. It now seems that at times, defects within the sensing arm of innate immunity contribute to diseases of this type. The initiation of an immune response is often microbe dependent and, in many cases, Toll-like receptor (TLR) dependent. Positive feedback loops triggering immune activation may occur when TLR signaling pathways stimulate host cells in an unchecked manner. Or, immune activation may persist because of failure to eradicate an inciting infection. Or on occasion, endogenous DNA may trigger specific immune responses that beget further responses in a TLR-dependent autoamplification loop. Specific biochemical defects that cause loop-related autoimmunity have been revealed by random germline mutagenesis and by gene targeting. We have also developed some insight into critical points at which feedback loops can be interrupted.

DOI: 10.1111/j.1600-065X.2008.00733.x

PMCID: PMC2713013

PMID: 19120489 [Indexed for MEDLINE]

3593. Immunol Rev. 2009 Jan;227(1):95-105. doi: 10.1111/j.1600-065X.2008.00730.x.

Inflammasomes: guardians of cytosolic sanctity.

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The innate immune system is critical in recognizing bacterial and viral infections to evoke a proper immune response. Certain members of the

intracellular nucleotide-binding and oligomerization domain (NOD)-like receptor (NLR) family detect microbial components in the cytosol and trigger the assembly of large caspase-1-activating complexes termed inflammasomes. Autoproteolytic maturation of caspase-1 zymogens within these inflammasomes leads to maturation and secretion of the pro-inflammatory cytokines interleukin-1 beta (IL-1 beta) and IL-18. The NLR proteins ICE protease-activating factor (IPAF), NALP1b (NACHT domain-, leucine-rich repeat-, and PYD-containing protein 1b), and cryopyrin/NALP3 assemble caspase-1-activating inflammasomes in a stimulus-dependent manner. Bacterial flagellin is sensed by IPAF, whereas mouse NALP1b detects anthrax lethal toxin. Cryopyrin/NALP3 mediates caspase-1 activation in response to a wide variety of microbial components and in response to crystalline substances such as the endogenous danger signal uric acid. Genetic variations in Nalp1 and cryopyrin/Nalp3 are associated with autoinflammatory disorders and increased susceptibility to microbial infection. Further understanding of inflammasomes and their role in innate immunity should provide new insights into the mechanisms of host defense and the pathogenesis of autoimmune diseases.

DOI: 10.1111/j.1600-065X.2008.00730.x

PMID: 19120479 [Indexed for MEDLINE]

3594. Br J Haematol. 2009 Feb;144(3):279-302. doi: 10.1111/j.1365-2141.2008.07036.x. Epub 2008 Dec 11.

Dysregulation of innate immunity: hereditary periodic fever syndromes.

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The hereditary periodic fever syndromes encompass a rare group of diseases that have lifelong recurrent episodes of inflammatory symptoms and an acute phase response in common. Clinical presentation can mimic that of lymphoproliferative disorders and patients often go undiagnosed for many years. These syndromes follow an autosomal inheritance pattern, and the major syndromes are linked to specific genes, most of which are involved in regulation of the innate immune

response through pathways of apoptosis, nuclear factor kappaBeta activation and cytokine production. In others, the link between the protein involved and inflammation is less clear. The recurrent inflammation can lead to complications, such as renal impairment due to amyloidosis and vasculitis, visual impairment, hearing loss, and joint destruction, depending on the specific syndrome. In recent years, treatment options for these diseases have improved significantly. Early establishment of an accurate diagnosis and start of appropriate therapy improves prognosis in these patients.

DOI: 10.1111/j.1365-2141.2008.07036.x

PMID: 19120372 [Indexed for MEDLINE]

3595. Arthritis Rheum. 2009 Jan;60(1):264-8. doi: 10.1002/art.24174.

Successful treatment of idiopathic recurrent pericarditis in children with interleukin-1beta receptor antagonist (anakinra): an unrecognized autoinflammatory disease?

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Comment in

Arthritis Rheum. 2009 Aug;60(8):2543; author reply 2543-4.

Recurrent pericarditis occurs in association with various medical conditions, but in most cases the condition appears to be idiopathic. Although high-dose steroid treatment is often effective, it may have serious side effects. Herein we describe 3 children with recurrent pericarditis who were treated at our hospital, during flares, with the interleukin-1beta receptor antagonist anakinra, with immediate response. Pericarditis recurred when anakinra treatment was discontinued, and no further episodes occurred after it was resumed. Idiopathic recurrent pericarditis shares several features with autoinflammatory diseases, and anakinra has been efficacious in the treatment of the latter diseases. The findings in these patients suggest that idiopathic recurrent pericarditis may be a previously unrecognized autoinflammatory disease.

DOI: 10.1002/art.24174

PMID: 19116906 [Indexed for MEDLINE]

3596. Arthritis Rheum. 2009 Jan;60(1):269-80. doi: 10.1002/art.24147.

Novel markers of inflammation identified in tumor necrosis factor receptor-associated periodic syndrome (TRAPS) by transcriptomic analysis of effects of TRAPS-associated tumor necrosis factor receptor type I mutations in an endothelial cell line.

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Comment in

Arthritis Rheum. 2009 Jan;60(1):8-11.

**OBJECTIVE:** To analyze the effects of tumor necrosis factor receptor-associated periodic syndrome (TRAPS)-associated mutant tumor necrosis factor receptor type I (TNFRI) expression in a cell type directly relevant to the inflammation in TRAPS, and to identify novel markers associated with mutant TNFRI expression.

**METHODS:** Transcriptome analysis on 30,000 human genes was performed on SK-Hep-1 human endothelial cells transfected with either wild-type (WT) or TRAPS-associated mutant TNFRI. Quantitative reverse transcriptase-polymerase chain reaction and protein expression levels measured by enzyme-linked immunosorbent assay verified transcriptional changes for selected genes both in supernatants from cells expressing mutant TNFRI and in patient plasma.

**RESULTS:** Cells expressing mutant TNFRI showed up-regulation of multiple proinflammatory genes relative to WT transfectants, including genes for pentraxin 3, granulocyte-macrophage colony-stimulating factor, granulocyte colony-stimulating factor, CCL2, and CCL5, which were also expressed as proteins. In addition, the expression of most of these markers was increased in the plasma and peripheral blood mononuclear cells from TRAPS patients relative to those from healthy controls. The cysteine mutations (C33Y and C52F), which are associated

with a more severe clinical phenotype, induced more genes than the low-penetrance mutation R92Q, which is associated with a milder phenotype. The expression of most genes was induced by a death domain (DD)-dependent mechanism, since they were not induced by expression of TNFRI mutants with an inactivated DD.

CONCLUSION: TRAPS-associated TNFRI mutants induce the expression of multiple genes encoding inflammatory molecules, cellular receptors, transcription factors, and regulators of apoptosis in endothelial cells that require the cytoplasmic signaling properties of the receptor. Different mutants have specific expression profiles, indicating mutation-specific effects. The expression of some of these markers was also elevated in samples from TRAPS patients.

DOI: 10.1002/art.24147

PMID: 19116900 [Indexed for MEDLINE]

3597. Arthritis Rheum. 2009 Jan;60(1):8-11. doi: 10.1002/art.24145.

Tumor necrosis factor receptor-associated periodic syndrome: toward a molecular understanding of the systemic autoinflammatory diseases.

Ryan JG, Aksentijevich I.

Comment on

Arthritis Rheum. 2009 Jan;60(1):269-80.

DOI: 10.1002/art.24145

PMCID: PMC2743258

PMID: 19116899 [Indexed for MEDLINE]

3598. J Turk Ger Gynecol Assoc. 2009 Dec 1;10(4):235-7. eCollection 2009.

Familial mediterranean fever: a diagnostic challenge in pregnancy.

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Familial Mediterranean Fever (FMF) is an autosomal recessive disease which is characterized by recurrent, self-limiting, short attacks of serositis while abdominal pain is the most common symptom. The underlying clinical and pathological picture is that of acute peritonitis. These abdominal signs are often so striking that they mimic an acute abdominal calamity suggesting several possible gastrointestinal, gynecologic or urologic diagnoses. Diagnosis of acute abdomen in pregnancy also remains one of the most challenging conditions as the physiological consequence of pregnancy and nonspecific laboratory parameters. A limited number of studies addressed FMF in pregnancy and none of them mentioned the diagnostic challenging of FMF during pregnancy because the patients had al been diagnosed previously. In this paper, we discussed a 20 year old, gravida 1, parity 0 patient whose twin pregnancy wash complicated by an acute abdominal condition after amniocentesis and the difficulties of making the diagnosis of FMF with the complications during this diagnostic period in pregnancy.

Publisher: Ailevi Akdeniz Ateşi (AAA) en yaygın belirtisi karın ağrısı olan; tekrarlayıcı, kendi kendini sınırlayan, kısa serozit ataklarıyla karakterize, otozomal resesif geçişli bir hastalıktır. Altta yatan klinik ve patolojik görünüm akut peritonitle uyumludur. Bu batın bulguları bazen o kadar dikkat çekici bir duruma gelir ki, bazı gastrointestinal, jinekolojik ve ürolojik tanıları düşündüren akut karın tablosunu taklit eder. Gebelik sırasında akut karın tanısı koymak, gebeliğin fizyolojik sonuçlarına ve spesifik olmayan laboratuvar parametrelere bağlı olarak en zor durumlardan biridir. Gebelikte AAA ile ilgili sınırlı sayıda çalışma mevcuttur ve hiçbirinde AAA' nin gebelik sürecindeki tanısız zorluğundan bahsedilmemiştir, çünkü hepsi de gebelikten önce AAA tanısı almışlardır. Bu yazıda biz, 20 yaşında, gravida 1, parite 0 bir hastada amniosentez sonrasında akut karın tablosunu taklit ederek ikiz bir gebeliği komplike eden AAA' nin gebelik sürecinde tanısının konulmasındaki zorlukları ve bu tanısız süreçte meydana gelen komplikasyonları tartıştık.

PMCID: PMC3939172

PMID: 24591879

3599. BMJ Case Rep. 2009;2009. pii: bcr09.2008.0992. doi: 10.1136/bcr.09.2008.0992. Epub 2009 Feb 2.

Cytological vitreous findings in a patient with infantile neurological cutaneous and articular (CINCA) syndrome.

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The CINCA syndrome is an inflammatory disease characterised by persistent rash and chronic aseptic meningitis, with extensive infiltration of polymorphonuclear and macrophage cells at the sites of inflammation. The CINCA syndrome belongs to the group of systemic autoinflammatory diseases characterised by episodic or fluctuating degrees of inflammation, without evidence of high-titre autoantibodies or antigen-specific T cells. The disease is caused by mutations in the CIAS1 gene that encodes a protein cryopyrin, NALP3 or PYPAF1. Mutations in cryopyrin have a profound pro-inflammatory effect. Cryopyrin is a caspase 1 activator, which in turn causes the activation of interleukin (IL)1 $\beta$ . The activating mutations of cryopyrin induce an excessive activation of IL1 $\beta$ , which causes an influx of macrophages and polymorphonuclear cells to the site of inflammation, in our patient, in his eye.

DOI: 10.1136/bcr.09.2008.0992

PMCID: PMC3028483

PMID: 21686518

3600. Riv Biol. 2009 Sep-Dec;102(3):365-84.

The inflammasomes: the key regulators of inflammation.

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Following any threat to tissutal integrity, innate immune system promptly recognizes foreign/damage-associated molecules and orchestrates the global immune response, inducing inflammation, chemotaxis, phagocytosis and production of antimicrobial effector molecules, as well as providing instruction to the adaptive immune system. Innate immune cells detect both exogenous and endogenous

danger signals through invariant germline-encoded pattern recognition receptors, including Toll-like receptors, retinoic acid-inducible gene I-like receptors, and nucleotide binding domain and leucine rich repeat containing receptors (NLRs). The recruitment of NLRs, namely IPAF, NAIPs and NALPs, by various potentially harmful stimuli leads to the assembly of inflammasomes, multimeric caspase-activating complexes entailing the sensor NLR, intracellular adaptor proteins, and procaspase-1 and -5. The caspase activation is necessarily required for the processing and secretion of proinflammatory cytokines, such as interleukin (IL)-1 $\beta$ , IL-18, and IL-33. Therefore, the inflammasomes are critical regulators of the inflammatory response. Dysregulation of such a versatile sentry system is involved in the pathogenesis of human autoinflammatory diseases, autoimmune disorders, and microcrystalline arthritides. A better knowledge of the inflammasome crucial role in the immune response may provide possible future therapeutic improvements in protection against invading pathogens and in vaccine efficacy, as well as in the treatment of human inflammatory diseases.

PMID: 20533186 [Indexed for MEDLINE]

3601. Rheumatol Int. 2009 Sep;29(11):1279-85. doi: 10.1007/s00296-008-0831-1. Epub 2008 Dec 30.

The clinical and genetical features of 124 children with Familial Mediterranean fever: experience of a single tertiary center.

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The aim of the present study was to evaluate the clinical features of childhood-onset Familial Mediterranean fever (FMF) patients and to assess the phenotype-genotype correlation. The study included patients with childhood-onset FMF that followed up over a period of 18 years in the Division of Pediatric Allergy and Immunology clinic. Twelve MEFV mutations were investigated in all patients. The patients were classified into four groups according to mutations: 1, M694V homozygote; 2, M694V heterozygote; 3, compound heterozygote for M694V;

and 4, other-other gene mutation group. The following parameters were evaluated: gender, age of onset, age at diagnosis, time interval between disease onset and diagnosis, fever, abdominal pain, chest pain, arthralgia, arthritis, myalgia, vomiting, diarrhea, constipation, headache, erysipela-like erythema, protracted febrile myalgia, splenomegaly, hepatomegaly, consanguinity, number of attacks before and after treatment, severity score, response to colchicine treatment. Of the 124 patients included in the study, 105 had at least one MEFV gene mutation. M694V homozygosity was the most common mutation, followed by M694V heterozygotes and M694V-M680I compound heterozygotes. Severity score was found significantly higher in patients with M694V homozygote and compound heterozygote for M694V compared with other groups. The data supported the findings in literature that FMF patients with M694V homozygote and compound heterozygote for M694V gene mutations experience a more severe clinical course.

DOI: 10.1007/s00296-008-0831-1

PMID: 19115056 [Indexed for MEDLINE]

3602. J Exp Med. 2009 Jan 16;206(1):35-41. doi: 10.1084/jem.20072713. Epub 2008 Dec 29.

Lymphoid tissue inducer-like cells are an innate source of IL-17 and IL-22.

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The interleukin (IL) 17 family of cytokines has emerged to be critical for host defense as well as the pathogenesis of autoimmune and autoinflammatory disorders, and serves to link adaptive and innate responses. Recent studies have identified a new subset of T cells that selectively produce IL-17 (Th17 cells; Bettelli, E., T. Korn, and V.K. Kuchroo. 2007. Curr. Opin. Immunol. 19:652-657; Kolls, J.K., and A. Linden. 2004. Immunity. 21:467-476), but the regulation of IL-17 production by innate immune cells is less well understood. We report that in vitro stimulation with IL-23 induced IL-17 production by recombination activating gene (Rag) 2(-/-) splenocytes but not Rag2(-/-) common gamma chain(-/-)

splenocytes. We found that a major source of IL-17 was CD4(+)CD3(-)NK1.1(-)CD11b(-)Gr1(-)CD11c(-)B220(-) cells, a phenotype that corresponds to lymphoid tissue inducer-like cells (LTi-like cells), which constitutively expressed the IL-23 receptor, aryl hydrocarbon receptor, and CCR6. In vivo challenge with the yeast cell wall product zymosan rapidly induced IL-17 production in these cells. Genetic deletion of signal transducer and activator of transcription 3 reduced but did not abrogate IL-17 production in LTi-like cells. Thus, it appears that splenic LTi-like cells are a rapid source of IL-17 and IL-22, which might contribute to dynamic organization of secondary lymphoid organ structure or host defense.

DOI: 10.1084/jem.20072713

PMCID: PMC2626689

PMID: 19114665 [Indexed for MEDLINE]

3603. Exp Biol Med (Maywood). 2009 Jan;234(1):40-52. doi: 10.3181/0806-RM-184.

Pyrin and ASC co-localize to cellular sites that are rich in polymerizing actin.

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Familial Mediterranean fever (FMF) is an autoinflammatory disease caused by mutations in the MEFV locus, which encodes the protein pyrin. While it is known that pyrin is expressed in myeloid cells and several fibroblastic cell types, the exact function of pyrin in these cells and the mechanism underlying the pathological effect of pyrin mutations have yet to be revealed. Here, we document that in migrating human monocytes, pyrin protein is dramatically polarized at the leading edge, where it co-localizes with polymerizing actin. ASC (Apoptosis-associated Speck protein with CARD domain), a known pyrin-interacting protein and a critical component of the inflammasome, is also located at the leading edge in migrating monocytes. Similarly, both pyrin and ASC concentrate in dynamically polymerizing actin-rich tails generated by *Listeria monocytogenes*. Pyrin's B-box and coiled-coil region is required for its association with

Listeria tails. Pyrin also binds, with low affinity and via the same domains, to actin, VASP, and Arp3. Though disease-causing mutations in pyrin do not appear to alter its localization to the leading edge or to Listeria rocket tails, they could potentially have important functional consequences in the context of processes such as migration and cell synapse formation. The co-localization of pyrin and ASC together at such sites may provide an important link between cytoskeletal signaling and inflammasome function.

DOI: 10.3181/0806-RM-184

PMID: 19109554 [Indexed for MEDLINE]

3604. Acta Reumatol Port. 2008 Oct-Dec;33(4):415-20.

Screening of family members of children with Familial Mediterranean Fever: true-autosomal and pseudo-autosomal inheritance.

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**OBJECTIVES:** Screening of family members of children with Familial Mediterranean Fever (FMF) has been carried out to detect new potential patients and to analyze the type of inheritance other than autosomal recessive.

**METHODS:** Marenostin encoding fever gene mutational analysis has been performed in 83 subjects - including 19 newly diagnosed children with FMF and their family members.

**RESULTS:** Fourteen additional patients with FMF were diagnosed by screening family members. Pseudo-dominant and true dominant inheritances were detected in two families respectively, while the rest of the patients exhibited autosomal recessive mode of inheritance.

**CONCLUSION:** Screening the family members of newly diagnosed FMF patients provides the opportunity to reveal undiagnosed new cases and to understand the mode of inheritance.

PMID: 19107086 [Indexed for MEDLINE]

3605. Cell Cycle. 2009 Jan 1;8(1):27-30. Epub 2009 Jan 31.

NALP3 inflammasome functional polymorphisms and gout susceptibility.

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Gout is the most common autoinflammatory arthritis characterized by elevated serum urate and recurrent attacks of intra-articular crystal deposition of monosodium urate (MSU). Although the pathogenesis of gout is still unclear, accumulated studies indicate that genetic factors trigger gout development, including some susceptibility genes that control the production and clearance of urate and lead to hyperuricemia. However, the epidemiological evidence suggests that only less than 10% of hyperuricemia patients develop gout, indicating that other genes unrelated to the urate metabolism may also contribute to the diseases susceptibility. Accumulated evidences have implied that MSU crystal-induced inflammation is a paradigm of innate immunity and that NALP3 inflammasome, an innate immune complex containing NALP3, ASC and CARD-8, is involved in gout development. Recent studies suggest that NALP3 and CARD-8 functional mutations contribute to the development of autoinflammatory diseases including hereditary periodic fever syndrome, arthritis as well as hypertension susceptibility. Taking into account these genetic findings, here we would like to propose a novel hypothesis that functional mutations in NALP3 inflammasome may make NALP3 inflammasome as attractive susceptibility candidates and genetic markers for gout. Further clinical genetic studies need to be performed to confirm the role of NALP3 inflammasome in the etiology of gout.

DOI: 10.4161/cc.8.1.7325

PMID: 19106604 [Indexed for MEDLINE]

3606. Zhonghua Er Ke Za Zhi. 2008 Nov;46(11):842-7.

[Autoinflammatory disease].

[Article in Chinese]

Li CR.

PMID: 19099902 [Indexed for MEDLINE]

3607. Nat Genet. 2009 Jan;41(1):71-6. doi: 10.1038/ng.285. Epub 2008 Dec 21.

Common variants in the NLRP3 region contribute to Crohn's disease susceptibility.

Villani AC(1), Lemire M, Fortin G, Louis E, Silverberg MS, Collette C, Baba N, Libioulle C, Belaiche J, Bitton A, Gaudet D, Cohen A, Langelier D, Fortin PR, Wither JE, Sarfati M, Rutgeerts P, Rioux JD, Vermeire S, Hudson TJ, Franchimont D.

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We used a candidate gene approach to identify a set of SNPs, located in a predicted regulatory region on chromosome 1q44 downstream of NLRP3 (previously known as CIAS1 and NALP3) that are associated with Crohn's disease. The associations were consistently replicated in four sample sets from individuals of European descent. In the combined analysis of all samples (710 father-mother-child trios, 239 cases and 107 controls), these SNPs were strongly associated with risk of Crohn's disease ( $P(\text{combined}) = 3.49 \times 10^{-9}$ ), odds ratio = 1.78, confidence interval = 1.47-2.16 for rs10733113), reaching a level consistent with the stringent significance thresholds imposed by whole-genome association studies. In addition, we observed significant associations between SNPs in the associated regions and NLRP3 expression and IL-1 $\beta$  production. Mutations in NLRP3 are known to be responsible for three rare autoinflammatory disorders. These results suggest that the NLRP3 region is also implicated in the susceptibility of more common inflammatory diseases such as Crohn's disease.

DOI: 10.1038/ng.285



PMCID: PMC2728932

PMID: 19098911 [Indexed for MEDLINE]

3608. Acta Ophthalmol. 2009 Feb;87(1):39-43. doi: 10.1111/j.1755-3768.2008.01437.x. Epub 2008 Dec 16.

Conjunctival impression cytology and tear-film changes in patients with familial Mediterranean fever.

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Comment in

Acta Ophthalmol. 2010 Mar;88(2):e5; author reply e6.

**PURPOSE:** To evaluate the ocular surface changes and tear-film functions in patients with familial Mediterranean fever (FMF).

**METHODS:** This prospective case-control clinical study examined 35 patients with FMF (group 1) and 35 controls (group 2). All patients underwent a full ophthalmological examination. Ocular surface changes were evaluated by determining cell content of surface conjunctival epithelium using conjunctival impression cytology and tear-film functions using Schirmer-I, break-up time (BUT), corneal fluorescein and Rose Bengal tests. Subjective ocular complaints were scored with a four-point scale. Between-group results were compared.

**RESULTS:** In group 1, impression cytology revealed grade 0 changes in 15 eyes, grade 1 changes in 11 eyes and grade 2 changes in nine eyes in group 1; in group 2, it revealed grade 0 changes in 27 eyes, grade 1 changes in five eyes and grade 2 changes in three eyes ( $p = 0.013$ ). Mean goblet cell density was  $765 \pm 45$  cells/mm<sup>2</sup> in group 1 and  $1730 \pm 100$  cells/mm<sup>2</sup> in group 2 ( $P < 0.001$ ). Mean results on the Schirmer-I test results were  $17.36 \pm 3.18$  mm in group 1 and  $19.60 \pm 4.17$  mm in group 2 ( $p = 0.364$ ). Mean BUT was  $8.20 \pm 1.60$  seconds in group 1 and  $9.93 \pm 2.33$  seconds in group 2 ( $p = 0.001$ ). Mean corneal fluorescein and Rose Bengal staining scores were  $3.26 \pm 1.67$  and  $0.96 \pm 0.71$  in group 1 and  $1.37 \pm 0.34$  and  $0.40 \pm 0.49$  in group 2 ( $p = 0.037$ ,  $p = 0.005$ ). The presence of subjective ocular complaints was more frequent in group 1 than in

group 2.

CONCLUSION: Despite normal tear production, the ocular surface and tear-film functions of FMF patients differ from those of healthy individuals. These changes may be related to the chronic inflammatory nature of FMF.

DOI: 10.1111/j.1755-3768.2008.01437.x

PMID: 19094172 [Indexed for MEDLINE]

3609. Joint Bone Spine. 2009 May;76(3):227-33. doi: 10.1016/j.jbspin.2008.08.004. Epub 2008 Dec 16.

Familial Mediterranean Fever: a review for clinical management.

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Familial Mediterranean Fever (FMF) is a hereditary autosomal recessive, autoinflammatory disorder characterized by recurrent, self-limiting episodes of short duration (mean 24-72 h) of fever and serositis. FMF is the most frequent periodic febrile syndrome among the autoinflammatory syndromes (AS), a heterogeneous group of recently identified diseases clinically characterized by recurrent febrile attacks, in the absence of autoantibodies and antigen-specific T lymphocytes. In FMF, periodic attacks show inter- and intra-individual variability in terms of frequency and severity. Usually, they are triggered by apparently innocuous stimuli and may be preceded by a prodromal period. The Mediterranean Fever gene (MEFV) responsible gene maps on chromosome 16 (16p13) encoding the pyrin-marenostrin protein. The precise pathologic mechanism is still to be definitively elucidated; however a new macromolecular complex, called inflammasome, seems to play a major role in the control of inflammation and it might be involved in the pathogenesis of FMF. The most severe long-term complication is type AA amyloidosis, principally affecting the kidney and the cause of chronic renal failure. Two types of risk factors, genetic and non-genetic, have been identified for this complication. Currently, the only effective treatment of Familial Mediterranean Fever is the colchicine. New drugs

in a few colchicine resistant patients have been tried, but additional studies on larger series are necessary to draw definitive conclusions.

DOI: 10.1016/j.jbspin.2008.08.004

PMID: 19091621 [Indexed for MEDLINE]

3610. Dtsch Med Wochenschr. 2009 Jan;134(1-2):35-8. doi: 10.1055/s-0028-1105888. Epub 2008 Dec 17.

[Cathelicidins: multifunctional defense molecules of the skin].

[Article in German]

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The human skin is constantly exposed to microbial pathogens but infections only rarely occur. Innate cutaneous immunity is a primary system for protection against infection, and antimicrobial peptides (AMPs) expressed in skin are essential defence molecules. The AMPs include molecules such as the defensins that were first characterized for their antimicrobial properties as well as other peptides and proteins first known for their activity as chemokines, enzymes, enzyme inhibitors and neuropeptides. Cathelicidins are unique AMPs that act as defensive and signalling molecules. Two different pathways are involved in this function: cathelicidins have direct antimicrobial activity and they also initiate a host of cellular responses in cytokine release, inflammation and angiogenesis. Several skin diseases are associated with cathelicidin dysfunction. In atopic eczema, for example, cathelicidin expression is suppressed, whereas in rosacea cathelicidin peptides are abnormally processed to forms that induce cutaneous inflammation and a vascular response. In psoriasis cathelicidin peptide converts self-DNA to a potent stimulus in an autoinflammatory cascade. Current studies have unexpectedly identified vitamin D3 as a major factor for the regulation of cathelicidin expression. This finding may provide new strategies in the management of infectious and inflammatory diseases of the skin by targeting control of the expression and function of cathelicidin and other AMPs.

DOI: 10.1055/s-0028-1105888

PMID: 19090451 [Indexed for MEDLINE]

3611. Joint Bone Spine. 2009 Jan;76(1):7-9. doi: 10.1016/j.jbspin.2008.05.009. Epub 2008 Dec 11.

Is Still's disease an autoinflammatory syndrome?

Hayem F.

DOI: 10.1016/j.jbspin.2008.05.009

PMID: 19084456 [Indexed for MEDLINE]

3612. Neth J Med. 2008 Dec;66(11):489-91.

Anakinra suppresses familial Mediterranean fever crises in a colchicine-resistant patient.

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We describe a 34-year-old male patient suffering from familial Mediterranean fever and experiencing an increase in both the frequency and severity of disease attacks, suggesting resistance to chronic treatment with colchicine. Since no alternative treatment is established, anakinra, an interleukin-1 receptor antagonist, was administered, not daily, as it has been previously reported, but only during crises, with successful outcome.

PMID: 19075317 [Indexed for MEDLINE]

3613. Invest Ophthalmol Vis Sci. 2009 Apr;50(4):1746-53. doi: 10.1167/iovs.08-2852.

Epub 2008 Dec 13.

NOD1 expression in the eye and functional contribution to IL-1beta-dependent ocular inflammation in mice.

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**PURPOSE:** NOD1 plays an important role in host defense and recognizes the minimal component of bacterial cell walls, meso-diaminopimelic acid (iE-DAP).

Polymorphisms in NOD1 are associated with autoinflammatory diseases characterized by uveitis such as Crohn's disease and sarcoidosis. NOD1 is homologous to NOD2, which is responsible for an autosomal dominant form of uveitis. Nonetheless, the role of NOD1 in intraocular inflammation has not been explored. The induction of uveitis by iE-DAP in mice and the potential contribution of interleukin (IL)-1beta were investigated.

**METHODS:** BALB/c mice or mice deficient in caspase-1 or IL-1R1 and their congenic controls were injected intravitreally with iE-DAP or saline. The time course, dose response, and contribution of IL-1beta to ocular inflammation were quantified by intravital video microscopy, histology, and immunohistochemistry.

NOD1 and IL-1beta were measured in eye tissue by immunoblotting and ELISA.

**RESULTS:** NOD1 protein is expressed in the eye and promotes ocular inflammation in a dose- and time-dependent fashion. The authors previously defined the role of IL-1beta in NOD2 uveitis and tested whether NOD1 and NOD2 used similar mechanisms. Treatment with iE-DAP significantly increased IL-1beta, which was caspase-1 dependent. However, in contrast to NOD2, caspase-1 and IL-1R1 were essential mediators of iE-DAP-induced uveitis, suggesting that NOD1 and NOD2 induce ocular inflammation by distinct mechanisms involving IL-1beta.

**CONCLUSIONS:** These findings demonstrate that NOD1 is expressed within the eye and that its activation results in uveitis in an IL-1beta-dependent mechanism.

Characterizing the differences between NOD1 and NOD2 responses may provide insight into the pathogenesis of uveitis.

DOI: 10.1167/iovs.08-2852

PMCID: PMC3086269

PMID: 19074813 [Indexed for MEDLINE]

3614. Clin Exp Rheumatol. 2008 Jul-Aug;26(4 Suppl 50):S99-102.

The analysis of interleukin-1 receptor antagonist and interleukin-1beta gene polymorphisms in Turkish FMF patients: do they predispose to secondary amyloidosis?

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**OBJECTIVE:** Amyloid development in familial Mediterranean fever (FMF) patients is associated with acute phase response and the acute phase reactant serum amyloid A which is induced by IL-1Beta. Its concentration can increase to more than 1000 fold during inflammation. In view of the inflammatory nature of FMF disease we have investigated whether IL-1Beta and IL-1 receptor antagonist gene polymorphisms may be involved in amyloid development in FMF patients.

**METHODS:** Ninety-nine FMF patients without amyloidosis; 54 FMF patients with amyloidosis and 60 healthy controls samples were genotyped for IL-1Beta-511 (C/T) and IL-1Beta+3953 (C/T) polymorphisms using PCR-RFLP and for IL-1Ra VNTR polymorphism using PCR.

**RESULTS:** The allele and genotype frequencies of IL-1Beta-511 (C/T), IL-1Beta+3953 (C/T) and IL-1Ra VNTR polymorphisms in FMF patients with and without amyloidosis were all compared with those in controls. There were no significant differences between FMF patients with and without amyloidosis and healthy control samples for these polymorphisms (all P-values are >0.05). These polymorphisms were not associated with M694V mutation in FMF patients with and without amyloidosis.

**CONCLUSION:** IL-1Beta-511 (C/T), IL-1Beta+3953 (C/T) and IL-1Ra VNTR polymorphisms are not associated with the development of amyloid in FMF patients.

PMID: 19026124 [Indexed for MEDLINE]

3615. Clin Exp Rheumatol. 2008 Jul-Aug;26(4 Suppl 50):S72-6.

MEFV gene 3'-UTR Alu repeat polymorphisms in patients with familial Mediterranean fever.

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**OBJECTIVE:** Familial Mediterranean fever (FMF), an autosomal recessively inherited autoinflammatory disorder, is caused by missense mutations in the pyrin-encoding MEFV gene. The MEFV mutations can be detected in the majority of FMF patients, but there is an important proportion of patients with the FMF phenotype who carry a single or no coding region mutation. This study aimed to investigate the promoter region and 3'-UTR polymorphisms of the MEFV gene in a group of FMF patients with no coding region mutations, to identify variations with a possible role in the regulation of MEFV expression.

**METHODS:** The study group consisted of 289 patients with FMF and 103 ethnically-matched healthy individuals of Turkish origin. All individuals were first genotyped for the five most commonly observed mutations (M694V, M680I, V726A, E148Q and M694I). Then, the coding regions of the MEFV gene in patients carrying none of the 5 mutations were amplified and screened using single-stranded conformation polymorphism and DNA sequencing. After the exclusion of patients with mutations in exons, the promoter and 3'-UTR regions of the MEFV gene were investigated in the remainder. For the haplotype analysis, all study groups were genotyped for two of the 3'-UTR single nucleotide polymorphisms (SNP).

**RESULTS:** Genotyping for five mutations revealed 186 patients (64.4%) with two mutations, 61 patients (21.1%) with one mutation, and 42 patients (14.5%) with no mutation. The carrier rate for healthy controls was found to be 10%. After screening all 10 exons in the patients with none of the 5 mutations, we identified 36 patients (12.5%) who had no coding region mutations. Analysis of the 3'-UTR region in these patients showed two Alu repeats (AluSx and AluSq), which were located in the 3'-UTR of the reference mRNA sequence. Sequencing of the 3'-UTR of the MEFV gene showed several SNPs that were clustered in 2 haplotypes. When we genotyped all study groups for two of the 3'-UTR SNPs (rs2741918 and rs450021), we observed a significant increase in the frequency of

heterozygotes for the 3'-UTR haplotypes in the FMF patients with no coding region polymorphisms compared to the healthy controls (75% versus 48.5%,  $p=0.006$ ,  $OR=3.2$ , 95% CI 1.4-7.4).

**CONCLUSION:** This study showed a group of 3'-UTR polymorphisms in the MEFV gene that are clustered in two haplotypes. In addition, a genetic association was observed between 3'-UTR polymorphisms and the FMF patients with no coding region mutations. These findings may suggest a role for 3'-UTR sequences in the regulation of MEFV expression.

PMID: 19026119 [Indexed for MEDLINE]

3616. J Immunol. 2008 Dec 15;181(12):8504-12.

IL-17A enhances vitamin D3-induced expression of cathelicidin antimicrobial peptide in human keratinocytes.

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Cathelicidin is strongly expressed in lesional skin in psoriasis and may play an important role as both an antimicrobial peptide and as an autoinflammatory mediator in this chronic skin disease. The mechanism of increased cathelicidin in psoriatic keratinocytes is not known, but recent observations have found that psoriasis has abundant Th17 cells that produce IL-17A and IL-22. We found that human keratinocytes stimulated with supernatants from T cells isolated from lesional psoriatic skin increased expression of cathelicidin when stimulated in the presence of 1,25-dihydroxyvitamin D(3) (1,25D(3)). This increase was signaled through the IL-17RA. In vitro, IL-17A, but not IL-22, enhanced cathelicidin mRNA and peptide expression in keratinocytes dependent on the presence of 1,25D(3). At the same time, coincubation with 1,25D(3) blocked induction of human beta-defensin 2 (HBD2), IL-6, and IL-8, which are other target genes of IL-17A. Act1, an adaptor associated with IL-17RA and essential for IL-17A signaling, mediated cathelicidin induction, as its suppression by small interfering RNA



inhibited HBD2 and cathelicidin. Both, 1,25D(3) and IL-17A signaled cathelicidin induction through MEK-ERK. These results suggest that increased IL-17A in psoriatic skin increases cathelicidin through a vitamin D(3)-, Act1-, and MEK-ERK-dependent mechanism. Therapy targeting this cathelicidin-regulating system might be beneficial in patients suffering from psoriasis.

PMCID: PMC2655307

PMID: 19050268 [Indexed for MEDLINE]

3617. Med Sci Monit. 2008 Dec;14(12):CS139-41.

Recurrent pericarditis as the initial manifestation of Familial Mediterranean fever.

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**BACKGROUND:** Familial Mediterranean fever is an autosomal recessive disease largely restricted to certain ethnic groups and presenting with recurrent febrile serositis attacks. Peritonitis, pleuritis, and synovitis are common manifestations; however, the pericardium is rarely affected.

**CASE REPORT:** In this case report, we describe a 25-year-old Turkish woman who presented with recurrent pericarditis of no obvious cause, which eventually responded to colchicine therapy. Using gene mutation analysis to detect the MEFV gene, the patient's condition was finally diagnosed as Familial Mediterranean fever.

**CONCLUSIONS:** Familial Mediterranean fever should be considered in patients with idiopathic recurrent pericarditis unresponsive to nonsteroidal anti-inflammatory medications and corticosteroids. Mutation analyses should be done.

PMID: 19043372 [Indexed for MEDLINE]

3618. Ann Dermatol Venereol. 2008 Dec;135 Suppl 7:S317-25. doi: 10.1016/S0151-9638(08)75484-X.

[What's new in clinical dermatology].

[Article in French]

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This selection reviews several topics in the news: - in internal medicine, the cardiovascular and pulmonary risk factors in progressive systemic sclerosis (circulating lupus anticoagulant, smoking, NT-pro BNP marker); the relations between lupus erythematosus and polymorphic light eruption, or Jessner-Kanof syndrome; the diagnostic score of autoinflammatory syndromes; and the dysmetabolism syndrome of psoriasis; - in infectious diseases, the return of epidemic typhus; the emergence of TIBOLA rickettsiosis; the development of methicillin-resistant *Staphylococcus aureus* strains in both the nosocomial and community settings; and finally news on herpes group viral infections.

DOI: 10.1016/S0151-9638(08)75484-X

PMID: 19264207 [Indexed for MEDLINE]

3619. Arthritis Rheum. 2008 Dec;58(12):3924-31. doi: 10.1002/art.24137.

S100A12 is a novel molecular marker differentiating systemic-onset juvenile idiopathic arthritis from other causes of fever of unknown origin.

Wittkowski H(1), Frosch M, Wulffraat N, Goldbach-Mansky R, Kallinich T, Kuemmerle-Deschner J, Frühwald MC, Dassmann S, Pham TH, Roth J, Foell D.

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OBJECTIVE: Fever of unknown origin (FUO) in children presents a diagnostic

challenge. The differential diagnosis includes systemic-onset juvenile idiopathic arthritis (JIA), an autoinflammatory syndrome associated with activation of phagocytic cells that, at presentation, is difficult to differentiate from severe systemic infections. The aim of this study was to investigate whether serum concentrations of the phagocytic proinflammatory protein S100A12 may help in deciding whether to treat patients with FUO with antibiotics or immunosuppressive agents.

**METHODS:** Serum samples were obtained from 45 healthy control subjects and from 240 patients (60 with systemic-onset JIA, 17 with familial Mediterranean fever [FMF], 18 with neonatal-onset multisystem inflammatory disease [NOMID], 17 with Muckle-Wells syndrome [MWS], 40 with acute lymphoblastic leukemia [ALL], 5 with acute myeloblastic leukemia [AML], and 83 with systemic infections). All samples were collected at the time of presentation, before the initiation of any treatment, and concentrations of S100A12 were determined by enzyme-linked immunosorbent assay.

**RESULTS:** The mean  $\pm$  95% confidence interval serum levels of S100A12 were as follows: in patients with JIA, 7,190  $\pm$  2,690 ng/ml; in patients with FMF, 6,720  $\pm$  4,960 ng/ml; in patients with NOMID, 720  $\pm$  450 ng/ml; in patients with MWS, 150  $\pm$  60 ng/ml; in patients with infections, 470  $\pm$  160 ng/ml; in patients with ALL, 130  $\pm$  80 ng/ml; in patients with AML, 45  $\pm$  60 ng/ml; in healthy control subjects, 50  $\pm$  10 ng/ml. The sensitivity and specificity of S100A12 to distinguish between systemic-onset JIA and infections were 66% and 94%, respectively.

**CONCLUSION:** S100A12, a marker of granulocyte activation, is highly overexpressed in patients with systemic-onset JIA or FMF, which may point to as-yet unknown common inflammatory mechanisms in these diseases. The measurement of S100A12 serum levels may provide a valuable diagnostic tool in the evaluation of FUO.

DOI: 10.1002/art.24137

PMCID: PMC2680303

PMID: 19035478 [Indexed for MEDLINE]

3620. Eur J Pediatr. 2009 Aug;168(8):1017-9. doi: 10.1007/s00431-008-0875-y. Epub 2008 Nov 26.

Sulphasalazine treatment in protracted familial Mediterranean fever arthritis.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by self-limited attacks of fever and polyserositis. Articular involvement in early-onset FMF is a common finding characterized by non-erosive, generally asymmetric monoarthritis in large joints. Protracted FMF arthritis was reported in 2.6% of Turkish patients. An 8-year-old female who has a history of FMF for 5 years applied to our hospital with complaints of persistent swelling and pain of her left knee for 8 months. The patient had been tried to be managed with non-steroidal anti-inflammatory drugs as well as intra-articular steroids and colchicine. However, arthritis and acute phase response persisted. With sulphasalazine, complete recovery was achieved. It is our belief that sulphasalazine can be a choice of medical treatment in protracted FMF arthritis.

DOI: 10.1007/s00431-008-0875-y

PMID: 19034507 [Indexed for MEDLINE]

3621. Clin Appl Thromb Hemost. 2009 Jul-Aug;15(4):443-7. doi: 10.1177/1076029608325540. Epub 2008 Nov 24.

The effect of plasminogen activator inhibitor-1 -675 4G/5G polymorphism on familial Mediterranean fever (FMF) disease.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease that is the most common of a rare group of disorders collectively termed familial hereditary periodic fever syndromes, also known as autoinflammatory syndromes. FMF is predominantly affecting people of Mediterranean descent and clinically characterized by intermittent attacks of fever with peritonitis and abdominal pain, pleuritis, arthritis, or erysipelas-like rashes. Amyloidosis due to chronic

inflammation progressing to renal failure is one of the most serious potential complications of this disease. Patients with inflammatory diseases, such as systemic lupus erythematosus and rheumatoid arthritis, and conditions with chronic subclinical inflammation, like obesity and diabetes mellitus, are now considered to have an increased risk of atherosclerotic cardiovascular complications. FMF is also an inflammatory disease, and it is accepted that even during attack-free periods significant inflammatory reaction continues. However, whether this inflammatory process causes premature atherosclerosis is not known due to a lack of data. Different studies have investigated the association between the fibrinolytic and inflammatory process parameters. PAI-1 is paracrine secretion of pro- and antiinflammatory cytokines, thereby playing a possible role in the adiposity-related inflammation and atherosclerosis. The patients with IRS have higher values of fibrinogen, factor VII, VIII, Von Willebrand factor and Plasminogen Activator Inhibitor (PAI) compared to control subjects. So that we aimed in this study to investigate whether FMF patients with/without amyloidosis and with M694V homozygote mutation, have increased risk for atherosclerotic cardiovascular complications and to determine the strength of association between MEFV gene-mutation types. To our knowledge, this is the first case control and cross-sectional study in the pediatric age groups.

DOI: 10.1177/1076029608325540

PMID: 19033264 [Indexed for MEDLINE]

3622. Nephrol Dial Transplant. 2009 Feb;24(2):676-8. doi: 10.1093/ndt/gfn646. Epub 2008 Nov 25.

Successful treatment of familial Mediterranean fever with Anakinra and outcome after renal transplantation.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent episodes of fever and inflammation. The most severe

complication of FMF is the development of AA amyloidosis, which can be life threatening. The only current effective treatment for FMF is colchicine. Regular prophylactic treatment with colchicine at a dose of 1-2 mg daily prevents or substantially reduces the clinical manifestations of FMF in at least 90% of cases. However, approximately 10% of patients are reported to be resistant or non-responsive to colchicine and in these cases there is no consensus as to which second line agents should be used. We describe the first case, to our knowledge, of a patient with FMF and end-stage renal failure due to AA amyloidosis, successfully treated with IL-1 receptor blockade. Our data suggest that the IL-1 receptor antagonist Anakinra (Kineret; r-metHuIL-1 ra) may represent a safe and effective therapy for the treatment of colchicine-resistant FMF, in patients requiring renal replacement therapy, with dialysis or transplantation.

DOI: 10.1093/ndt/gfn646

PMID: 19033248 [Indexed for MEDLINE]

3623. Int Urol Nephrol. 2009 Dec;41(4):1047-53. doi: 10.1007/s11255-008-9500-2. Epub 2008 Nov 25.

Nutcracker syndrome in a child with familial Mediterranean fever (FMF) disease: renal ultrastructural features.

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Renal nutcracker syndrome is an uncommon clinical condition caused by compression of the left renal vein. It is usually accompanied by hematuria and/or orthostatic proteinuria. To date, the pathogenic mechanism of proteinuria and its ultrastructural features have not been clearly identified. Here, we present the glomerular ultrastructural features of nutcracker syndrome and our attempt to analyze the relationship between proteinuria and ultrastructural features. Two months prior to admission, a 11-year-old girl with familial Mediterranean fever who was treated with colchicine was found to have proteinuria. Accompanying hematuria was not identified, and laboratory findings were otherwise normal. Doppler ultrasonography and computerized tomography angiography revealed an

entrapment of the left renal vein. A kidney biopsy was performed due to the persistent proteinuria. Light microscopy revealed segmental, minimal increases in the mesangial cells and matrix. No amyloid deposition was present. Neither immunofluorescence nor electron microscopy showed immunoglobulin deposition. Increased thickness of the glomerular basement membrane due to the unequivocal radiolucent widening of the lamina rara interna was the most striking ultrastructural finding. At high magnification, there were no amyloid fibrils. It has been proposed that hemodynamic alterations and structural changes in glomerular basement membrane glycosaminoglycans may play a role in the pathogenesis of proteinuria. Radiolucent expansion of the lamina rara interna of the glomerular basement membrane in the presenting case would seem to support these data.

DOI: 10.1007/s11255-008-9500-2

PMID: 19031109 [Indexed for MEDLINE]

3624. Clin Rheumatol. 2009 Feb;28(2):239-40. doi: 10.1007/s10067-008-1041-7. Epub 2008 Nov 25.

Can we use faecal calprotectin to distinguish abdominal pain of familial Mediterranean fever (FMF) from acute appendicitis?

Makay B, Makay O, Unsal E.

Comment on

Clin Rheumatol. 2007 Dec;26(12):2059-62.

DOI: 10.1007/s10067-008-1041-7

PMID: 19031094 [Indexed for MEDLINE]

3625. Neurology. 2008 Nov 25;71(22):1812-20. doi: 10.1212/01.wnl.0000335930.18776.47.

Multiple sclerosis and the TNFRSF1A R92Q mutation: clinical characteristics of 21 cases.

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**OBJECTIVE:** Tumor necrosis factor receptor 1-associated periodic syndrome (TRAPS) is an autosomal dominantly inherited autoinflammatory disorder resulting from mutations in the TNFRSF1A gene, which encodes the p55 receptor for tumor necrosis factor alpha. We recently identified the R92Q mutation encoded by exon 4 in six patients with multiple sclerosis (MS) who reported at least two symptoms suggestive of TRAPS. The current study presents the characteristics of a larger cohort of MS patients carrying this mutation.

**METHODS:** Clinical and laboratory parameters, including human leukocyte antigen (HLA)-DR15 status, were evaluated, and genetic testing was performed. Whenever possible, family members were also invited for interview and mutation analysis.

**RESULTS:** Twenty TNFRSF1A R92Q carriers had MS according to the McDonald criteria, and 1 had clinically isolated syndrome. The majority of patients had typical onset and features of MS. Nine patients carried an HLA-DR15 haplotype. All individuals showed TRAPS-compatible symptoms, which consisted mainly of myalgias, arthralgias, headache, severe fatigue, and skin rashes; were milder than usually described; and appeared mainly in adulthood. Most patients experienced severe side effects during immunomodulatory therapy for MS. Seventeen family members carried the identical mutation, and 15 of them reported symptoms suggestive of TRAPS.

**CONCLUSION:** In most cases with multiple sclerosis (MS) and coexisting tumor necrosis factor receptor 1-associated periodic syndrome (TRAPS), features of MS were quite typical, whereas TRAPS presented mostly without the fever episodes observed in childhood. The penetrance of the R92Q mutation in affected family members was higher than reported. We recommend careful observation of MS patients with coexisting TRAPS with regard to unexpected side effects of immunomodulatory therapies.

DOI: 10.1212/01.wnl.0000335930.18776.47

PMID: 19029521 [Indexed for MEDLINE]



Autoinflammatory diseases.

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Autoinflammatory diseases (AIDs) are illnesses caused by primary dysfunction of the innate immune system. Proteins that are mutated in AIDs mediate the regulation of NFkappaB activation, cell apoptosis, and IL-1beta secretion through cross-regulated and sometimes common signaling pathways. AIDs include a broad number of monogenic [e.g., familial Mediterranean fever (FMF), cryopyrin-associated periodic syndrome (CAPS), mevalonate kinase deficiency (MKD), tumor necrosis factor (TNF)-receptor-associated periodic syndrome (TRAPS)] and multifactorial (e.g., Behçet's syndrome) disorders. These conditions are characterized by recurrent attacks of fever, abdominal pain, arthritis, and cutaneous signs; these symptoms sometimes overlap, obscuring diagnosis. Distinguishing signs and the use of specific functional tests where available (e.g., in MKD) are helpful. However, some patients remain hard to manage despite the advent of new genetic tests and/or due to lack of effective treatment.

DOI: 10.1016/j.berh.2008.08.009

PMID: 19028365 [Indexed for MEDLINE]

3627. Best Pract Res Clin Rheumatol. 2008 Oct;22(5):793-809. doi: 10.1016/j.berh.2008.08.005.

Behçet's syndrome.

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Recent epidemiological work suggests that genetic background overrides environmental factors in the pathogenesis of Behçet's syndrome (BS). There are at

least two clusters of disease expression. The first is the cluster of superficial vein thrombosis, deep vein thrombosis and dural sinus thrombi; the second cluster is that of acne, arthritis and enthesitis. The association of antibodies to anti-Saccharomyces cerevisiae antibodies and the presence of inflammatory bowel disease is perhaps another such cluster. The presence of such clusters suggests that there might be more than one disease mechanism operative in this complex disorder. There is a recent trend to classify BS with the autoinflammatory disorders. However, practically all autoinflammatory conditions are recurrent fever syndromes of children, and are genetically linked to well-defined loci; none of this is true for BS. Recent guidelines from the European League Against Rheumatism are quite useful for the management of the disease in organ systems other than the vascular, neurological and gastrointestinal systems, because of the lack of controlled studies related to these latter pathologies.

DOI: 10.1016/j.berh.2008.08.005

PMID: 19028364 [Indexed for MEDLINE]

3628. Hum Immunol. 2009 Jun;70(6):468-71. doi: 10.1016/j.humimm.2008.10.017. Epub 2008 Nov 19.

Lack of association between E148Q MEFV variant and Kawasaki disease.

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We investigated a possible association between Kawasaki disease (KD), a systemic vasculitis of unknown etiology, or its coronary artery lesions (CAL) and MEFV gene variants including E148Q, the most common and mild mutation in the MEFV gene for familial Mediterranean fever or vasculitis-related disorders. The study population comprised a total of 138 Japanese patients with KD, including 45 patients with CAL and 93 patients without CAL and 170 normal controls. Sequence variations for the MEFV gene were detected by direct sequencing, followed by the TaqMan SNP genotyping assay. The genotype and allele frequencies of MEFV gene variants (E148Q, L110P, R202Q, P369S, R408Q) were compared between KD patients with and without CAL or between KD patients with CAL and controls. E148Q

heterozygotes and homozygotes were observed in 37.1 and 5.5% of healthy controls, 33.3 and 5.1% of KD patients, and 37.8 and 4.4% of KD patients with CAL. No significant differences were observed in the genotype and allele frequencies of other MEFV gene variants (L110P, R202Q, P369S, R408Q) between KD patients with and without CAL or between KD patients with CAL and controls. No associations were detected between the MEFV gene variants and the development of KD or CAL formation in KD.

DOI: 10.1016/j.humimm.2008.10.017

PMID: 19026701 [Indexed for MEDLINE]

3629. Clin Exp Rheumatol. 2008 Jul-Aug;26(4 Suppl 50):S131.

Association of familial Mediterranean fever and celiac disease in a 14-year-old girl with recurrent arthritis.

Kuloğlu Z, Kansu A, Tutar E, Yalçinkaya F, Ensari A, Girgin N.

PMID: 19026136 [Indexed for MEDLINE]

3630. Clin Exp Rheumatol. 2008 Jul-Aug;26(4 Suppl 50):S128-9; author reply S129.

Saturday night fever: bizarre recurrence of fever attacks in a patient carrying a mutation in both the MEFV and TNFRSF1A genes.

Cantarini L, Baldari CT, Rossi Paccani S, Lucherini OM, Laghi Pasini F, Galeazzi M.

Comment on

Clin Exp Rheumatol. 2007 Jul-Aug;25(4 Suppl 45):S93-5.

PMID: 19026132 [Indexed for MEDLINE]

3631. Clin Exp Rheumatol. 2008 Jul-Aug;26(4 Suppl 50):S125.

Relapsing polychondritis in a patient with familial Mediterranean fever and amyloidosis.

Salihoglu A, Seyahi E, Celik S, Yurdakul S.

PMID: 19026131 [Indexed for MEDLINE]

3632. Clin Exp Rheumatol. 2008 Jul-Aug;26(4 Suppl 50):S114-6.

Tumor markers in familial Mediterranean fever and their correlation with the frequency of attacks.

Balaban YH(1), Simsek H, Yilmaz R, Sarer-Yurekli BP, Shorbagi A, Tatar G.

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**OBJECTIVE:** Serum levels of tumor markers can be elevated in several benign diseases affecting the serosal surfaces. Familial Mediterranean fever (FMF) is a genetic disease characterized by acute attacks of fever and inflammation of the serosal membranes. The aim of this study was to examine the levels of tumor markers in FMF patients and their correlation with the frequency of attacks.

**METHODS:** Serum levels of CA 125, CA 19-9, CA 15-3, CA 72-4, CEA, and AFP were measured by ELISA in 36 patients with a definitive diagnosis of FMF (21 males, 15 females, mean age 36.4+/-10.3 yrs) and in 19 healthy controls.

**RESULTS:** Serum levels of all tumor markers were normal in the controls. In FMF patients serum levels of CA 125, CA 19.9, CA 15.3, CEA and AFP were within normal ranges, whereas CA 72.4 was significantly higher than in the controls ( $p=0.001$ ). Half of the FMF patients showed increased levels of CA 72.4; the mean level was lower in those in complete remission. However, no statistically significant correlation was found between FMF attacks and acute phase reactant levels.

**CONCLUSION:** With the exception of Ca 72.4, serum levels of tumor markers are not affected by changes in inflammatory cytokines levels during FMF attacks.

PMID: 19026128 [Indexed for MEDLINE]

3633. Clin Exp Rheumatol. 2008 Jul-Aug;26(4 Suppl 50):S49-51.

Non-response to colchicine in FMF--definition, causes and suggested solutions.

Ben-Chetrit E, Ozdogan H.

PMID: 19026114 [Indexed for MEDLINE]

3634. Bull Exp Biol Med. 2008 Feb;145(2):202-6.

Behavior of lymphoid cell population, cell nuclei and nucleoli in periodic disease and leukemia.

Magakian YA(1), Karalova EM, Abroyan LO, Akopyan LA.

Author information:

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Similar behavior of lymphoid cells, their nuclei and nucleoli in periodic disease and leukemia attest to nonspecific reaction of the immune system to these diseases, but the intensity of this reaction and mechanisms of the population recovery are different. DNA hyperreplication plays an important role in this process: in periodic disease it is realized via gene amplification, which manifests by the formation of H2c nuclei and increase in the number of nucleoli, while in leukemia bone marrow lymphoblasts double the DNA content during S phase, mature during G2 phase, and then divide. We called this mechanism "reserve lymphopoiesis" by analogy with reserve erythropoiesis discovered previously by us.

PMID: 19023969 [Indexed for MEDLINE]

3635. Turk J Pediatr. 2008 Jul-Aug;50(4):326-30.

Relation between microalbuminuria and gene mutations in familial Mediterranean fever.

Ergüven M(1), Emeksiz C, Deveci M, Özlü SG.

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(1)Department of Pediatrics, Ministry of Health Göztepe Training Hospital, Istanbul, Turkey.

We aimed to investigate the urinary microalbumin level, which is a sensitive marker of glomerular function for establishing probable renal involvement in early stages of the disease in patients with familial Mediterranean fever (FMF), and to determine the relation between gene mutations of these cases and urinary microalbumin levels. Fifty patients with FMF who were admitted to our department and had been followed up in the pediatric rheumatology outpatient clinic for five years were included in the study. Diagnosis was based on Tel-Hashomer criteria. Gene mutations (M694V, V726A, M680I) and acute phase reactants were determined as supportive findings. Routine renal function tests with 24 hour urinary microalbumin levels and urinary microalbumin/creatinine ratios were evaluated. There was a statistically significant difference between the study and control groups in terms of microalbumin/creatinine ratios, whereas no difference was observed with respect to the other parameters. Comparison of subgroups (gene mutations) in terms of all parameters (age, age at diagnosis, duration of delay in treatment, glomerular filtration rate, tubular reabsorption of phosphorus, and microalbumin/creatinine ratios) showed no difference. We suggest measurement of urinary microalbumin levels at regular intervals in order to establish renal injury early and decrease related complications.

PMID: 19014044 [Indexed for MEDLINE]

3636. Medicine (Baltimore). 2008 Nov;87(6):301-10. doi: 10.1097/MD.0b013e318190cfb7.

Long-term follow-up, clinical features, and quality of life in a series of 103 patients with hyperimmunoglobulinemia D syndrome.

van der Hilst JC(1), Bodar EJ, Barron KS, Frenkel J, Drenth JP, van der Meer JW, Simon A; International HIDS Study Group.

Collaborators: Rippel S, Knockaert DC, Jilek D, Pohunek P, Vaclava K, Darina S, Koné-Paut I, Pillet P, Touitou I, Lawrence A, Merlini G, Obici L, Scolozzi RM, Armbrust W, van Deuren M, Bijlsma JW, Hendrickxs G, Schreuder MC, Tribolet de Abreu T, Hammoudeh M, Vahab A, Arnal Guimera MC, Topaloglu R, Fisher NC, Gardner-Medwin J, Hawkins PN, Lachmann HJ, Moira T, Powell RJ, McDermott L, David JJ, Ellison JW, Granowitz EV, Saulsbury FT.

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The hyperimmunoglobulinemia D and periodic fever syndrome (HIDS), one of the autoinflammatory syndromes, is caused by mutations in the gene coding for mevalonate kinase (MVK). We conducted the current study to assess the genetic, laboratory, and clinical features as well as the complications and course of disease in patients with genetically confirmed HIDS. In addition, we studied the quality of life and course of life in a selection of patients. Follow-up data were obtained by a questionnaire sent to all physicians of patients in the International HIDS Database. In addition, we assessed the course of life and quality of life in Dutch patients aged >16 years using validated quality of life instruments. Data were obtained from 103 patients from 18 different countries. The median age of first attack was 6 months (range, 0-120 mo), with a median period of 9.9 years from onset of disease to diagnosis. The most frequent symptoms that accompanied attacks of fever were lymphadenopathy, abdominal pain, arthralgia, diarrhea, vomiting, skin lesions, and aphthous ulcers. Amyloidosis was a severe but infrequent complication (2.9%). The median serum IgD level was 400 U/mL. IgD levels were normal in 22% of patients. The 4 most prevalent mutations (V377I, I268T, H20P/N, P167L) accounted for 71.5% of mutations found. The frequency of attacks decreased with the patient's increasing age, although 50% of patients over the age of 20 years still had 6 or more attacks per year. Many drugs have been tried in HIDS. Some patients responded to high-dose prednisone (24.4% response). Anakinra and etanercept can also be effective (33.3% response). Quality of life was determined in a subgroup of patients (n = 28). Social functioning, general health perception, and vitality were significantly lower in patients with HIDS than in controls, as were autonomy and social

development. In addition, HIDS had an adverse impact on educational achievements and employment status. In conclusion, HIDS is an early-onset disease that is accompanied by an array of inflammatory symptoms. Although the frequency of attacks decreases during the patient's life, many patients continue to have frequent attacks. HIDS impairs several aspects of quality of life.

DOI: 10.1097/MD.0b013e318190cfb7

PMID: 19011501 [Indexed for MEDLINE]

3637. Rheumatology (Oxford). 2009 Jan;48(1):23-5. doi: 10.1093/rheumatology/ken409. Epub 2008 Nov 4.

MEFV mutations in systemic onset juvenile idiopathic arthritis.

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**OBJECTIVES:** Autoinflammatory diseases constitute a large spectrum of monogenic diseases like FMF or cryopyrin-associated periodic syndromes (CAPS) and complex genetic trait diseases such as systemic onset juvenile idiopathic arthritis (SoJIA). An increased rate of MEFV mutations has been shown among patients with PAN and HSP, in populations where FMF is frequent. The aim of the study is to search for MEFV mutations in our patients with SoJIA and see whether these mutations had an effect on disease course or complications.

**METHODS:** Thirty-five children with the diagnosis of SoJIA were screened for 12 MEFV mutations. The control data were obtained from a previous study of our centre determining the carrier frequency in Turkish population.

**RESULTS:** Two patients were homozygous and three patients were heterozygous for the M694V mutation. One patient was a compound heterozygote for the M680I/V726A mutations. Heterozygous V726A mutation was found in one patient. The overall mutation frequency of patients was 14.28%. This figure had been compared with the previously published rate of disease-causing mutations in this country, which is 5%. Disease-causing mutations were found to be significantly more frequent in the SoJIA patients than the population ( $P < 0.01$ ). Among these, M694V was the leading



mutation with a frequency of 10% in SoJIA. Six patients carrying MEFV mutations were among the most resistant cases requiring biological therapy.

CONCLUSION: SoJIA patients had a significantly higher frequency of MEFV mutations but clinical studies with large number of patients are needed to confirm the association of MEFV mutations with SoJIA and its course.

DOI: 10.1093/rheumatology/ken409

PMID: 18984609 [Indexed for MEDLINE]

3638. J Periodontal Res. 2009 Jun;44(3):354-61. doi: 10.1111/j.1600-0765.2008.01115.x. Epub 2008 Oct 7.

Periodontal disease in patients with familial Mediterranean fever: from inflammation to amyloidosis.

Cengiz MI(1), Bagci H, Cengiz S, Yigit S, Cengiz K.

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BACKGROUND AND OBJECTIVE: Familial Mediterranean fever stimulates a very intense acute-phase reactants response and if left untreated eventually leads to amyloidosis. The aim of this study was to determine the prevalence of periodontal disease among patients with familial Mediterranean fever in the Black Sea region in Turkey and to evaluate whether periodontitis is related to amyloidosis in patients with familial Mediterranean fever.

MATERIAL AND METHODS: One-hundred and thirty three patients with familial Mediterranean fever and 50 healthy subjects were included in this study. Periodontal health and disease were evaluated using the gingival index, papillary bleeding index, plaque index and periodontal disease index. The concentrations of serum acute-phase reactants were measured at baseline and at 4-6 wk after completion of the nonsurgical periodontal therapy. Genetic testing for familial Mediterranean fever was performed using the familial Mediterranean fever StripAssay. Kidney biopsy was carried out on all proteinuric patients.

RESULTS: The prevalence of moderate to severe periodontitis in familial Mediterranean fever patients with amyloidosis (80.6%) was significantly greater ( $p < 0.01$ ) than in familial Mediterranean fever patients without amyloidosis

(38%) and in controls (20%). Serum levels of acute-phase reactants in familial Mediterranean fever patients were reduced significantly following nonsurgical periodontal therapy ( $p < 0.01$ ).

**CONCLUSION:** Periodontal therapy seems to reduce the serum levels of acute-phase reactants in patients with familial Mediterranean fever. Therefore, treating periodontitis might help to alleviate the disease burden in patients with familial Mediterranean fever.

DOI: 10.1111/j.1600-0765.2008.01115.x

PMID: 18973533 [Indexed for MEDLINE]

3639. Annu Rev Med. 2009;60:431-42. doi: 10.1146/annurev.med.60.103007.132540.

Genetic testing in clinical practice.

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In the practice of internal medicine, the value of genetic testing in common (mono)genetic diseases such as familial hemochromatosis, hypercholesterolemia, Mediterranean fever, and thrombophilia is limited. The genotype insufficiently predicts the phenotype because of the powerful effects of other modifying genes, environmental influences, and lifestyle factors. Many common diseases, including diabetes mellitus, osteoporosis, and cardiovascular disease, have strong genetic influences but are called complex genetic traits. The underlying genetic factors are currently investigated using new molecular tools such as genome-wide association studies, analyzing up to 500,000 markers in huge numbers of patients. Many new (often unexpected) markers have been identified, and in many instances their functional significance is unknown. Genomic profiles play a rapidly growing role in the field of pharmacogenomics. A number of recently identified pharmacogenomic biomarkers are helpful to predict drug-related toxic effects.

DOI: 10.1146/annurev.med.60.103007.132540

PMID: 18947300 [Indexed for MEDLINE]

3640. Tuberk Toraks. 2008;56(3):319-24.

Development of interferon induced sarcoidosis in a patient with familial mediterranean fever.

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A 42-year-old male patient, who had been on colchicine therapy for familial mediterranean fever admitted with dyspnea on exertion. He had a history of interferon-alpha (IFN-alpha) administration. The chest X-ray showed diffuse distribution of reticulonodular opacities in both lungs. A computerized tomography scan of the lungs revealed mediastinal and bilateral hilar lymphadenopathies, translucent densities, consolidations, reticular opacities and subpleural milimetric cystic spaces. Pulmonary-function studies demonstrated defects in diffusing and vital capacity. Histopathological evaluation was compatible with granulomatous lymphadenitis. The patient was diagnosed as having pulmonary sarcoidosis. He reflects the characteristics of IFN-induced sarcoidosis, but the duration between the cessation of IFN therapy and the development of symptoms is 42 months, which is longer than usually expected. In this case, history of IFN-alpha administration led us to suspect sarcoidosis because of a possible association between IFN therapy and the development of sarcoidosis.

PMID: 18932035 [Indexed for MEDLINE]

3641. Free Radic Biol Med. 2008 Dec 15;45(12):1601-9. doi: 10.1016/j.freeradbiomed.2008.09.019. Epub 2008 Sep 27.

Measurement of formamidopyrimidines in DNA.

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Formamidopyrimidines, 4,6-diamino-5-formamidopyrimidine (FapyAde) and 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FapyGua), are among major lesions in DNA generated by hydroxyl radical attack, UV radiation, or photosensitization in vitro and in vivo. FapyAde and FapyGua exist in living cells at detectable background levels and are formed by exposure of cells to DNA-damaging agents. Numerous prokaryotic and eukaryotic DNA glycosylases exist for the repair of formamidopyrimidines by base excision repair pathways in cells, indicating their biological significance. Moreover, they are premutagenic lesions, albeit to different extents, revealing a possible role in disease processes. Methodologies using gas chromatography/mass spectrometry (GC/MS) with capillary columns have been developed to accurately measure FapyAde and FapyGua in DNA in vitro and in vivo. Stable isotope-labeled analogues of these compounds have been synthesized and are commercially available to be used as internal standards for accurate quantification. GC/MS with isotope dilution provides excellent sensitivity and selectivity for positive identification and accurate quantification, and has widely been applied in the past to the measurement of formamidopyrimidines under numerous experimental conditions. This paper reports on the details of this GC/MS methodology.

DOI: 10.1016/j.freeradbiomed.2008.09.019

PMID: 18926902 [Indexed for MEDLINE]

3642. Platelets. 2008 Sep;19(6):405-8. doi: 10.1080/09537100802187121.

Platelet activation in patients with Familial Mediterranean Fever.

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Increased platelet activation and aggregation are central processes in the pathophysiology of atherosclerosis. Increased platelet activity is associated

with increased platelet volume. Mean platelet volume (MPV), a determinant of platelet function, is a newly emerging risk factor for atherothrombosis. Familial Mediterranean Fever (FMF) is an autosomal recessive disease characterized by recurrent inflammatory febrile attacks of serosal and synovial membranes. Recently few studies have shown that FMF is associated with increased atherosclerosis risk. The present study was designed to evaluate levels of MPV in FMF patients compared with healthy subjects. We selected 35 FMF patients and 35 healthy control subjects matched for age, gender, and body mass index. Metabolic parameters and MPV levels were measured in all groups. Metabolic parameters were not different among the study groups ( $p > 0.05$ ). The levels of MPV were significantly higher in the FMF group than in the control group ( $8.6 \pm 0.9$  fl vs  $7.8 \pm 0.5$  fl,  $p = 0.001$ ). The MPV levels were negatively correlated with duration of colchicine treatment ( $r = -0.40$ ,  $p = 0.017$ ). Also MPV levels showed positive correlation with delay of diagnosis ( $r = 0.58$ ,  $p = 0.001$ ). In conclusion, our results suggest that patients with FMF tend to have an increased platelet activation. Increased platelet activity could contribute to increasing the atherosclerotic risk in FMF patients.

DOI: 10.1080/09537100802187121

PMID: 18925507 [Indexed for MEDLINE]

3643. Neurol Sci. 2008 Dec;29(6):471-5. doi: 10.1007/s10072-008-1015-1. Epub 2008 Oct 14.

Clustering of organ-specific autoimmunity: a case presentation of multiple sclerosis and connective tissue disorders.

Kale N(1), Icen M, Agaoglu J, Yazici I, Tanik O.

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Multiple sclerosis (MS) is the most common demyelinating disease caused by an autoimmune inflammatory process in the central nervous system (CNS) and is associated with aberrant immune response to myelin selfantigens. Coexistence of MS with other autoimmune disorders, including connective tissue disorders including systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome

and scleroderma have been reported previously. In the present article we report the coexistence of MS, familial mediterranean fever and ankylosing spondylitis in a patient and review the clinical presentation, neurologic findings, cerebrospinal fluid and radiologic characteristics and treatment options. We further discuss the immunopathogenetic mechanisms for a possible association between MS and autoimmune disorders.

DOI: 10.1007/s10072-008-1015-1

PMID: 18854919 [Indexed for MEDLINE]

3644. Anadolu Kardiyol Derg. 2008 Oct;8(5):395; author reply 395-6.

Assessment of aortic stiffness and ventricular functions in familial Mediterranean fever.

Yildiz M, Biteker M, Ozkan M.

Comment on

Anadolu Kardiyol Derg. 2008 Aug;8(4):271-8.

PMID: 18849241 [Indexed for MEDLINE]

3645. J Rheumatol. 2008 Dec;35(12):2427-9. Epub 2008 Oct 1.

MEFV mutations modify the clinical presentation of Henoch-Schönlein purpura.

Ozçakar ZB(1), Yalçinkaya F, Cakar N, Acar B, Kasapçopur O, Ugüten D, Soy D, Kara N, Uncu N, Arisoy N, Ekim M.

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**OBJECTIVE:** To investigate the prevalence of MEFV gene mutations in Turkish patients with Henoch-Schönlein purpura (HSP) but with no symptoms of familial Mediterranean fever (FMF). In addition, we assessed the clinical and laboratory

characteristics of HSP patients with and without MEFV mutations.

**METHODS:** Eighty pediatric patients with HSP (44 boys and 36 girls) were enrolled. Blood for mutation analysis was obtained either at the time of the diagnosis of HSP or during followup visits in previously diagnosed patients. No patient had the diagnosis of FMF in their history and in the followup period. Exon 10 of the MEFV gene was screened, together with p.E148Q mutation analysis.

**RESULTS:** Twenty-seven (34%) patients were found to be heterozygous for one of the screened MEFV mutations; p.M694V in 16, p.M680I in 5, p.V726A in 3, and p.E148Q in 3 patients. Patients with MEFV mutations were younger than those without mutations and they had edema and arthritis more frequently. Also, the frequencies of elevated erythrocyte sedimentation rate and C-reactive protein values were found to be significantly higher in patients who had MEFV mutations.

**CONCLUSION:** Alterations in the MEFV gene are important susceptibility factors for the development of HSP and also affect the clinical presentation of it.

PMID: 18843775 [Indexed for MEDLINE]

3646. Adv Med Sci. 2008;53(2):149-57. doi: 10.2478/v10039-008-0038-4.

Indications and results of videocapillaroscopy in clinical practice.

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Nailfold videocapillaroscopy (NVC) is one of the best diagnostic non-invasive imaging techniques to evaluate microcirculation in vivo and is increasingly employed in the field of rheumatology. Indeed, at present, the most important utility of NVC is in the identification of microvascular involvement in many rheumatic diseases, particularly in systemic sclerosis. More recently, this technique has been shown to be applicable to the study of many other extra-rheumatic diseases, such as arterial hypertension, diabetes mellitus, acromegaly, hyperthyroidism, cardiac syndrome X, primary biliary cirrhosis, Crohn's disease, psoriasis, familial Mediterranean fever. This article sets down the methodology of examination and normal pattern of capillary vessels and reviews the applications of NVC in clinical practice and its results in rheumatic

and non-rheumatic diseases.

DOI: 10.2478/v10039-008-0038-4

PMID: 18842560 [Indexed for MEDLINE]

3647. Eur J Pediatr. 2009 Jul;168(7):825-31. doi: 10.1007/s00431-008-0843-6. Epub 2008 Oct 7.

B cell cytopenia in two brothers with hyper-IgD and periodic fever syndrome.

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We report on two brothers with hyperimmunoglobulinemia D (patient 1: serum immunoglobulin D [IgD] concentration initially 61 IU/ml, later on 340 IU/ml; patient 2: serum IgD concentration 144 IU/ml; normal <100 IU/ml, 97th centile) and periodic fever syndrome (HIDS). Both are compound heterozygous for the mevalonate kinase (MVK) mutations V377I and I268T. They developed significant B cell cytopenia (7%, 129/microl and 11%, 132/microl, respectively; normal ranges 12-22%, 300-500/microl) with hypogammaglobulinemia (IgG 5.48 g/l and IgG 5.22 g/l, respectively; normal range IgG 6-13 g/l). Furthermore, the clinical spectrum shows an interesting atypical autoinflammatory symptomatology. The therapy consisted of prednisone, azathioprine, and intravenous immunoglobulins (IVIG), which results in reduced incidence and severity of febrile attacks. CONCLUSION: The pathogenesis and clinical presentation of HIDS is still not fully understood and show a great variability. To our knowledge, severe B cell cytopenia in children with HIDS has not been reported before. Furthermore, the therapy of febrile episodes is still performed on an individual basis in affected patients.

DOI: 10.1007/s00431-008-0843-6

PMID: 18839211 [Indexed for MEDLINE]

3648. Clin Pediatr (Phila). 2009 Mar;48(2):215-9. doi: 10.1177/0009922808324130. Epub 2008 Oct 2.



A child with recurrent episodes of fever and joint pain.

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DOI: 10.1177/0009922808324130

PMID: 18832548 [Indexed for MEDLINE]

3649. J Am Pharm Assoc (2003). 2008 Sep-Oct;48(5):688-91. doi: 10.1331/JAPhA.2008.08537.

New drugs: methylnaltrexone bromide, alvimopan, and riloncept.

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Author information:

(1)College of Pharmacy, University of the Sciences, Philadelphia, PA, USA.

DOI: 10.1331/JAPhA.2008.08537

PMID: 18826910 [Indexed for MEDLINE]

3650. J Pediatr Endocrinol Metab. 2008 Aug;21(8):789-92.

Growth in familial mediterranean fever: effect of attack rate, genotype and colchicine treatment.

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We evaluated the effect of attack frequency, homozygosity for the M694V mutation

and colchicine treatment on growth in children with familial Mediterranean fever (FMF). Prepubertal patients with FMF (19 M, 14 F) were evaluated retrospectively for height SDS, weight SDS and body mass index (BMI) before and after 46.2 +/- 39.8 months of colchicine therapy. Pretreatment attack frequency and acute phase markers at diagnosis were also recorded. While acute phase markers were not correlated to anthropometric variables, attack rate was negatively, albeit insignificantly, correlated to height and weight SDS. Height SDS did not change, while BMI showed a slight but significant increase during colchicine therapy (16.2 +/- 2.6 to 17.3 +/- 3.1 kg/m<sup>2</sup>, p = 0.035). Homozygosity for M694V did not affect time from the onset of symptoms to diagnosis, anthropometric variables and acute phase markers. In conclusion, pre-treatment attack rate and anthropometric development correlated negatively. Colchicine therapy improved BMI slightly, but significantly. Homozygosity for M694V had no effect on anthropometric development.

PMID: 18825879 [Indexed for MEDLINE]

3651. Acta Haematol. 2008;120(1):57-62. doi: 10.1159/000158578. Epub 2008 Sep 30.

Familial Mediterranean fever gene as a possible modifier of Sweet syndrome with chronic myelogenous leukemia.

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Sweet syndrome is a multisystem inflammatory disorder characterized by acute fever, as well as painful erythematous plaques infiltrated with mature neutrophils in the absence of vasculitis. The pathogenesis of the disease has not yet been clarified, although several proinflammatory cytokines have been reported to be involved in the disease process. We describe here a patient clinically diagnosed with Sweet syndrome with chronic myelogenous leukemia. The mutational analysis of the patient revealed a compound heterozygous E148Q/R202Q mutation in exon 2 of MEFV gene, which is a causative gene for familial Mediterranean fever.

This is the first report to describe MEFV gene mutations in Sweet syndrome. Our results suggest that Sweet syndrome may be mediated through similar inflammatory mechanisms to those of familial Mediterranean fever.

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DOI: 10.1159/000158578

PMID: 18824843 [Indexed for MEDLINE]

3652. Arthritis Rheum. 2008 Oct;58(10):3275-6. doi: 10.1002/art.23887.

First report of rapidly progressive glomerulonephritis in tumor necrosis factor receptor-associated periodic syndrome.

Harambat J(1), Desjonqueres M, Garaix F, Cochat P, Ranchin B, Cimaz R, Dodé C, Bouvier R.

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DOI: 10.1002/art.23887

PMID: 18821681 [Indexed for MEDLINE]

3653. Presse Med. 2008 Nov;37(11):1676-82. doi: 10.1016/j.lpm.2008.08.002. Epub 2008 Sep 24.

[Auto-inflammatory syndromes and pregnancy].

[Article in French]

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In familial mediterranean fever (FMF), fertility is normal in treated patients. There is no abnormality of spermatogenesis under usual therapeutic doses of colchicine. The risk of early abortion is increased if inflammatory attacks occur during the pregnancy. It is recommended to continue colchicine treatment during the conception and the pregnancy. Careful follow-up must be organized, even more in patients with renal amyloidosis. Breast-feeding is allowed under colchicine with no risk for the baby. There is no indication for systematic amniocentesis in FMF patients treated with colchicine.

DOI: 10.1016/j.lpm.2008.08.002

PMID: 18818048 [Indexed for MEDLINE]

3654. Rev Neurol (Paris). 2008 Nov;164(11):943-7. doi: 10.1016/j.neurol.2008.04.004. Epub 2008 May 16.

[Multiple sclerosis and familial Mediterranean fever: a case report].

[Article in French]

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**INTRODUCTION:** Few cases of patients with both Familial Mediterranean Fever (FMF) and Multiple Sclerosis (MS) have been reported, mainly from Turkey. Central nervous system manifestations are rare in FMF.

**CASE REPORT:** We report the case of a 37-year-old right-handed man with FMF diagnosed at 17 the age of years and successfully treated with colchicine. The patient was born in Algeria and lived in France since he was four years old. He had a brother who had multiple sclerosis. When the patient was 23 years old, he experienced diplopia and leg numbness that resolved spontaneously without treatment. Ten years later, new neurological events appeared every six months and were treated with corticoid-steroids. The diagnosis of MS was made. In 2006, he was hospitalized for new explorations in order to search for neuro-Behçet's disease, because of the development of a canker sore. There was no argument for

neuro-Behçet's disease.

**DISCUSSION:** Neurological complications of FMF are rare. It is important to rule out a neuro-Behçet disease in a FMF patient with neurological disorders. Previous studies and case reports on the association between FMF and MS have failed to draw a clear conclusion as to whether this is a true association or a simple coincidence. In our patient's clinical situation, we found no argument for changing the treatment of MS and FMF.

DOI: 10.1016/j.neurol.2008.04.004

PMID: 18808786 [Indexed for MEDLINE]

3655. Proc Natl Acad Sci U S A. 2008 Sep 30;105(39):15028-33. doi: 10.1073/pnas.0806619105. Epub 2008 Sep 19.

Inflammation and autoimmunity caused by a SHP1 mutation depend on IL-1, MyD88, and a microbial trigger.

Crocker BA(1), Lawson BR, Rutschmann S, Berger M, Eidenschenk C, Blasius AL, Moresco EM, Sovath S, Cengia L, Shultz LD, Theofilopoulos AN, Pettersson S, Beutler BA.

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Erratum in

Proc Natl Acad Sci U S A. 2008 Dec 9;105(49):19561. Rutschmann, Sophie [added].

A recessive phenotype called spin (spontaneous inflammation) was induced by N-ethyl-N-nitrosourea (ENU) mutagenesis in C57BL/6J mice. Homozygotes display chronic inflammatory lesions affecting the feet, salivary glands and lungs, and antichromatin antibodies. They are immunocompetent and show enhanced resistance to infection by *Listeria monocytogenes*. TLR-induced TNF and IL-1 production are normal in macrophages derived from spin mice. The autoinflammatory phenotype of spin mice is fully suppressed by compound homozygosity for *Myd88*(poc), *Irak4*(otiose), and *Il1r1*-null mutations, but not *Ticam1*(Lps2), *Stat1*(m1Btlr), or *Tnf*-null mutations. Both autoimmune and autoinflammatory phenotypes are suppressed when spin homozygotes are derived into a germ-free environment. The

spin phenotype was ascribed to a viable hypomorphic allele of Ptpn6, which encodes the tyrosine phosphatase SHP1, mutated in mice with the classical motheaten alleles me and me-v. Inflammation and autoimmunity caused by SHP1 deficiency are thus conditional. The SHP1-deficient phenotype is driven by microbes, which activate TLR signaling pathways to elicit IL-1 production. IL-1 signaling via MyD88 elicits inflammatory disease.

DOI: 10.1073/pnas.0806619105

PMCID: PMC2567487

PMID: 18806225 [Indexed for MEDLINE]

3656. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008 Dec;106(6):845-52. doi: 10.1016/j.tripleo.2008.07.014. Epub 2008 Sep 20.

Recurrent oral ulceration: aphthous-like ulcers in periodic syndromes.

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Recurrent oral ulceration that clinically resembles recurrent aphthous stomatitis but presents atypically, including commencement after adolescence, with fever, with a strong family history, or failing to resolve with age, has been termed aphthous-like ulceration (ALU). It may be seen in some immunodeficiency states, chronic viral infections, rheumatologic disorders, skin diseases, and the periodic syndromes. The periodic syndromes, considered to be the prototypic autoinflammatory diseases, present with recurrent short attacks of myalgia, arthralgia, rashes, abdominal pain, lymphadenopathy, and fever. Several of the syndromes can result in amyloidosis. Genetic studies have enhanced the clinical characterization of these conditions and elucidation of their molecular etiopathogenesis. This paper describes 2 patients with periodic syndromes presenting with ALU and reviews the present understanding of the syndromes.

DOI: 10.1016/j.tripleo.2008.07.014

PMID: 18805719 [Indexed for MEDLINE]

3657. Ann Rheum Dis. 2009 Feb;68(2):246-8. doi: 10.1136/ard.2008.092031. Epub 2008 Sep 18.

Disease severity in children and adolescents with familial Mediterranean fever: a comparative study to explore environmental effects on a monogenic disease.

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**BACKGROUND:** Worldwide, familial Mediterranean fever (FMF) is the most common autoinflammatory disease. It has been suggested that environmental factors affect the phenotype as some patients do not develop the complication of secondary amyloidosis.

**OBJECTIVE:** To analyse whether disease severity in Turkish children with FMF, living in Turkey and Germany is different.

**PATIENTS AND METHODS:** A total of 55 Turkish children living in Turkey were compared with 45 Turkish children born and raised in Germany. Mean age among the group from Turkey and Germany was 42.2 and 44.29 months, respectively. M694V was the leading mutation in both groups. The severity scores were compared with two scoring systems, modified according to published paediatric data for dosage.

**RESULTS:** There was no significant difference between the mean C-reactive protein and erythrocyte sedimentation rate levels of the two groups. According to the modified Sheba Center score, 78.2% of patients from the group living in Turkey had a severe course compared with 34.1% from the group living in Germany. The modified score of Pras et al also showed more severe disease in the patients from Turkey. The difference between the two groups for both scoring systems were significant (both  $p < 0.05$ ).

**CONCLUSIONS:** We believe the modified scores that we introduce can be widely used for children. Our results suggest that the environment affects the phenotype of a monogenic disease of the innate inflammatory pathway.

DOI: 10.1136/ard.2008.092031

PMID: 18801759 [Indexed for MEDLINE]

3658. Clin Exp Rheumatol. 2008 Jul-Aug;26(4):568-73.

Appendectomy in familial Mediterranean fever: clinical, genetic and pathological findings.

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**BACKGROUND:** Abdominal attacks of familial Mediterranean fever (FMF) may simulate acute appendicitis and bring about considerable uncertainty. The similar presentation of the two clinical entities often leads to an unnecessary appendectomy.

**METHODS:** 182 consecutive FMF patients were retrospectively reviewed for this study. Clinical and genetic data was compared between those who had undergone an appendectomy (n=71) and those who had not (n=111).

**RESULTS:** The frequency of appendectomy found in FMF was far above the reported rate in the general population (40% vs. 12-25%). The rate of non-inflamed appendectomies was extremely high (80% vs. 20%) and remained constant over time. Tertiary hospitals and improved therapeutic and diagnostic measures that have evolved over the years did not reduce misdiagnosis of acute appendicitis in FMF.

Severe phenotype and homozygosity for M694V were identified as risk factors for appendectomy in FMF. A change from the regular diffuse involvement to right lower quadrant abdominal pain was found to be the best predictor of inflamed appendix in FMF patients undergoing appendectomy for suspected acute appendicitis.

**CONCLUSION:** Reliance on clinical parameters should improve diagnostic accuracy of acute appendicitis in the FMF patient population.

PMID: 18799086 [Indexed for MEDLINE]

3659. Clin Rheumatol. 2009 Jan;28(1):41-6. doi: 10.1007/s10067-008-0980-3. Epub 2008 Sep 16.

The frequency of sacroiliitis in familial Mediterranean fever and the role of HLA-B27 and MEFV mutations in the development of sacroiliitis.



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The objective of this study was to investigate the frequency of sacroiliitis in familial Mediterranean fever (FMF) patients and the role of HLA-B27 and MEFV mutations in the development of sacroiliitis. The study group consisted of 256 FMF patients (male 128, female 128, mean age 27.2 +/- 6.3 years). After evaluation of the medical records, 70 patients (27.4%) were determined to have one or more of musculoskeletal manifestations. Sacroiliitis was determined in 18 (32.7%) FMF patients. The frequency of sacroiliitis among all FMF patients was found to be 7%. HLA-B27 was 47% and 6.3% in FMF patients with and without sacroiliitis, respectively. The frequency of M694V mutations in FMF patients with sacroiliitis was 93.7%. Sacroiliitis may be seen more frequently in FMF patients than expected. HLA-B27 positivity and/or M694V mutation may play a role in the development of sacroiliitis and the severity of seronegative spondyloarthropathy.

DOI: 10.1007/s10067-008-0980-3

PMID: 18795391 [Indexed for MEDLINE]

3660. Clin Nephrol. 2008 Jul;70(1):62-4.

Familial Mediterranean fever and IgA nephropathy: case report and review of the literature.

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Familial Mediterranean fever (FMF) is the most common form of autoinflammatory syndromes and is characterized by recurrent inflammatory attacks of fever and serositis. Amyloidosis is the most common renal complication of FMF. In addition to amyloidosis, many renal lesions have been anecdotally reported in patients

with FMF and other hereditary periodic fevers. We report a Turkish child with FMF presenting with hematuria during attacks, in whom kidney biopsy documented the presence of mesangial IgA deposits and the absence of amyloidosis. Kidney biopsy should be performed in patients showing microscopic or gross hematuria during attacks of familial Mediterranean fever in order to gain additional epidemiological data about specific features of renal involvement and to allow adequate treatment.

PMID: 18793551 [Indexed for MEDLINE]

3661. Exp Biol Med (Maywood). 2008 Nov;233(11):1324-33. doi: 10.3181/0803-RM-106. Epub 2008 Sep 12.

Expression of ASC in renal tissues of familial mediterranean fever patients with amyloidosis: postulating a role for ASC in AA type amyloid deposition.

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Familial Mediterranean fever (FMF) is characterized by recurrent attacks of fever and serositis; in some cases, ensuing amyloidosis results in kidney damage. Treatment with colchicine reduces the frequency and severity of FMF attacks and prevents amyloidosis, although the mechanisms behind these effects are unknown. Pyrin, the protein product of the MEFV gene, interacts with ASC, a key molecule in apoptotic and inflammatory processes. ASC forms intracellular speck-like aggregates that presage cell death. Here we show that cell death after ASC speck formation is much slower in nonmyeloid cells than in myeloid cells. Additionally, we demonstrate that colchicine prevents speck formation and show that specks can survive in the extracellular space after cell death. Because we also found that ASC is expressed in renal glomeruli of patients with FMF but not in those of control patients, we posit that high local ASC expression may result in speck formation and that specks from dying cells may persist in the extracellular space where they have the potential (perhaps in association with pyrin) to nucleate

amyloid. The fact that speck formation requires an intact microtubule network as shown here could potentially account for the ability of prophylactic colchicine to prevent or reverse amyloidosis in patients with FMF.

DOI: 10.3181/0803-RM-106

PMID: 18791131 [Indexed for MEDLINE]

3662. J Rheumatol. 2008 Oct;35(10):2024-9. Epub 2008 Sep 1.

Increased asymmetric dimethylarginine levels in young men with familial Mediterranean fever (FMF): is it early evidence of interaction between inflammation and endothelial dysfunction in FMF?

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**OBJECTIVE:** Unlike in many other chronic inflammatory rheumatic diseases, studies investigating endothelial dysfunction and atherosclerosis in familial Mediterranean fever (FMF) are limited, and the results are controversial. Asymmetric dimethylarginine (ADMA) is considered an indicator for endothelial dysfunction and a sensitive marker for cardiovascular risk. There have been no reports on serum ADMA levels in patients with FMF.

**METHODS:** We aimed (1) to determine serum ADMA concentrations in 38 young male patients with FMF and 23 age- and body mass index-matched healthy volunteers; (2) to evaluate its correlations with MEFV mutations, C-reactive protein (CRP) levels, and lipid profile; and (3) to compare effects of colchicine on circulating ADMA concentrations.

**RESULTS:** In patients with FMF, ADMA and CRP levels were higher than in healthy controls. The mean levels of ADMA and CRP were higher during acute attacks than in attack-free periods. Patients taking colchicine had lower serum ADMA levels than non-colchicine users. There was a positive strong correlation between ADMA and CRP in patients with FMF. Stepwise linear regression analysis in patients with FMF revealed that age and CRP levels were independently associated with serum ADMA levels.

CONCLUSION: Our data imply that higher serum ADMA levels in FMF may indicate inflammation-related "endothelial dysfunction." It seems likely that regular use of colchicine is effective in preventing the development of and reversing not only amyloidosis but also endothelial dysfunction in patients with FMF.

PMID: 18785307 [Indexed for MEDLINE]

3663. J Cell Physiol. 2009 Jan;218(1):32-4. doi: 10.1002/jcp.21585.

Skin toxicity caused by EGFR antagonists-an autoinflammatory condition triggered by deregulated IL-1 signaling?

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Acneiform skin eruptions associated with sterile inflammation frequently accompany pharmacological inhibition of signaling through the epidermal growth factor receptor (EGFR) in cancer patients. Here we discuss possible pathogenic mechanisms for this phenomenon linked to control of inflammatory mediators by EGFR blockade in keratinocytes of the outer root sheath of the hair follicle. This discussion is focused on the putative role of EGFR activation in restraining interleukin (IL)-1-dependent inflammatory networks at the hair follicle.

(c) 2008 Wiley-Liss, Inc.

DOI: 10.1002/jcp.21585

PMID: 18781585 [Indexed for MEDLINE]

3664. PLoS One. 2008 Sep 9;3(9):e3172. doi: 10.1371/journal.pone.0003172.

Elevated systemic antibodies towards commensal gut microbiota in autoinflammatory condition.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is an autoinflammatory condition, which is characterized by acute, self-limiting episodes of fever and serositis and chronic subclinical inflammation in remission. Here we investigated the consequence of this condition on the level of systemic antibodies directed towards common intestinal bacteria.

**METHODOLOGY/PRINCIPAL FINDINGS:** The level of systemic antibodies towards the antigens of *Bacteroides*, *Parabacteroides*, *Escherichia*, *Enterococcus* and *Lactobacillus* was measured by ELISA in FMF patients at various stages of the disease and in healthy controls. The difference between remission and attack was not significant. IgG antibodies against the antigens of *Bacteroides*, *Parabacteroides*, *Escherichia* and *Enterococcus* were significantly increased in FMF compared to control while IgA levels were not significantly affected. Western blot analyses demonstrated the IgG reactivity against multiple antigens of commensal bacteria in FMF. Serological expression cloning was performed to identify these antigens. No single dominant antigen was identified; the response was generalized and directed against a variety of proteins from *Bacteroides*, *Parabacteroides*, *Escherichia*, and other gut commensals.

**CONCLUSIONS/SIGNIFICANCE:** This autoinflammatory syndrome is characterized by the increased systemic reactivity against commensal gut microbiota. This is probably the consequence of hypersensitivity of the inflammasome in FMF that triggers the inflammation and contributes to the excessive translocation of bacteria and bacterial antigens through the gut barrier.

DOI: 10.1371/journal.pone.0003172

PMCID: PMC2525839

PMID: 18779861 [Indexed for MEDLINE]

3665. Eur J Obstet Gynecol Reprod Biol. 2008 Dec;141(2):115-8. doi: 10.1016/j.ejogrb.2008.07.025. Epub 2008 Sep 3.

Familial Mediterranean fever during pregnancy: an independent risk factor for

preterm delivery.

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**OBJECTIVE:** To investigate pregnancy outcome of patients with Familial Mediterranean fever (FMF).

**STUDY DESIGN:** A population-based study comparing all pregnancies of women with and without FMF between the years 1988 and 2006 was conducted. Stratified analyses, using the Mantel-Haenszel procedure and multiple logistic regression models, were performed to control for confounders.

**RESULTS:** During the study period there were 175,572 deliveries, of which 239 occurred in patients with FMF. Using a multivariable analysis, the following conditions were significantly associated with FMF: preterm delivery (PTD, <37 weeks) (odds ratio (OR)=1.5; 95% confidence interval (CI) 1.1-2.2), fertility treatments (OR=2.5; 95% CI 1.4-4.4), recurrent abortions (OR=2.2; 95% CI 1.5-3.2), labor induction (OR=1.9; 95% CI 1.5-2.5) and malpresentations (OR=1.8; 95% CI 1.2-2.8). Patients with FMF were more likely to deliver by cesarean delivery (CD) as compared to the comparison group (18.0% vs. 12.8%;  $P=0.017$ ). However, while controlling for possible confounders such as malpresentations, labor dystocia and failed induction, using multivariable analysis with CD as the outcome variable, FMF was not found as an independent risk factor for CD (adjusted OR=1.2; 95% CI 0.8-1.8,  $P=0.388$ ). No significant differences were noted between the groups regarding perinatal outcomes such as low Apgar scores (<7) at 1 and 5 min (2.4% vs. 4.3%,  $P=0.153$  and 0.4% vs. 0.6%,  $P=0.692$ ; respectively), congenital malformations (5.2% vs. 4.9%,  $P=0.838$ ), or perinatal mortality (0.8% vs. 1.4%,  $P=0.445$ ). Stratified analysis, using the Mantel-Haenszel technique, was used to assess the association between FMF and PTD while controlling for possible confounders such as iatrogenic labor induction, fertility treatments, recurrent abortions and placental abruption. None of those variables explained the higher incidence of PTD in the group of patients with FMF.

**CONCLUSION:** Familial Mediterranean fever is an independent risk factor for preterm delivery. Nevertheless, perinatal outcome is comparable to the general population.

DOI: 10.1016/j.ejogrb.2008.07.025  
PMID: 18771840 [Indexed for MEDLINE]

3666. Proc Natl Acad Sci U S A. 2008 Sep 2;105(35):13009-14. doi: 10.1073/pnas.0806874105. Epub 2008 Aug 28.

B cells are required for Aire-deficient mice to develop multi-organ autoinflammation: A therapeutic approach for APECED patients.

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Autoimmune regulator (Aire)-deficient mice and humans have circulating autoantibodies against a multitude of organs and multiorgan autoinflammatory infiltrates. It is not known to what extent autoantibodies or their source, B lymphocytes, are required for disease onset or progression. We show in this research that B cells must be present for Aire-deficient mice to develop fulminant infiltrates. We found no evidence that autoantibodies were directly pathogenic; rather, B cells appeared to play a critical early role in T cell priming or expansion. A therapeutic reagent directed against B cells, Rituximab, induced remission of the autoimmune disease in Aire-deficient mice, raising the hope of applying it to human patients with autoimmune-polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED).

DOI: 10.1073/pnas.0806874105  
PMCID: PMC2529049  
PMID: 18755889 [Indexed for MEDLINE]

3667. Curr Top Microbiol Immunol. 2008;321:169-84.

Fevers, genes, and innate immunity.

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The characterization of patients with recurrent inflammatory syndromes into distinct clinical phenotypes provided early clues to the mode of inheritance of these conditions and facilitated the subsequent identification of causative gene mutations. The prototype autoinflammatory syndrome, familial Mediterranean fever, is characterized by self-limiting episodes of localized inflammation. Hallmarks of the classical autoimmune response are largely absent. The use of positional cloning techniques led to the identification of the causative gene, MEFV, and its product pyrin. This previously unrecognized protein plays an important role in modulating the innate immune response. Cryopyrin, the protein encoded by CIAS1, is mutated in a spectrum of autoinflammatory conditions, the cryopyrinopathies. In response to a wide range of potential pathogens, it forms a macromolecular complex termed the "inflammasome," resulting in caspase-1 activation and subsequent release of the active proinflammatory cytokine interleukin-1beta (IL-1beta). The role of an established biochemical pathway in regulating inflammation was uncovered by the discovery that the hyperimmunoglobulin D with periodic fever syndrome (HIDS) results from mutations in MVK, which encodes an enzyme in the isoprenoid pathway. The discovery that mutations in the gene encoding tumor necrosis factor (TNF) receptor 1 (TNFR1) cause a proinflammatory phenotype was unanticipated, as it seemed more likely that such mutations would instead have resulted in an immunodeficiency pattern. This review describes the clinical phenotypes of autoinflammatory syndromes, the underlying gene mutations, and current concepts regarding their pathophysiology.

PMID: 18727492 [Indexed for MEDLINE]

3668. PLoS One. 2008 Aug 26;3(8):e3064. doi: 10.1371/journal.pone.0003064.

Predominant role of host genetics in controlling the composition of gut microbiota.

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**BACKGROUND:** The human gastrointestinal tract is inhabited by a very diverse symbiotic microbiota, the composition of which depends on host genetics and the environment. Several studies suggested that the host genetics may influence the composition of gut microbiota but no genes involved in host control were proposed. We investigated the effects of the wild type and mutated alleles of the gene, which encodes the protein called pyrin, one of the regulators of innate immunity, on the composition of gut commensal bacteria. Mutations in MEFV lead to the autoinflammatory disorder, familial Mediterranean fever (FMF, MIM249100), which is characterized by recurrent self-resolving attacks of fever and polyserositis, with no clinical signs of disease in remission.

**METHODOLOGY/PRINCIPAL FINDINGS:** A total of 19 FMF patients and eight healthy individuals were genotyped for mutations in the MEFV gene and gut bacterial diversity was assessed by sequencing 16S rRNA gene libraries and FISH analysis. These analyses demonstrated significant changes in bacterial community structure in FMF characterized by depletion of total numbers of bacteria, loss of diversity, and major shifts in bacterial populations within the Bacteroidetes, Firmicutes and Proteobacteria phyla in attack. In remission with no clinical signs of disease, bacterial diversity values were comparable with control but still, the bacterial composition was substantially deviant from the norm. Discriminant function analyses of gut bacterial diversity revealed highly specific, well-separated and distinct grouping, which depended on the allele carrier status of the host.

**CONCLUSIONS/SIGNIFICANCE:** This is the first report that clearly establishes the link between the host genotype and the corresponding shifts in the gut microbiota (the latter confirmed by two independent techniques). It suggests that the host genetics is a key factor in host-microbe interaction determining a specific profile of commensal microbiota in the human gut.

DOI: 10.1371/journal.pone.0003064

PMCID: PMC2516932

PMID: 18725973 [Indexed for MEDLINE]

3669. Scand J Rheumatol. 2009 Jan-Feb;38(1):71-3. doi: 10.1080/03009740802192068.

A patient with periodic fever syndrome: a 20-year delay in diagnosis.

Ben-Chetrit E, Touitou I.

DOI: 10.1080/03009740802192068

PMID: 18720265 [Indexed for MEDLINE]

3670. Autoimmun Rev. 2009 Jan;8(3):228-32. doi: 10.1016/j.autrev.2008.07.034. Epub 2008 Aug 19.

Clinical and genetic aspects of Blau syndrome: a 25-year follow-up of one family and a literature review.

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Blau syndrome (BS) is a rare familial disease transmitted as an autosomal dominant trait, characterized by arthritis, uveitis, skin rash and granulomatous inflammation. Until now BS has been observed in 136 persons belonging to 28 families as well as in 4 sporadic cases. The gene responsible for BS has recently been identified in the nucleotide-binding domain (NBD) of caspase recruitment domain (CARD15/NOD2), also involved in the pathogenesis of Crohn's disease. In addition to three missense mutations (R334Q, R334W and L469F) previously identified, a new CARD 15 mutation (E383K) has recently been described in a family followed by us for the past 25 years. The characteristics of this family which, to our knowledge, is the only one affected with BS in Italy, are the object of this manuscript. Both the proband and her daughter were originally affected with a papulonodular skin eruption and then with mild arthritis of the hands and feet. The proband, but not the daughter, complained of severe chronic bilateral uveitis, followed by glaucoma and, a few years later, by cataracts. Histological examination of skin biopsies from both subjects and a joint biopsy (daughter only), showed non-caseating granulomas with multinucleated giant cells which, at electron microscopy, revealed "comma-shaped bodies" in epithelioid cells, thought to be a marker for BS. The disease is presently well controlled with low doses of prednisone for the mother and non-steroidal anti-inflammatory drugs (NSAIDs) plus low doses of prednisone, when necessary, for the daughter. As

in Crohn's disease, CARD15/NOD2 mutation is believed to be responsible for the granulomatous autoinflammatory reactions probably triggered by microorganisms in BS.

DOI: 10.1016/j.autrev.2008.07.034

PMID: 18718560 [Indexed for MEDLINE]

3671. Clin Rheumatol. 2009 Jan;28(1):23-8. doi: 10.1007/s10067-008-0976-z. Epub 2008 Aug 8.

Left ventricular diastolic function evaluated with tissue Doppler imaging in children with familial Mediterranean fever.

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The aim of this study was to assess the left ventricular diastolic function using conventional echocardiography and tissue Doppler imaging in children with familial Mediterranean fever. This study included 29 (13 males and 16 females) patients and 30 healthy subjects as controls. Body mass index was calculated and arterial blood pressure was monitored. After an overnight fast, venous blood samples were taken and serum amyloid A protein, C-reactive protein, serum-fasting glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol, very low density lipoprotein cholesterol, and serum low-density lipoprotein cholesterol levels were measured. A complete 2-dimensional, M-mode, pulse wave Doppler, and pulse wave tissue Doppler echocardiographic examination was performed. There were no significant differences between the groups regarding age, body mass index values, systolic and diastolic blood pressures, heart rates, serum-fasting glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol, very low density lipoprotein cholesterol, and serum low-density lipoprotein cholesterol. Serum levels of inflammatory markers were higher in patients' group (C-reactive protein and serum amyloid A protein levels were 10.84 mg/dl, 22.32 mg/l in patients' group, respectively, and 4.11 mg/dl, 3.65 mg/l, respectively, in the healthy controls.) Peak mitral A wave, E and A wave ratio differed significantly in both groups. There were statistically significant

differences regarding parameters observed by tissue Doppler imaging such as E'm, A'm, E'm, and A'm ratio between patients' group and controls. Tissue Doppler imaging provided additional information on left ventricular diastolic function. While systolic functions were in normal range, some of the diastolic function parameters were impaired in patients with familial Mediterranean fever during childhood.

DOI: 10.1007/s10067-008-0976-z

PMID: 18716732 [Indexed for MEDLINE]

3672. PLoS One. 2008 Aug 21;3(8):e3025. doi: 10.1371/journal.pone.0003025.

Administration of *M. leprae* Hsp65 interferes with the murine lupus progression.

Marengo EB(1), de Moraes LV, Faria M, Fernandes BL, Carvalho LV, Tambourgi DV, Rizzo LV, Portaro FC, Camargo AC, Sant'anna OA.

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The heat shock protein [Hsp] family guides several steps during protein synthesis, are abundant in prokaryotic and eukaryotic cells, and are highly conserved during evolution. The Hsp60 family is involved in assembly and transport of proteins, and is expressed at very high levels during autoimmunity or autoinflammatory phenomena. Here, the pathophysiological role of the wild type [WT] and the point mutated K(409)A recombinant Hsp65 of *M. leprae* in an animal model of Systemic Lupus Erythematosus [SLE] was evaluated in vivo using the genetically homogeneous [NZBxNZW]F(1) mice. Anti-DNA and anti-Hsp65 antibodies responsiveness was individually measured during the animal's life span, and the mean survival time [MST] was determined. The treatment with WT abbreviates the MST in 46%, when compared to non-treated mice [ $p < 0.001$ ]. An increase in the IgG2a/IgG1 anti-DNA antibodies ratio was also observed in animals injected with the WT Hsp65. Incubation of BALB/c macrophages with F(1) serum from WT treated mice resulted in acute cell necrosis; treatment of these cells with serum from K(409)A treated mice did not cause any toxic effect. Moreover, the involvement of WT correlates with age and is dose-dependent. Our data suggest that Hsp65 may be a central molecule intervening in the progression of the SLE, and that the point mutated K(409)A recombinant immunogenic molecule, that counteracts the

deleterious effect of WT, may act mitigating and delaying the development of SLE in treated mice. This study gives new insights into the general biological role of Hsp and the significant impact of environmental factors during the pathogenesis of this autoimmune process.

DOI: 10.1371/journal.pone.0003025

PMCID: PMC2515089

PMID: 18716655 [Indexed for MEDLINE]

3673. Autoimmun Rev. 2008 Oct;8(1):44-7. doi: 10.1016/j.autrev.2008.07.024. Epub 2008 Aug 15.

Recurrent pericarditis: infectious or autoimmune?

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The etiology and pathogenesis of idiopathic recurrent acute pericarditis (IRAP) remain controversial standing like a bridge that crosses infectious, autoimmune and autoinflammatory pathways. Anything may cause acute pericarditis; Echo-virus, and Coxsackie are the most frequently involved viruses, Mycobacterium tuberculosis and Coxiella burnetii the most common bacteria, but in 85% of cases it remains "idiopathic". Recurrences occur in up to 20-50% of patients. An immuno-mediated pathogenesis is suggested by the presence of pro-inflammatory cytokines in pericardial fluid, the presence of antinuclear autoantibodies (ANA) in sera of the patients, the occurrence of new autoimmune diagnoses and the good response to anti-inflammatory or immunosuppressive therapy. Nonsteroidal anti-inflammatory drugs (NSAIDs) must be used at recommended dosages, till the resolution of symptoms and normalization of C-reactive protein and erythrocyte sedimentation rate. Corticosteroids should be used rarely, at low doses, with an extremely low tapering and with osteoporosis prevention. Colchicine leads to a clinically important and statistically significant benefit, reducing recurrences by 50%. The long term outcome of IRAP is good, without evidence of constriction even after a very long follow-up.

DOI: 10.1016/j.autrev.2008.07.024  
PMID: 18708165 [Indexed for MEDLINE]

3674. Rheumatol Int. 2009 Jan;29(3):321-3. doi: 10.1007/s00296-008-0660-2. Epub 2008 Aug 12.

Osteopoikilosis coexistent with ankylosing spondylitis and familial Mediterranean fever.

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Osteopoikilosis (OPK) is a rare benign sclerosing disease of the skeleton and inherited as an autosomal dominant trait. OPK is associated with inflammatory rheumatic disorders, such as rheumatoid arthritis, scleroderma, reactive arthritis and familial Mediterranean fever (FMF). We report a rare case of OPK coexistent with ankylosing spondylitis and FMF. The patient presented multiple sclerotic lesions within and around the sacroiliac joints and a series of radiological diagnostic challenges.

DOI: 10.1007/s00296-008-0660-2  
PMID: 18696073 [Indexed for MEDLINE]

3675. Ann Hum Genet. 2008 Nov;72(Pt 6):752-61. doi: 10.1111/j.1469-1809.2008.00471.x. Epub 2008 Aug 6.

The population genetics of familial mediterranean fever: a meta-analysis study.

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Our aim was to construct a Familial Mediterranean Fever (FMF) cumulative database and to propose a MEFV based phylogenetic tree. Data were collected from published studies. A meta-analysis based on 16,756 chromosomes from FMF patients and normal individuals from 14 affected populations was performed. Arlequin 2.0 and Phylip 3.2 software were used for population genetics analysis and phylogenetic tree construction. We have shown that MEFV mutations are distributed non-uniformly along the Mediterranean Sea area. The most frequent mutations detected in FMF patients are M694V (39.6%), V726A (13.9%), M680I (11.4%), E148Q (3.4%), and M694I (2.9%), while 28.8% of chromosomes carry unidentified or no mutations, especially in Western Europeans. The mean overall carrier rate is 0.186 with peak values in Arabs, Armenians, Jews, and Turks. Only V726A obeys the Hardy-Weinberg law in FMF patients implying that this mutation is the most ancient. Jews present the most intense genetic isolation and drift; thus they might have nested de novo mutations and accelerated evolution. Besides Jews, three population groups might follow distinct evolutionary lines (Asia Minor, Eastern European, and Western European). In conclusion, the MEFV mutation pattern is non-uniform regarding distribution, phenotypic expression, neutrality and population genetics characteristics. Jews are the candidate population for founder effects in MEFV.

DOI: 10.1111/j.1469-1809.2008.00471.x

PMID: 18691160 [Indexed for MEDLINE]

3676. J Clin Rheumatol. 2008 Dec;14(6):342-5. doi: 10.1097/RHU.0b013e31817d109b.

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) or familial Hibernian fever: presentation in a four-day-old infant.

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Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is one of a number of well described hereditary periodic febrile syndromes. We report a case in an infant, with a strong family history of this disorder, who presented on day-of-life 4 with high fever, irritability, diarrhea, lethargy, and raised acute

phase reactants. An extensive work-up, including a full sepsis evaluation, proved negative. Symptoms resolved spontaneously. Representation with similar symptoms at 7 months of age prompted successful diagnosis after full evaluation. Subsequent genetic mutation analysis has proven positive for the T50M mutation in exon 2 of the TNFRSF1A gene. To our knowledge, this is the youngest reported age of presentation of this rare autoinflammatory disorder which should be considered even at such a young age.

DOI: 10.1097/RHU.0b013e31817d109b

PMID: 18690165 [Indexed for MEDLINE]

3677. Neth J Med. 2008 Jun;66(6):261; author reply 261.

The utility of genetic testing in the diagnosis of familial Mediterranean fever.

Tischkowitz M.

Comment on

Neth J Med. 2007 Oct;65(9):318-24.

PMID: 18689912 [Indexed for MEDLINE]

3678. Blood. 2008 Nov 1;112(9):3563-73. doi: 10.1182/blood-2008-03-144667. Epub 2008 Aug 6.

HMG-CoA reductase inhibition induces IL-1beta release through Rac1/PI3K/PKB-dependent caspase-1 activation.

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Mevalonate kinase deficiency (MKD) is an autoinflammatory disorder characterized by recurring fever episodes and results from disturbed isoprenoid biosynthesis.



Lipopolysaccharide-stimulated peripheral blood mononuclear cells from MKD patients secrete high levels of interleukin-1beta (IL-1beta) because of the presence of hyperactive caspase-1, and this has been proposed to be the primary cause of recurring inflammation. Here we show that inhibition of HMG-CoA reductase by simvastatin treatment, mimicking MKD, results in increased IL-1beta secretion in a Rac1/PI3K-dependent manner. Simvastatin treatment was found to activate protein kinase B (PKB)/c-akt, a primary effector of PI3K, and ectopic expression of constitutively active PKB was sufficient to induce IL-1beta release. The small GTPase Rac1 was activated by simvastatin, and this was required for both PKB activation and IL-1beta secretion. IL-1beta release is mediated by caspase-1, and simvastatin treatment resulted in increased caspase-1 activity in a Rac1/PI3K-dependent manner. These data suggest that, in MKD, dysregulated isoprenoid biosynthesis activates Rac1/PI3K/PKB, resulting in caspase-1 activation with increased IL-1beta release. Importantly, inhibition of Rac1 in peripheral blood mononuclear cells isolated from MKD patients resulted in a dramatic reduction in IL-1beta release. These data suggest that pharmacologic inhibition of Rac1 could provide a novel therapeutic strategy for treatment of MKD.

DOI: 10.1182/blood-2008-03-144667

PMID: 18684863 [Indexed for MEDLINE]

3679. Allergol Immunopathol (Madr). 2008 May-Jun;36(3):164-75.

A new era for innate immunity.

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In recent years our concept of the non-specific nature of innate immunity has changed following the identification of a network of germline-encoded receptors that recognise with substantial specificity molecular motifs of microorganisms and many other cues produced during tissue injury. Stimulation of these innate sensors by their specific ligands triggers signalling pathways that result in the activation of innate effector mechanisms as well as the priming of naive

lymphocytes for the type of response that must be induced. These events culminate in the generation of an immune response appropriately adapted to the damage that has occurred. These new insights into innate immunity herald an entirely new era in the understanding of the molecular events that initiate and drive a host-protective response, changing many concepts about susceptibility to infections and providing greater insight into the underlying inflammatory pathology of other diseases. Targeted manipulation of innate immunity has enormous potential for the development of new vaccines and innovative therapies for the treatment of diseases such as infections, cancer, allergy, autoimmunity and autoinflammatory diseases. This article provides an overview of current trends in the field of innate immunity and its role in the control of infection and disease.

PMID: 18680705 [Indexed for MEDLINE]

3680. Anadolu Kardiyol Derg. 2008 Aug;8(4):271-8.

Assessment of aortic stiffness and ventricular functions in familial Mediterranean fever.

Sari I(1), Arican O, Can G, Akdeniz B, Akar S, Birlik M, Tunca M, Akkoç N, Güneri S, Onen F.

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Comment in

Anadolu Kardiyol Derg. 2009 Apr;9(2):148-9; author reply 149-50.

Anadolu Kardiyol Derg. 2008 Oct;8(5):395; author reply 395-6.

**OBJECTIVE:** To investigate systolic and diastolic ventricular functions, aortic elastic properties and the presence of pericardial effusion in familial Mediterranean fever (FMF) patients.

**METHODS:** A case-controlled, cross-sectional study was performed on 44 FMF patients and 27 controls. Subjects with hypertension, diabetes mellitus and hyperlipidemia were excluded. Left and right ventricular functions were measured

using echocardiography including two-dimensional, M-mode, and conventional Doppler as well as pulsed wave tissue Doppler imaging (TDI). Aortic elasticity was analyzed using M-mode tracing guided by the two-dimensional echocardiography. Statistical analysis was performed using Mann Whitney U, Spearman rho correlation and Fisher's exact tests.

RESULTS: Age, sex, body mass index, smoking status and lipids were comparable in patients and controls ( $p>0.05$ ). None of the subjects had pericarditis and/or pericardial effusion. Aortic wall properties were similar between groups ( $p>0.05$ ). The TDI parameters of mitral lateral annulus revealed significantly lower Em/Am ratios in patients compared to controls [1.77 (0.6-3.4) vs. 1.79 (0.9-4.8),  $p=0.02$ ]. Mitral flow propagation velocity was significantly lower in patients than healthy subjects [63 (39-100) vs. 74 (40-94) cm/s,  $p=0.008$ ]. Tricuspid annular plane systolic excursion (TAPSE) was significantly reduced in FMF group than in controls [2 (1.3-2.5) vs. 2.5 (1.7-3.2) cm;  $p<0.001$ ]. Eight of the patients and one control had impaired TAPSE ( $<2$  cm;  $p=0.025$ ). There was no difference regarding right ventricular diastolic dysfunction (RVDD) as assessed by using standard Doppler echocardiography ( $p>0.05$ ). However, pronounced RVDD was observed in FMF patients documented by TDI ( $Em/Am<1$ ; 19 patients vs. 0 controls,  $p<0.001$ ).

CONCLUSION: Subclinical myocardial involvement is present in a cohort of relatively young FMF patients who were also free of classical cardiovascular risk factors. Pericardium and aorta seem to be spared during attack free periods of FMF.

PMID: 18676303 [Indexed for MEDLINE]

3681. Expert Opin Pharmacother. 2008 Aug;9(12):2175-80. doi: 10.1517/14656566.9.12.2175

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Eprodinate in amyloid A amyloidosis: a novel therapeutic approach?

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**BACKGROUND:** Amyloid A (AA) amyloidosis can complicate chronic inflammatory diseases, chronic infections and recurrent periodic fever syndromes. Its treatment is challenging, given its heterogeneous spectrum of etiologies.

**OBJECTIVE:** To review the available literature regarding treatment options for AA amyloidosis, particularly focusing on eprodisate, a newly developed inhibitor of fibrillogenesis.

**METHODS:** A PubMed search was performed without any date limits, mainly using the search terms 'amyloidosis', 'colchicine', 'eprodisate', '1,3-propanedisulfonate', 'NC-503', 'Fibrillex' and 'TNF-blockers'.

**RESULTS/CONCLUSION:** Antibiotics and colchicine are effective in preventing and treating infection-related and familial Mediterranean fever-related AA amyloidosis, respectively. Recently, TNF-alpha blockers have emerged as effective agents in inflammatory AA amyloidosis. Eprodisate binds to the glycosaminoglycan binding site on amyloid fibrils, thus targeting amyloid fibril polymerization and tissue deposition. Eprodisate has possible applicability to other types of amyloidosis; the results of a recent randomized trial showed that it may slow the progression of AA amyloidosis-related renal disease but confirmatory studies are necessary.

DOI: 10.1517/14656566.9.12.2175

PMID: 18671471 [Indexed for MEDLINE]

3682. Arthritis Rheum. 2008 Aug;58(8):2432-42. doi: 10.1002/art.23620.

A pilot study to evaluate the safety and efficacy of the long-acting interleukin-1 inhibitor rilonacept (interleukin-1 Trap) in patients with familial cold autoinflammatory syndrome.

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Comment in

Nat Clin Pract Rheumatol. 2009 Jan;5(1):14-5.

**OBJECTIVE:** Familial cold autoinflammatory syndrome (FCAS) is caused by mutations in the CIAS1 gene, leading to excessive secretion of interleukin-1beta (IL-1beta), which is associated with cold-induced fevers, joint pain, and systemic inflammation. This pilot study was conducted to assess the safety and efficacy of rilonacept (IL-1 Trap), a long-acting IL-1 receptor fusion protein, in patients with FCAS.

**METHODS:** Five patients with FCAS were studied in an open-label trial. All patients received an initial loading dose of 300 mg of rilonacept by subcutaneous injection, were evaluated 6 and 10 days later for clinical efficacy, and remained off treatment until a clinical flare occurred. At the time of flare, patients were again treated with 300 mg of rilonacept and then given maintenance doses of 100 mg/week. Patients whose FCAS was not completely controlled were allowed a dosage increase to 160 mg/week and then further to 320 mg/week during an inpatient dosage-escalation phase. Safety, disease activity measures (daily diary reports of rash, joint pain and/or swelling, and fevers), health quality measures (Short Form 36 health survey questionnaire), and serum markers of inflammation (erythrocyte sedimentation rate [ESR], high-sensitivity C-reactive protein [hsCRP], serum amyloid A [SAA], and IL-6) were determined at 3, 6, 9, 12, and 24 months after initiation of rilonacept and were compared with baseline values.

**RESULTS:** In all patients, clinical symptoms typically induced by cold (rash, fever, and joint pain/swelling) improved within days of rilonacept administration. Markers of inflammation (ESR, hsCRP, and SAA) showed statistically significant reductions ( $P < 0.01$ ,  $P < 0.001$ , and  $P < 0.001$ , respectively) at doses of 100 mg. Dosage escalation to 160 mg and 320 mg resulted in subjectively better control of the rash and joint pain. Furthermore, levels of the acute-phase reactants ESR, hsCRP, and SAA were lower at the higher doses; the difference was statistically significant only for the ESR. All patients continued taking the study drug. The drug was well-tolerated. Weight gain in 2 patients was noted. No study drug-related serious adverse events were seen.

**CONCLUSION:** In this study, we present 2-year safety and efficacy data on rilonacept treatment in 5 patients with FCAS. The dramatic improvement in clinical and laboratory measures of inflammation, the sustained response, and the good tolerability suggest that this drug may be a promising therapeutic option in patients with FCAS, and the data led to the design of a phase III study in this patient population.

3683. Arthritis Rheum. 2008 Aug;58(8):2443-52. doi: 10.1002/art.23687.

Efficacy and safety of rilonacept (interleukin-1 Trap) in patients with cryopyrin-associated periodic syndromes: results from two sequential placebo-controlled studies.

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Comment in

Nat Clin Pract Rheumatol. 2009 Jan;5(1):14-5.

**OBJECTIVE:** To assess the efficacy and safety of rilonacept (Interleukin-1 [IL-1] Trap), a long-acting and potent inhibitor of IL-1, in patients with cryopyrin-associated periodic syndromes (CAPS), including familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS).

**METHODS:** Forty-seven adult patients with CAPS, as defined by mutations in the causative NLRP3 (CIAS1) gene and pathognomonic symptoms, were enrolled in 2 consecutive phase III studies. Study 1 involved a 6-week randomized double-blind comparison of weekly subcutaneous injections of rilonacept (160 mg) versus placebo. Study 2 consisted of 9 weeks of single-blind treatment with rilonacept (part A), followed by a 9-week, randomized, double-blind, placebo-controlled withdrawal procedure (part B). Primary efficacy was evaluated using a validated composite key symptom score.

**RESULTS:** Forty-four patients completed both studies. In study 1, rilonacept therapy reduced the group mean composite symptom score by 84%, compared with 13% with placebo therapy (primary end point;  $P < 0.0001$  versus placebo). Rilonacept also significantly improved all other efficacy end points in study 1 (numbers of multisymptom and single-symptom disease flare days, single-symptom scores, physician's and patient's global assessments of disease activity, limitations in daily activities, and C-reactive protein and serum amyloid A [SAA] levels). In study 2 part B, rilonacept was superior to placebo for maintaining the

improvements seen with rilonacept therapy, as shown by all efficacy parameters (primary end point;  $P < 0.0001$  versus placebo). Rilonacept was generally well tolerated; the most common adverse events were injection site reactions.

CONCLUSION: Treatment with weekly rilonacept provided marked and lasting improvement in the clinical signs and symptoms of CAPS, and normalized the levels of SAA from those associated with risk of developing amyloidosis. Rilonacept exhibited a generally favorable safety and tolerability profile.

DOI: 10.1002/art.23687

PMID: 18668535 [Indexed for MEDLINE]

3684. Nat Clin Pract Rheumatol. 2008 Sep;4(9):481-9. doi: 10.1038/ncprheum0874. Epub 2008 Jul 29.

Cryopyrinopathies: update on pathogenesis and treatment.

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Cryopyrinopathies are a group of rare autoinflammatory diseases that includes familial cold autoinflammatory syndrome, Muckle-Wells syndrome and chronic infantile neurologic cutaneous articular syndrome (also termed neonatal-onset multisystemic inflammatory disease). These syndromes were initially considered to be distinct disease entities despite some clinical similarities; however, mutations of the same gene have since been found in all three cryopyrinopathies. These diseases, therefore, are not separate but represent a continuum of subphenotypes. The gene in question, CIAS1 (now renamed NLRP3) encodes NALP3 (also known as cryopyrin). NALP3 is an important mediator of inflammation and interleukin 1 $\beta$  processing. New therapies based on biologic agents that specifically target interleukin 1 $\beta$  are currently being developed. These new agents have provided very encouraging results for patients with these long-lasting inflammatory conditions--which used to be considered refractory to treatment. The development of therapeutic options for these cryopyrinopathies illustrates effective translation of basic science to clinical practice and the convergence of human genetics and targeted therapies.

DOI: 10.1038/ncprheum0874

PMID: 18665151 [Indexed for MEDLINE]

3685. Genet Test. 2008 Sep;12(3):341-4. doi: 10.1089/gte.2008.0009.

Analysis of familial Mediterranean fever gene mutations in 202 patients with familial Mediterranean fever.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is an autosomal recessive disorder, caused by mutations in MEFV gene that encodes pyrin protein. In this study, we analyzed the most common five mutations in MEFV gene of 202 patients who were diagnosed formerly as FMF according to Tel-Hashomer criteria. The results of genetical analysis, clinical symptoms, and demographical aspects of those patients were evaluated retrospectively.

**METHODS AND RESULTS:** Between the dates of February 2005 and March 2007, we analyzed five common MEFV gene mutations, which were M680I, M694V, M694I, V726A, and E148Q, in 202 patients by the PCR-ELISA method in our medical genetics laboratory. The most frequent mutation detected in our patients was M694V, and other mutations according to frequency were E148Q, M680I, V726A, and M694I. The detected mutations were homozygous in 45 of the patients (22.2%), heterozygous in 103 (51%), compound heterozygous in 52 (25.8%), and in 2 patients (1%) complex alleles were defined. The most common symptom was abdominal pain (80.4%) and other symptoms, respectively, were fever (57.8%), arthralgia (36.7%), chest pain (4.5%), and skin rash (2%). Amyloidosis was present in seven patients, and five of them had M694V mutation (homozygous), one of them had E148Q (heterozygous) mutation, and the other one had M694V/M694I mutation.

**CONCLUSION:** In our patients, we defined 21 different genotypes of MEFV gene and the most common mutation was M694V. The most common symptoms were abdominal pain and fever. We detected significant correlation between the M694V, E148Q, and V726A mutations and clinical findings.



DOI: 10.1089/gte.2008.0009

PMID: 18662100 [Indexed for MEDLINE]

3686. *Pediatr Blood Cancer*. 2008 Nov;51(5):701-3. doi: 10.1002/pbc.21685.

Intermittent chronic neutropenia in a patient with familial Mediterranean fever.

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A 12-year-old daughter of consanguineous Moroccan parents was diagnosed with cyclic neutropenia, based on a combination of recurrent gingivostomatitis, a fluctuating neutrophil count, and several episodes of severe neutropenia. No ELA2 gene mutations were found. At age 19 years she presented with edema of the limbs, proteinuria and renal failure. Renal amyloidosis AA was diagnosed by biopsy. Gene mutations associated with family Mediterranean fever (FMF) were sought, and a homozygous mutation (M694V) was found in the MFEV gene. This is the novel finding of FMF that masqueraded as cyclic neutropenia.

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DOI: 10.1002/pbc.21685

PMID: 18661496 [Indexed for MEDLINE]

3687. *Dtsch Med Wochenschr*. 2008 Aug;133(31-32):1621-4. doi: 10.1055/s-0028-1082777.

[Familial Mediterranean fever. Rare manifestation without fever and with inconspicuous family case history].

[Article in German]

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**HISTORY AND ADMISSION FINDINGS:** A 33-year-old man of Turkish descent had suffered from recurrent diffuse abdominal pain and shoulder pain since 13 years.

Repeatedly performed investigations in the past had produced numerous diagnoses. The symptoms had been recurring quarterly to weekly, lasted three days on average and resolved spontaneously. He never had fever and the family history was unremarkable.

**DIAGNOSIS, TREATMENT, AND COURSE:** Blood tests demonstrated increased parameters for systemic inflammation and mild normochromic normocytic anemia. In addition to splenomegaly the abdominal computed tomography revealed signs of sacroiliitis. There was no arthritis of the shoulder radiologically. Despite lack of familial history and fever genetic analysis of the Mediterranean fever gene (MEFV) revealed two heterozygous mutations in this MEFV gene for M694 and V726A. The patient was treated with colchicine and has now remained free of symptoms for meanwhile 10 months. There had been no comparable symptom-free period during the last 10 years.

**CONCLUSION:** Sometimes the name "Familial Mediterranean Fever" (FMF) is misleading because this disease may, although rarely, occur without both, fever and familial history. Because of the increasing number of immigrants FMF should be considered in the initial differential diagnosis of patients of Mediterranean origin presenting with abdominal pain. Genetic analysis of the MEFV-gene as well as a therapeutic trial with colchicine, may help to detect FMF.

DOI: 10.1055/s-0028-1082777

PMID: 18651363 [Indexed for MEDLINE]

3688. Rheumatol Int. 2008 Oct;28(12):1239-43. doi: 10.1007/s00296-008-0648-y. Epub 2008 Jul 23.

Familial Mediterranean fever attacks do not alter functional and morphologic tissue Doppler echocardiographic parameters.

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The aim of this study is to investigate the tissue Doppler echocardiographic (TDE) characteristics of acute familial Mediterranean fever (FMF) attack on young Turkish males. Thirty-four young males with FMF were investigated utilizing echocardiography both before and after FMF attacks. Echocardiographic findings were assessed by two cardiologist utilizing Vingmed system V echocardiography machine and a 2.5 MHz probe by two-dimensional and color Doppler examination, as well as tissue Doppler parameters. The incidence of pericardial effusion was found to be 23.3% during acute FMF attack. There was no significant difference between the patients in attack-free period and attack period with respect to TDE measurements. TDE measurements did not differ between the patients with and without pericardial effusion. There was no correlation between pericardial effusion and disease duration, family history, and physical findings. In conclusion, our results suggest preserved systolic and diastolic ventricular functions in attack period. Pericardial effusion is not associated with impaired TDE parameters.

DOI: 10.1007/s00296-008-0648-y

PMID: 18648816 [Indexed for MEDLINE]

3689. Eur J Hum Genet. 2008 Nov;16(11):1404-6. doi: 10.1038/ejhg.2008.135. Epub 2008 Jul 23.

Search for copy number alterations in the MEFV gene using multiplex ligation probe amplification, experience from three diagnostic centres.

van Gijn ME(1), Soler S, de la Chapelle C, Mulder M, Ritorre C, Kriek M, Philibert L, van der Wielen M, Frenkel J, Grandemange S, Bakker E, Ploos van Amstel JK, Touitou I.

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Familial mediterranean fever (FMF) is a hereditary autoinflammatory autosomal recessive disease caused by mutations in the MEFV gene. Despite the identification of many disease associated MEFV mutations, often the clinical

diagnosis cannot be genetically confirmed. The currently used diagnostic sequencing techniques only allow the detection of point mutations, small deletions or duplications. The question as to whether larger genetic alterations are also involved in the pathophysiology of FMF remains to be answered. To address this question, we used multiplex ligation-dependent probe amplification (MLPA) on a total of 216 patients with FMF symptoms. This careful analysis revealed that not a single deletion/duplication could be detected in this large cohort of patients. This result suggests that single or multiexon MEFV gene copy number changes do not contribute substantially, if at all, to the MEFV mutation spectrum.

DOI: 10.1038/ejhg.2008.135

PMID: 18648395 [Indexed for MEDLINE]

3690. J Clin Rheumatol. 2008 Aug;14(4):222-5. doi: 10.1097/RHU.0b013e318181b46b.

Protracted febrile myalgia mimicking polyarteritis nodosa.

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An insidious onset of unexplained fever, weight loss, skin lesions, abdominal pain, and musculoskeletal pain should suggest the diagnosis of polyarteritis nodosa (PAN). However, familial Mediterranean fever (FMF) with protracted febrile myalgia (PFM) should be kept in mind in the differential diagnosis. In this report, 6 cases of PFM mimicking PAN are described. Patients presented with severe muscle and abdominal pain lasting longer than 4 weeks. Their common medical history included recurrent febrile abdominal pain or arthritis. Physical examination revealed hypertension together with severe muscle tenderness. Laboratory examination revealed high acute phase reactants, negative p-ANCA, normal creatine kinase, and complement levels. Duplex abdominal ultrasonography was normal. Four of 6 patients were hospitalized with initial diagnoses of PAN. Renal and mesenteric angiography performed in 1 patient was normal. Steroid therapy controlled all the severe symptoms including hypertension in all of the cases. FMF with PFM is important in the differential diagnosis of patients with

suspected vasculitis especially when myalgia is present. Hypertension may be present as a result of sympathetic discharge because of severe myalgia. Because PFM rapidly responds to a short course of corticosteroids, a rapid diagnosis of PFM in FMF patients can reduce unnecessary workup and decrease the time patients have to suffer.

DOI: 10.1097/RHU.0b013e318181b46b

PMID: 18636021 [Indexed for MEDLINE]

3691. PLoS One. 2008 Jul 16;3(7):e2701. doi: 10.1371/journal.pone.0002701.

Defects in actin dynamics lead to an autoinflammatory condition through the upregulation of CXCL5.

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**BACKGROUND:** Destrin (DSTN) is a member of the ADF/cofilin family of proteins and is an important regulator of actin dynamics. The primary function of destrin is to depolymerize filamentous actin into its monomeric form and promote filament severing. While progress has been made in understanding the biochemical functions of the ADF/cofilin proteins, the study of an animal model for cells deficient for DSTN provides an opportunity to investigate the physiological processes regulated by proper actin dynamics in vivo. A spontaneous mouse mutant, corneal disease 1(corn1), is deficient for DSTN, which causes epithelial hyperproliferation and neovascularization in the cornea. Dstn(corn1) mice exhibit an actin dynamics defect in the cornea as evidenced by the formation of actin stress fibers in the epithelial cells. Previously, we observed a significant infiltration of leukocytes into the cornea of Dstn(corn1) mice as well as the upregulation of proinflammatory molecules. In this study, we sought to characterize this inflammatory condition and explore the physiological mechanism through which a loss of Dstn function leads to inflammation.

**METHODOLOGY/PRINCIPAL FINDINGS:** Through immunofluorescent analyses, we observed a significant recruitment of neutrophils and macrophages to the Dstn(corn1) cornea, demonstrating that the innate immune system is spontaneously activated in this

mutant. The inflammatory chemokine, CXCL5, was ectopically expressed in the corneal epithelial cells of Dstn(corn1) mice, and targeting of the receptor for this chemokine inhibited neutrophil recruitment. An inflammatory reaction was not observed in the cornea of allelic mutant strain, Dstn(corn1-2J), which has a milder defect in actin dynamics in the corneal epithelial cells.

CONCLUSIONS/SIGNIFICANCE: This study shows that severe defects in actin dynamics lead to an autoinflammatory condition that is mediated by the expression of CXC chemokines.

DOI: 10.1371/journal.pone.0002701

PMCID: PMC2442876

PMID: 18628996 [Indexed for MEDLINE]

3692. Lupus. 2008 Aug;17(8):752-3. doi: 10.1177/0961203308089449.

Possible familial Mediterranean fever in a Caucasian patient with systemic lupus erythematosus.

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We report the case of a Caucasian man with systemic lupus erythematosus who had recurrent fevers and abdominal pain. He was later found to carry E148Q polymorphism of MEFV, the gene responsible for familial Mediterranean fever.

DOI: 10.1177/0961203308089449

PMID: 18625654 [Indexed for MEDLINE]

3693. Lupus. 2008 Jul;17(7):663-9. doi: 10.1177/0961203308089403.

Systemic lupus erythematosus and familial Mediterranean fever: a possible negative association between the two disease entities--report of four cases and review of the literature.

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Serositis is a common clinical manifestation of systemic lupus erythematosus (SLE), as well as being the hallmark of familial Mediterranean fever (FMF), the most prevalent monogenic disease in the Jewish population. We have treated four patients who suffered from both SLE and FMF since 2001 in our clinic, which also serves as the national center for FMF. Our cases illustrate both similarities and dissimilarities between the clinical manifestations of these two diseases, an aspect which should be borne in mind, especially in the young female patients. In general, it seems that co-occurrence of FMF moderates the presentation of lupus.

DOI: 10.1177/0961203308089403

PMID: 18625639 [Indexed for MEDLINE]

3694. J Clin Pharm Ther. 2008 Aug;33(4):451-2. doi: 10.1111/j.1365-2710.2008.00927.x.

Colchicine intoxication and infection risk: a case report.

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Colchicine is widely used, primarily for the treatment of gouty arthritis and familial Mediterranean fever. Colchicine intoxication is a rare but potentially life-threatening event. Herein, we reported a 26-year-old woman who presented to the emergency department after ingesting 27.5 mg of colchicine in a suicide attempt. She exhibited signs typical of colchicine-poisoning and developed infectious complications but with subsequent complete recovery. This paper discusses the role of colchicine poisoning in increasing susceptibility to infections. This aspect is usually under-appreciated in the clinical picture of colchicine overdose.

DOI: 10.1111/j.1365-2710.2008.00927.x

PMID: 18613863 [Indexed for MEDLINE]

3695. Scand J Rheumatol. 2008 Sep-Oct;37(5):385-9. doi: 10.1080/03009740801978889.

Good response to IL-1beta blockade by anakinra in a 23-year-old CINCA/NOMID patient without mutations in the CIAS1 gene. Cytokine profiles and functional studies.

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Chronic infantile neurological cutaneous and articular (CINCA) syndrome is an autoinflammatory disease, defined by the triad of urticarial rash, neurological manifestations, and arthropathy, accompanied by recurrent fevers and systemic inflammation. Increasing neurological deficits result from aseptic meningitis. Sensorineural hearing loss and progressive loss of vision caused by keratoconjunctivitis or papilloedema may emerge. An autosomal-dominant inheritance is suspected although sporadic cases are reported frequently. Sixty per cent of CINCA patients carry mutations in the cold-induced autoinflammatory syndrome (CIAS1) gene. We report the favourable response of a 23-year-old CINCA patient without CIAS1 mutations to treatment with the recombinant interleukin-1 (IL-1) receptor antagonist anakinra.

DOI: 10.1080/03009740801978889

PMID: 18609262 [Indexed for MEDLINE]

3696. Curr Allergy Asthma Rep. 2008 Jul;8(4):288-98.

The spectrum of monogenic autoinflammatory syndromes: understanding disease mechanisms and use of targeted therapies.



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Monogenic autoinflammatory diseases encompass a distinct and growing clinical entity of multisystem inflammatory diseases with known genetic defects in the innate immune system. The diseases present clinically with episodes of seemingly unprovoked inflammation (fever, rashes, and elevation of acute phase reactants). Understanding the genetics has led to discovery of new molecules involved in recognizing exogenous and endogenous danger signals, and the inflammatory response to these stimuli. These advances have furthered understanding of innate inflammatory pathways and spurred collaborative research in rheumatology and infectious diseases. The pivotal roles of interleukin (IL)-1beta in cryopyrin-associated periodic syndromes, tumor necrosis factor (TNF) in TNF receptor-associated periodic syndrome, and links to inflammatory cytokine dysregulation in other monogenic autoinflammatory diseases have resulted in effective therapies targeting proinflammatory cytokines IL-1beta and TNF and uncovered other new potential targets for anti-inflammatory therapies.

PMCID: PMC2735099

PMID: 18606080 [Indexed for MEDLINE]

3697. Rheumatol Int. 2008 Nov;29(1):37-42. doi: 10.1007/s00296-008-0637-1. Epub 2008 Jul 3.

The rate and significance of Mediterranean fever gene mutations in patients with ankylosing spondylitis: a three-month, longitudinal clinical study.

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In this study, our aim was to investigate the prevalence of Mediterranean fever (MEFV) gene mutations in patients with ankylosing spondylitis (AS) and assessing their clinical significance. Ninety-five consecutive patients (12 women, 83 men) with active AS were included to the study. All patient's relevant clinical data were recorded at the beginning and patient assessment measures were performed. The frequency of the eight most common MEFV mutations: M694V, V726A, E148Q, M680I, M694I, P369S, F479L, and the R761H were determined. Genetic analysis was carried out by the NanoChip Molecular Genetics Workstation. NSAIDs were given to patients for treatment. The rate of MEFV mutations and their clinical significance were assessed. With regard to the MEFV mutation analysis, 30.5% of AS patients were found to have at least one mutation. The response rate to the NSAIDs ( $P=0.825$ ) or frequency of patients having active disease ( $P=0.066$ ) after the treatment, were not found different between the patients those have MEFV mutations and the patients those were non-carriers. Furthermore, no clinical and laboratory difference between MEFV mutation carriers and non-carriers were found. We think that although prevalence of MEFV mutations is significantly high in AS patients without clinical features of familial Mediterranean fever, its influence to the prognosis is less likely. Further investigations are needed to define the impact of MEFV mutations on the disease course of ankylosing spondylitis.

DOI: 10.1007/s00296-008-0637-1

PMID: 18597091 [Indexed for MEDLINE]

3698. Rheumatol Int. 2008 Nov;29(1):77-9. doi: 10.1007/s00296-008-0631-7. Epub 2008 Jul 1.

Intramuscular gold for the treatment of seronegative spondyloarthropathy associated with familial Mediterranean fever.

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Articular attack is a common feature of familial Mediterranean fever (FMF). FMF arthritis commonly resolves without any sequale within a few weeks. However,

approximately 10% of the patients develop protracted arthritis persisting for months to years. Treatment with colchicine may not be effective and nonsteroidal antiinflammatory drugs or second line agents may be needed for the management of protracted arthritis. In this paper, we describe a 22-year-old patient with FMF who was complicated with protracted arthritis in the knee and shoulder joints and bilateral sacroiliitis. He was successfully treated by intramuscular gold 50 mg weekly. However, gold treatment was discontinued 8 months later because of the development of asymptomatic proteinuria. In conclusion, FMF should be considered in the evaluation of peripheral oligoarthritis, particularly in patients with Mediterranean origin. Intramuscular gold might be an effective agent. However, care should be taken regarding the development of proteinuria.

DOI: 10.1007/s00296-008-0631-7

PMID: 18592246 [Indexed for MEDLINE]

3699. Clin Exp Rheumatol. 2008 Jan-Feb;26(1 Suppl 48):S74-80.

Autoimmune diseases and infections: controversial issues.

Baio P(1), Brucato A, Buskila D, Gershwin ME, Giacomazzi D, Lopez LR, Luzzati R, Matsuura E, Selmi C, Sarzi-Puttini P, Atzeni F.

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The etiology and pathogenesis of certain types of disease remain controversial and stand like a bridge that crosses infectious, autoimmune and autoinflammatory pathways. Infection, for example, may initiate a disease, although it is the genetic regulation in the host, the interplay between virus or bacteria persistence and autoimmunity that produces the later phases of disease, the antigenic determinants responsible for inducing autoimmune disease, and the pathogenetic effector mechanisms. Infections agents cause pericarditis, but in 85% of cases it is "idiopathic". It has also been shown that persistent *Chlamydia pneumoniae*, *Porphyromonas gingivalis*, and *Helicobacter pylori* infections cause host immunity and promote atherogenesis. A number of infectious agents have been suggested as potential triggers for primary biliary cirrhosis. Infections and vaccinations have also been linked to the pathogenesis of fibromyalgia syndrome, a common, chronic syndrome of widespread pain. Many factors are also responsible

for fever of unknown origin such as: infections, autoimmunity disease, etc. However, it is difficult to determine a direct correlation between the infections agents in such a large group of diseases. The aim of this review is to analyze some of the controversies about the role of infections in autoimmune diseases.

PMID: 18570758 [Indexed for MEDLINE]

3700. Clin Exp Rheumatol. 2008 Jan-Feb;26(1 Suppl 48):S53-61.

Autoinflammatory syndromes and infections: pathogenetic and clinical implications.

Efthimiou P(1), Flavell RA, Furlan A, Gasbarrini G, Gava A, Koné-Paut I, Manna R, Punzi L, Sutterwala FS, Touitou I, Doria A.

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The autoinflammatory syndromes are a group of disorders characterized by recurrent episodes of seemingly unprovoked inflammation without significant levels of autoantibodies and antigen specific T cells. Although a direct association between defective innate immune responses to bacterial components and these diseases has not been formally established, much ongoing research is aimed towards confirmation of that hypothesis. This article will review recent advances in the study of a subset of NOD-like receptors (NLRs), which control the activation of caspase-1 through the assembly of a large protein complex called inflammasome. Moreover, we will review recent progresses in understanding of a range of autoinflammatory conditions in humans.

PMID: 18570755 [Indexed for MEDLINE]

3701. Expert Rev Clin Immunol. 2008 Jul;4(4):425-8. doi: 10.1586/1744666X.4.4.425.

Fifth International Congress on Familial Mediterranean Fever and Systemic Autoinflammatory Diseases.

Touitou I(1), Savic S, Mathews RJ, Grateau G, McDermott MF.

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The Fifth International Congress on Familial Mediterranean Fever and Systemic Autoinflammatory Diseases (Rome, Italy, 4-8 April, 2008) reviewed developments in the field of innate immunity and discussed their relevance to the pathogenesis of associated diseases. The meeting gathered over 300 participants from 32 countries. New modes of inheritance of autoinflammatory diseases, animal models, novel related genes and the remarkable efficacy of IL-1beta blockage in most of these diseases were emphasized.

DOI: 10.1586/1744666X.4.4.425

PMID: 20477570

3702. Nat Clin Pract Rheumatol. 2008 Aug;4(8):428-38. doi: 10.1038/ncprheum0836. Epub 2008 Jun 24.

Therapy insight: the changing spectrum of rheumatic disease in HIV infection.

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HIV infection and AIDS have protean and multisystem manifestations throughout the various stages of infection. Progression from HIV infection to AIDS is associated with a gradual loss of immunocompetence and the occurrence of opportunistic infections and malignancies; it is also associated with immune dysregulation and persistent, prolonged immune activation that leads to autoimmune phenomena such as vasculitis and serological abnormalities. In people who are infected with HIV, the recognition of autoinflammatory disorders, their differentiation from infections or lymphoproliferative malignancies and their treatment using potentially immunosuppressive drugs is a challenging clinical scenario. The spectrum of rheumatologic diseases reported in HIV-infected individuals has

changed dramatically since the introduction of highly active antiretroviral therapy in 1995. Complications such as metabolic abnormalities, osteoporosis, and immune restoration inflammatory syndrome have emerged.

DOI: 10.1038/ncprheum0836

PMID: 18577999 [Indexed for MEDLINE]

3703. Blood. 2008 Sep 1;112(5):1794-803. doi: 10.1182/blood-2008-01-134932. Epub 2008 Jun 24.

The familial Mediterranean fever protein, pyrin, is cleaved by caspase-1 and activates NF-kappaB through its N-terminal fragment.

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Familial Mediterranean fever (FMF) is an autoinflammatory disease caused by mutations in MEFV, which encodes a 781-amino acid protein denoted pyrin. We have previously shown that pyrin regulates caspase-1 activation and IL-1beta production through interaction of its N-terminal PYD motif with the ASC adapter protein, and also modulates IL-1beta production by interaction of its C-terminal B30.2 domain with the catalytic domains of caspase-1. We now asked whether pyrin might itself be a caspase-1 substrate, and found that pyrin is cleaved by caspase-1 at Asp330, a site remote from the B30.2 domain. Pyrin variants harboring FMF-associated B30.2 mutations were cleaved more efficiently than wild-type pyrin. The N-terminal cleaved fragment interacted with the p65 subunit of NF-kappaB and with IkappaB-alpha through its 15-aa bZIP basic domain and adjacent sequences, respectively, and translocated to the nucleus. The interaction of the N-terminal fragment with p65 enhanced entrance of p65 into the nucleus. The interaction of N-terminal pyrin with IkappaB-alpha induced calpain-mediated degradation of IkappaB-alpha, thus potentiating NF-kappaB activation. Absolute and relative quantities of cleaved pyrin and IkappaB-alpha degradation products were substantially increased in leukocytes from FMF patients

compared with healthy controls. Our data support a new pyrin/caspase-1 pathway for NF-kappaB activation.

DOI: 10.1182/blood-2008-01-134932

PMCID: PMC2518886

PMID: 18577712 [Indexed for MEDLINE]

3704. Arthritis Rheum. 2008 Jul;58(7):2142-6. doi: 10.1002/art.23604.

Autoinflammatory genes and susceptibility to psoriatic juvenile idiopathic arthritis.

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**OBJECTIVE:** To investigate the association of NLRP3, NOD2, MEFV, and PSTPIP1, genes that cause 4 of the autoinflammatory hereditary periodic fever syndromes (HPFS), with juvenile idiopathic arthritis (JIA).

**METHODS:** Fifty-one single-nucleotide polymorphisms (SNPs) across the 4 loci were investigated using MassArray genotyping in 950 Caucasian patients with JIA living in the UK and 728 ethnically matched healthy controls.

**RESULTS:** Prior to Bonferroni correction for multiple testing, significant genotype associations between 6 SNPs in MEFV and JIA were observed and, in subgroup analysis, associations between 12 SNPs across all 4 loci and the subgroup of patients with psoriatic JIA were found. After Bonferroni correction for multiple testing, 2 genotype associations remained significant in the subgroup of patients with psoriatic JIA (MEFV SNP rs224204 [corrected P = 0.025] and NLRP3 SNP rs3806265 [corrected P = 0.04]).

**CONCLUSION:** These findings support the use of monogenic loci as candidates for investigating the genetic component of complex disease and provide preliminary evidence of association between SNPs in autoinflammatory genes and psoriatic JIA. Our findings raise the interesting possibility of a shared disease mechanism between the HPFS and psoriatic JIA, potentially involving abnormal production of interleukin-1beta.

DOI: 10.1002/art.23604

PMCID: PMC2688675

PMID: 18576390 [Indexed for MEDLINE]

3705. Arthritis Rheum. 2008 Jul;58(7):2213-4; author reply 2214-5. doi: 10.1002/art.23551.

Cell surface expression of TNFRI in tumor necrosis factor receptor-associated periodic syndrome: comment on the article by Nedjai et al.

Todd I, Tighe P, Rebelo S, Powell R.

Comment on

Arthritis Rheum. 2008 Jan;58(1):273-83.

DOI: 10.1002/art.23551

PMID: 18576329 [Indexed for MEDLINE]

3706. Proc Natl Acad Sci U S A. 2008 Jul 1;105(26):9017-22. doi: 10.1073/pnas.0710445105. Epub 2008 Jun 23.

Differential function of the NACHT-LRR (NLR) members Nod1 and Nod2 in arthritis.

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The pathogenesis of chronic joint inflammation remains unclear, although the involvement of pathogen recognition receptors has been suggested recently. In the present article, we describe the role of two members of the NACHT-LRR (NLR) family, Nod1 (nucleotide-binding oligomerization domain) and Nod2 in a model of acute joint inflammation induced by intraarticular injection of *Streptococcus pyogenes* cell wall fragments. Here, we show that Nod2 deficiency resulted in



reduced joint inflammation and protection against early cartilage damage. In contrast, Nod1 gene-deficient mice developed enhanced joint inflammation with concomitant elevated levels of proinflammatory cytokines and cartilage damage, consistent with a model in which Nod1 controls the inflammatory reaction. To explore whether the different function of Nod1 and Nod2 occurs also in humans, we exposed peripheral blood mononuclear cells (PBMCs) carrying either Nod1ins/del or Nod2fs mutation with SCW fragments in vitro. Production of both TNFalpha and IL-1beta was clearly impaired in PBMCs carrying the Nod2fs compared with PBMCs isolated from healthy controls. In line with results in Nod1 gene-deficient mice, PBMCs from individuals bearing a newly described Nod1 mutation produced enhanced levels of proinflammatory cytokines after 24-h stimulation with SCW fragments. These data indicate that the NLR family members Nod1 and Nod2 have different functions in controlling inflammation, and that intracellular Nod1-Nod2 interactions may determine the severity of arthritis in this experimental model. Whether a distorted balance between the function of Nod1 and/or Nod2 is involved in the pathogenesis of human autoinflammatory or autoimmune disease, such as rheumatoid arthritis, remains to be elucidated.

DOI: 10.1073/pnas.0710445105

PMCID: PMC2449357

PMID: 18574154 [Indexed for MEDLINE]

3707. Exp Dermatol. 2008 Aug;17(8):633-9. doi: 10.1111/j.1600-0625.2008.00768.x. Epub 2008 Jun 28.

The vitamin D pathway: a new target for control of the skin's immune response?

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The surface of our skin is constantly challenged by a wide variety of microbial pathogens, still cutaneous infections are relatively rare. Within cutaneous innate immunity the production of antimicrobial peptides (AMPs) is a primary system for protection against infection. Many AMPs can be found on the skin, and these include molecules that were discovered for their antimicrobial properties,

and other peptides and proteins first known for activity as chemokines, enzymes, enzyme inhibitors and neuropeptides. Cathelicidins were among the first families of AMPs discovered on the skin. They are now known to have two distinct functions; they have direct antimicrobial activity and will initiate a host cellular response resulting in cytokine release, inflammation and angiogenesis. Dysfunction of cathelicidin is relevant in the pathogenesis of several cutaneous diseases including atopic dermatitis where cathelicidin induction is suppressed, rosacea, where cathelicidin peptides are abnormally processed to forms that induce cutaneous inflammation and a vascular response, and psoriasis, where a cathelicidin peptide can convert self-DNA to a potent stimulus of an autoinflammatory cascade. Recent work has unexpectedly identified vitamin D3 as a major factor involved in the regulation of cathelicidin expression. Therapies targeting the vitamin D3 pathway and thereby cathelicidin may provide new treatment modalities in the management of infectious and inflammatory skin diseases.

DOI: 10.1111/j.1600-0625.2008.00768.x

PMCID: PMC2729115

PMID: 18573153 [Indexed for MEDLINE]

3708. Drug News Perspect. 2008 May;21(4):232.

Molecule of the month. Rilonacept.

[No authors listed]

PMID: 18560622 [Indexed for MEDLINE]

3709. Actas Dermosifiliogr. 2008 Jul-Aug;99(6):481-4.

[Exacerbation of skin lesions during fever in a patient with chronic infantile neurologic cutaneous articular (CINCA) syndrome].

[Article in Spanish]

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Chronic infantile neurologic cutaneous articular (CINCA) syndrome is a serious chronic systemic inflammatory disease that presents at a young age and that is characterized by skin, joint, and central nervous system disease. Skin symptoms are the first to appear, in the form of a longstanding nonpruritic urticarial rash, with exacerbations coinciding with episodes of fever, arthritis, and enlarged lymph nodes. The findings of biopsy of skin lesions are extremely variable but characterized by perivascular neutrophilic infiltrate. With the discovery of mutations in the CIAS1 gene, which encodes a protein known as cryopyrin, this entity has been classified as one of the cryopyrin-associated autoinflammatory diseases, along with familial cold urticaria and Muckle-Wells syndrome. This discovery has also made available new therapeutic options. We present the case of a boy diagnosed with CINCA syndrome who presented with an outbreak of painful skin lesions and fever. These lesions were thought to be an exacerbation of underlying lesions during an episode of fever.

PMID: 18558058 [Indexed for MEDLINE]

3710. Pathol Biol (Paris). 2009 May;57(3):213-6. doi: 10.1016/j.patbio.2008.04.008. Epub 2008 Jun 13.

[Molecular bases of hereditary recurrent fevers].

[Article in French]

Jéru I, Grateau G, Amselem S.

DOI: 10.1016/j.patbio.2008.04.008

PMID: 18554823 [Indexed for MEDLINE]

3711. Clin Rheumatol. 2008 Sep;27(9):1171-5. doi: 10.1007/s10067-008-0930-0. Epub 2008

Jun 14.

Decreased bone mineral density in adult familial Mediterranean fever patients: a pilot study.

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We investigated the association between familial Mediterranean fever (FMF) and osteoporosis (OP) in adult patients. Thirty-five attack-free FMF patients (28 females, 7 males; mean age 36.9 +/- 5.7 years) were individually matched to control subjects on the basis of age (within 2 years) and sex. All patients were taking regular colchicine. Subjects having any condition that can cause decreased bone mineral density (BMD) were excluded from the study. BMD was measured at the spine and femur by dual X-ray absorptiometry (DXA). Data was given as the median (IQR). T scores of the spine were -0.700 (-1.097 to -0.262) and -0.450 (-0.830 to 0.112) in FMF patients and healthy controls, respectively ( $p > 0.05$ ). T scores of the femur neck were -0.900 (-1.480 to -0.570) and -0.430 (-1.472 to 0.247) in FMF patients and healthy controls, respectively ( $p > 0.05$ ). Total femur T scores were significantly lower in FMF patients than healthy controls (-0.780 [-1.222 to -0.085] vs. -0.100 [-0.765 to 0.537], respectively,  $p = 0.021$ ). Total femur T scores were significantly decreased in adult patients with FMF. Ongoing subclinical inflammation may be associated with decreased bone mineral content in those patients.

DOI: 10.1007/s10067-008-0930-0

PMID: 18553115 [Indexed for MEDLINE]

3712. Isr Med Assoc J. 2008 Apr;10(4):318-9.

Episcleritis associated with familial Mediterranean fever.

Berestizschevsky S(1), Weinberger D, Avisar I, Avisar R.

Author information:

(1)External Eye Disease Clinic, Department of Ophthalmology, Rabin Medical Center, Golda Campus, Petah Tikva, Israel.

PMID: 18548993 [Indexed for MEDLINE]

3713. Joint Bone Spine. 2008 Jul;75(4):504-5. doi: 10.1016/j.jbspin.2008.04.001. Epub 2008 Jun 9.

Anakinra: new therapeutic approach in children with Familial Mediterranean Fever resistant to colchicine.

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Familial Mediterranean fever (FMF), a recessively inherited autoinflammatory disorder, is the prototype of a group of disorders termed systemic autoinflammatory diseases. Such diseases are characterized by seemingly unprovoked episodes of inflammation without evidence of high-titer autoantibodies or antigen-specific T cell. Repeated bouts of inflammation may lead to systemic AA protein deposition, making FMF a potentially fatal disease. Pyrin, the protein mutated in FMF, regulates caspase-1 activation and consequently IL-1beta production. Although colchicine is the standard prophylactic therapy for attacks and amyloid deposition, some patients fail to respond or cannot tolerate its side effects. Anticytokine therapies have shown promise in the treatment of autoinflammatory disorders in children. We report on the use of the recombinant interleukin 1 receptor antagonist anakinra in one child with therapy-resistant FMF. The patient experienced immediate, sustained resolution of symptoms and laboratory markers of inflammation, and also, possibly, a reduced long-term risk of AA amyloidosis.

DOI: 10.1016/j.jbspin.2008.04.001

PMID: 18541452 [Indexed for MEDLINE]

3714. Curr Pharm Des. 2008;14(13):1295-301.

Central nervous system involvement in pediatric rheumatic diseases: current concepts in treatment.

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Central nervous system (CNS) manifestations are not rare in pediatric rheumatic diseases. They may be a relatively common feature of the disease, as in systemic lupus erythematosus (SLE) and Behçet's disease. Direct CNS involvement of a systemic rheumatic disease, primary CNS vasculitis, indirect involvement secondary to hypertension, hypoxia and metabolic changes, and drug associated adverse events may all result in CNS involvement. We have reviewed the CNS manifestations of SLE, Behçet's disease, Henoch-Schönlein purpura, polyarteritis nodosa, juvenile idiopathic arthritis, juvenile ankylosing spondylitis, familial Mediterranean fever, scleroderma, sarcoidosis, Wegener's granulomatosis, Takayasu's arteritis, CINCA syndrome, Kawasaki disease, and primary CNS vasculitis; and adverse CNS effects of anti-rheumatic drugs in pediatric patients. The manifestations are diverse; ranging from headache, seizures, chorea, changes in personality, depression, memory and concentration problems, cognitive impairment, cerebrovascular accidents to coma, and death. The value of cerebrospinal fluid (CSF) examination (pleocytosis, high level of protein), auto-antibodies in serum and CSF, electroencephalography, neuroimaging with computerized tomography, magnetic resonance imaging, SPECT, PET, and angiography depends on the disease. Brain biopsy is gold standard for the diagnosis of CNS vasculitis, however it may be inconclusive in 25% of cases. A thorough knowledge of the rheumatic diseases and therapy-related adverse events is mandatory for the management of a patient with rheumatic disease and CNS involvement. Severe CNS involvement is associated with poor prognosis, and high mortality rate. High dose steroid and cyclophosphamide (oral or intravenous) are first choice drugs in the treatment; plasmapheresis, IVIG, thalidomide, and intrathecal treatment may be valuable in treatment-resistant, and serious cases.

PMID: 18537653 [Indexed for MEDLINE]

3715. J Rheumatol. 2008 Jul;35(7):1362-5. Epub 2008 Jun 1.

Interferon-alpha as a treatment modality for colchicine- resistant familial Mediterranean fever.

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**OBJECTIVE:** Previous reports on interferon-alpha (IFN-alpha) were conflicting with respect to its efficacy in familial Mediterranean fever (FMF) refractory to colchicine treatment. We investigated the effect of IFN-alpha in patients with colchicine-resistant FMF.

**METHODS:** In a prospective, patient self-controlled, open-label study evaluating the safety and efficacy of IFN-alpha in patients with FMF with a severe phenotype, refractory to intensified (oral plus intravenous) colchicine therapy, we advised patients to subcutaneously inject IFN-alpha, 3 million international units, at the onset of the FMF attack. Attacks not treated with IFN-alpha of the same patients and in the same sites served as control attacks. Features of each attack were recorded in a questionnaire, eventually used to compare between IFN-alpha-treated and non-treated attacks.

**RESULTS:** Ten patients with a total of 80 attacks were recruited. Compared to 22 untreated attacks, a > 20% and > 50% reduction in the duration of the attacks was noted in 100% and 90% of the 58 IFN-alpha-treated attacks, respectively ( $p < 0.001$  for both). The severity (degree of pain) of the IFN-alpha-treated attacks was attenuated by > 20% and > 50% in 88% and 49% of these attacks, respectively ( $p < 0.001$  for both). The most common drug-related adverse events were chills and fatigue.

**CONCLUSION:** Early intervention with IFN-alpha injections was associated with reduced attack length and/or severity in a substantial number of bouts, with an acceptable cost of adverse events.

PMID: 18528960 [Indexed for MEDLINE]

3716. Arthritis Rheum. 2008 Jun;58(6):1885; author reply 1885-6. doi: 10.1002/art.23550.

MEFV mutations and palindromic rheumatism: comment on the article by Cañete et al.

Lidar M, Livneh A.

Comment on  
Arthritis Rheum. 2007 Aug;56(8):2784-8.

DOI: 10.1002/art.23550  
PMID: 18512803 [Indexed for MEDLINE]

3717. Arthritis Rheum. 2008 Jun;58(6):1883-4; author reply 1884. doi: 10.1002/art.23478.

Possible correlation between reversible and irreversible lesions in familial Mediterranean fever, soluble Fas, and C5a inhibitor activity: comment on the letter by Yasui and Yamazaki.

Rozenbaum M, Rosner I.

Comment on  
Arthritis Rheum. 2007 Nov;56(11):3879-80; author reply 3880.

DOI: 10.1002/art.23478  
PMID: 18512795 [Indexed for MEDLINE]

3718. Arthritis Rheum. 2008 Jun;58(6):1823-32. doi: 10.1002/art.23474.

A diagnostic score for molecular analysis of hereditary autoinflammatory syndromes with periodic fever in children.

Gattorno M(1), Sormani MP, D'Osualdo A, Pelagatti MA, Caroli F, Federici S,



Cecconi M, Solari N, Meini A, Zulian F, Obici L, Breda L, Martino S, Tommasini A, Bossi G, Govers A, Touitou I, Woo P, Frenkel J, Koné-Paut I, Baldi M, Ceccherini I, Martini A.

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**OBJECTIVE:** To identify a set of clinical parameters that can predict the probability of carrying mutations in one of the genes associated with hereditary autoinflammatory syndromes.

**METHODS:** A total of 228 consecutive patients with a clinical history of periodic fever were screened for mutations in the MVK, TNFRSF1A, and MEFV genes, and detailed clinical information was collected. A diagnostic score was formulated based on univariate and multivariate analyses in genetically positive and negative patients (training set). The diagnostic score was validated in an independent set of 77 patients (validation set).

**RESULTS:** Young age at onset (odds ratio [OR] 0.94,  $P = 0.003$ ), positive family history of periodic fever (OR 4.1,  $P = 0.039$ ), thoracic pain (OR 4.6,  $P = 0.05$ ), abdominal pain (OR 33.1,  $P < 0.001$ ), diarrhea (OR 3.3,  $P = 0.028$ ), and oral aphthosis (OR 0.2,  $P = 0.007$ ) were found to be independently correlated with a positive genetic test result. These variables were combined in a linear score whose ability to predict a positive result on genetic testing was validated in an independent data set. In this latter set, the diagnostic score revealed high sensitivity (82%) and specificity (72%) for discriminating patients who were genetically positive from those who were negative. In patients with a high probability of having a positive result on genetic testing, a regression tree analysis provided the most reasonable order in which the genes should be screened.

**CONCLUSION:** The proposed approach in patients with periodic fever will increase the probability of obtaining positive results on genetic testing, with good specificity and sensitivity. Our results further help to optimize the molecular analysis by suggesting the order in which the genes should be screened.

DOI: 10.1002/art.23474

PMID: 18512793 [Indexed for MEDLINE]

[Recurrent pleurisy as sole manifestation of familial Mediterranean fever].

[Article in Dutch]

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Recurrent pleurisy as sole manifestation of familial Mediterranean fever. An 18-year-old woman of Turkish descent visited our outpatient department with a 12-year history of recurrent self-limiting febrile attacks accompanied by chest pain. At first the symptoms were attributed to recurrent lower airway infections. However, the persistent nature of the attacks combined with her ethnic background and the spontaneous recovery from the short paroxysmal episodes, led to the consideration of familial Mediterranean fever (FMF). After undergoing treatment with colchicine the patient was free of symptoms. Later it became clear that her 28-year-old brother had the same clinical manifestations of FMF. He was also successfully treated with colchicine. The often long interval from disease onset to correct diagnosis reflects the unfamiliarity of physicians with this disease and the frequency with which it is confused with other syndromes. In patients with paroxysmal febrile attacks and chest pain, especially if they originate from the eastern Mediterranean area, FMF should be considered and colchicine be prescribed to relieve symptoms and prevent amyloidosis.

PMID: 18512530 [Indexed for MEDLINE]

3720. Minerva Pediatr. 2008 Aug;60(4):469-72.

Unusual Gilbert's syndrome genotype in a Greek patient suffering from both Gilbert's syndrome and familial mediterranean fever. A case report.

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Gilbert's syndrome is a genetically controlled non-hemolytic unconjugated hyperbilirubinemia, caused by reduced activity of UDP-glucuroniltransferase 1, an enzyme critical in bilirubin metabolism. Several molecular configurations may be implicated in a Gilbert's phenotype. Familial mediterranean fever (FMF) is an inherited acute relapsing inflammatory disorder, affecting Mediterranean and Middle East populations. The molecular basis of the disorder concerns the MEFV gene coding for a protein named pyrin; several point mutations of MEFV gene have been associated with the disease. The authors present an unusual patient co-affected by both Gilbert's syndrome and FMF who carried a peculiar Gilbert's genotype. The coexistence of these two genetic conditions seems to be rare but interesting as the potentially overlapping clinical symptoms may rise interesting diagnostic problems.

PMID: 18511900 [Indexed for MEDLINE]

3721. Clin Rheumatol. 2008 Oct;27(10):1317-20. doi: 10.1007/s10067-008-0911-3. Epub 2008 May 28.

Hyperimmunoglobulinemia D and periodic fever syndrome; treatment with etanercept and follow-up.

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The hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) is an autoinflammatory syndrome. It is caused by the mutations of the mevalonate kinase gene. There is no consensus for specific therapy of HIDS, but there are some case reports and studies in regards to its treatment with drugs like colchicine, steroids, nonsteroid anti-inflammatory drugs, simvastatin, anakinra, thalidomide, and etanercept. We are reporting a case evaluated for the complaints of abdominal pain and febrile episodes with massive hepatomegaly, not common finding on physical examination, its treatment with etanercept, and long-term follow-up.

DOI: 10.1007/s10067-008-0911-3

PMID: 18506569 [Indexed for MEDLINE]

3722. Rheumatol Int. 2008 Oct;28(12):1211-6. doi: 10.1007/s00296-008-0605-9. Epub 2008 May 24.

Evaluation of intima media thickness of the common and internal carotid arteries with inflammatory markers in familial Mediterranean fever as possible predictors for atherosclerosis.

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The aim of the present study was to determine whether intima-media thickness (IMT) of the common (CCA) and internal carotid arteries (ICA) was increased due to chronic inflammation occurring in familial Mediterranean fever (FMF) patients compared to healthy controls. Erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP), serum amyloid A protein (SAA), lipid profile and homocysteine levels were examined in 70 FMF patients [median age 14 years (range 4-24)] in an attack free period and in 50 healthy controls [median age 14 years (range 4-18)]. All the patients were homozygous or compound heterozygous for MEFV mutations. IMT of both CCA and ICA was evaluated with a high resolution B-mode ultrasonography. ESR, CRP, fibrinogen and SAA levels were significantly higher in FMF patients as compared to healthy controls ( $P < 0.05$ ). Intima media thickness of the common carotid artery was found to be significantly higher in FMF patients when compared to those in healthy controls [0.37 mm (0.26-0.61) vs. 0.28 mm (0.21-0.35),  $P < 0.001$ ]. The median ICA-IMT was significantly increased in the patients when compared to those in the controls [0.25 mm (0.18-0.44) vs. 0.22 mm (0.10-0.26),  $P < 0.001$ ]. A positive correlation between CCA-IMT and SAA levels ( $r = 0.24$ ,  $P = 0.04$ ) was found while ICA-IMT positively correlated with ESR ( $r = 0.31$ ,  $P = 0.008$ ) and fibrinogen levels ( $r = 0.30$ ,  $P = 0.012$ ). Intima media thickness, an early predictor of atherosclerosis, may be associated with subclinical inflammation in children with FMF. Further studies will enlighten

whether these patients will be predisposed more to coronary artery disease.

DOI: 10.1007/s00296-008-0605-9

PMID: 18500463 [Indexed for MEDLINE]

3723. Rheumatol Int. 2008 Nov;29(1):107-10. doi: 10.1007/s00296-008-0616-6. Epub 2008 May 24.

Coexistence of familial Mediterranean fever and psoriasis in a patient with seronegative spondyloarthropathy.

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Familial Mediterranean fever (FMF) is a self-limited disease characterized by fever and polyserositis attacks. Arthritis caused by synovitis is either in acute monoarthritis or chronic mono-oligoarthritis form, usually affecting the lower extremities. Another potential but rare form of involvement is spondyloarthropathy (SSpA). Psoriatic arthritis (PsA) is inflammatory arthropathy of peripheral joints, spine and entheses areas. Some PsA cases are classified as psoriatic spondyloarthropathy. A 43-year-old male patient with concomitant FMF and psoriasis presenting with bilateral sacroiliitis, chronic hip and knee arthritis has been presented along with follow-up findings and treatment options used.

DOI: 10.1007/s00296-008-0616-6

PMID: 18500460 [Indexed for MEDLINE]

3724. Genet Med. 2008 May;10(5):349-52. doi: 10.1097/GIM.0b013e3181723cc8.

Prevalence of known mutations in the familial Mediterranean fever gene (MEFV) in various carrier screening populations.

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**PURPOSE:** To determine the carrier frequency of familial Mediterranean fever (FMF) mutations of individuals in three different US testing populations: Cystic fibrosis, Factor V Leiden, and Ashkenazi Jews.

**METHODS:** DNA samples from 1234 anonymous samples were screened for 12 FMF mutations using a laboratory-developed test.

**RESULTS:** Genotyping revealed carrier frequencies of 1:16, 1:46, and 1:8, respectively.

**CONCLUSION:** MEFV mutation frequency seems to correlate positively with Mediterranean influence of the tested population and the high overall carrier rate for MEFV mutations in the Factor V Leiden testing population (1:46) suggests that the disease may be under-diagnosed in the US population or that the mutant alleles have a low penetrance.

DOI: 10.1097/GIM.0b013e3181723cc8

PMID: 18496034 [Indexed for MEDLINE]

3725. Eur J Ophthalmol. 2008 May-Jun;18(3):459-61.

Macular involvement in secondary systemic amyloidosis.

Altiparmak UE(1), Koklu B, Unlu N, Yagci R, Bayrak R, Gul Yilmaz Cinar F, Duman S.

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(1)Department of Ophthalmology, Ankara Training and Research Hospital, Ankara - Turkey. ealtiparmak@hotmail.com

**PURPOSE:** A patient with subretinal and preretinal hemorrhage after secondary systemic amyloidosis due to familial Mediterranean fever is presented.

**METHODS:** Case presentation.

**RESULTS:** A 30-year-old woman with secondary systemic amyloidosis secondary to familial Mediterranean fever presented with painless visual loss in the right eye. The examination demonstrated multiple subretinal and preretinal hemorrhages,

massive deposits which may represent amyloid material at the left macular region.

After 6 months, the hemorrhages disappeared, but deposits persisted.

CONCLUSIONS: The macular deposition and hemorrhage is an uncommon manifestation of secondary systemic amyloidosis secondary to familial Mediterranean fever.

Further evidence is necessary to understand the nature of these deposits and their relevance to secondary systemic amyloidosis and/or familial Mediterranean fever.

PMID: 18465734 [Indexed for MEDLINE]

3726. Hepatol Res. 2008 Aug;38(8):745-61. doi: 10.1111/j.1872-034X.2008.00366.x. Epub 2008 May 7.

New insights into autoimmune liver diseases.

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Autoinflammatory liver disease represents an important aspect of global hepatological practice. The three principal disease divisions recognized are autoimmune hepatitis, primary sclerosing cholangitis and primary biliary cirrhosis. Largely, but not exclusively, these diseases are considered to be autoimmune in origin. Increased recognition of outlier and overlap syndromes, changes in presentation and natural history, as well as the increased awareness of IgG4-associated sclerosing cholangitis, all highlight the limitations of the classic terminology. New insights continue to improve the care given to patients, and have arisen from carefully conducted clinical studies, therapeutic trials, as well as genetic and laboratory investigations. The challenges remain to treat patients before liver injury becomes permanent and to prevent the development of organ failure.

DOI: 10.1111/j.1872-034X.2008.00366.x

PMID: 18462376

3727. Curr Dir Autoimmun. 2008;10:244-57. doi: 10.1159/000131501.

The genetics of generalized vitiligo.

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Generalized vitiligo is an acquired disorder in which patches of depigmented skin, overlying hair and oral mucosa result from progressive autoimmune loss of melanocytes from the involved areas. Perhaps the most common pigmentary disorder, vitiligo results from a complex interaction of environmental, genetic and immunologic factors that ultimately contribute to melanocyte destruction, resulting in the characteristic depigmented lesions. In the past few years, studies of the genetic epidemiology of generalized vitiligo have led to the recognition that vitiligo is part of a broader, genetically determined, autoimmune and autoinflammatory diathesis. Attempts to identify genes involved in vitiligo susceptibility have involved gene expression studies, allelic association studies of candidate genes and genome-wide linkage analyses to discover new genes, and these studies have begun to shed light on the mechanisms of vitiligo pathogenesis. It is anticipated that the discovery of biological pathways of vitiligo pathogenesis will provide novel therapeutic and prophylactic targets for future approaches to the treatment and prevention of vitiligo and its associated autoimmune diseases.

DOI: 10.1159/000131501

PMID: 18460890 [Indexed for MEDLINE]

3728. Clin Biochem. 2008 Jul;41(10-11):920-2. doi: 10.1016/j.clinbiochem.2008.03.017. Epub 2008 Apr 11.

Cytokine profile of Armenian patients with Familial Mediterranean fever.

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**OBJECTIVES:** Despite the well-defined genetics of FMF, limited information is available regarding the regulation of inflammation by cytokines.

**DESIGN AND METHODS:** The levels of systemic cytokines and other markers of inflammation in FMF patients and control were measured by ELISA and Cytometric Bead Array (CBA).

**RESULTS:** In FMF attack the levels of IL-6, IL-10, IL-17, TGF-beta, CRP, and sIL-2R were significantly different from the norm and FMF remission.

**CONCLUSIONS:** Inflammation in FMF involves Treg and Th17 lineages.

DOI: 10.1016/j.clinbiochem.2008.03.017

PMID: 18440310 [Indexed for MEDLINE]

3729. J Allergy Clin Immunol. 2008 Aug;122(2):261-6. doi: 10.1016/j.jaci.2008.03.027. Epub 2008 Apr 25.

Antimicrobial peptides and the skin immune defense system.

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Republished in

J Allergy Clin Immunol. 2009 Sep;124(3 Suppl 2):R13-8.

Our skin is constantly challenged by microbes but is rarely infected. Cutaneous production of antimicrobial peptides (AMPs) is a primary system for protection, and expression of some AMPs further increases in response to microbial invasion. Cathelicidins are unique AMPs that protect the skin through 2 distinct pathways: (1) direct antimicrobial activity and (2) initiation of a host response resulting in cytokine release, inflammation, angiogenesis, and reepithelialization.

Cathelicidin dysfunction emerges as a central factor in the pathogenesis of several cutaneous diseases, including atopic dermatitis, in which cathelicidin is suppressed; rosacea, in which cathelicidin peptides are abnormally processed to forms that induce inflammation; and psoriasis, in which cathelicidin peptide converts self-DNA to a potent stimulus in an autoinflammatory cascade. Recent work identified vitamin D3 as a major factor involved in the regulation of cathelicidin. Therapies targeting control of cathelicidin and other AMPs might provide new approaches in the management of infectious and inflammatory skin diseases.

DOI: 10.1016/j.jaci.2008.03.027

PMCID: PMC2639779

PMID: 18439663 [Indexed for MEDLINE]

3730. Arthritis Rheum. 2008 May;58(5):1516-20. doi: 10.1002/art.23475.

Persistent efficacy of anakinra in patients with tumor necrosis factor receptor-associated periodic syndrome.

Gattorno M(1), Pelagatti MA, Meini A, Obici L, Barcellona R, Federici S, Buoncompagni A, Plebani A, Merlini G, Martini A.

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**OBJECTIVE:** To evaluate the efficacy and safety of treatment with the interleukin-1 receptor antagonist anakinra in patients with tumor necrosis factor receptor-associated periodic syndrome (TRAPS) requiring high cumulative doses of steroids.

**METHODS:** Four children (mean age 9.1 years [range 4-13 years]) and 1 adult (age 33 years) with TRAPS were enrolled in the study. The 3 children with cysteine mutations (C52Y, C55Y, C43R) had prolonged and frequent attacks of fever. One child with the R92Q mutation and the adult patient with the C43R mutation displayed a more chronic disease course, with fluctuating, nearly continuous symptoms and persistent elevation of acute-phase reactant levels (including serum amyloid A [SAA]). All patients were treated with anakinra (1.5 mg/kg/day).

**RESULTS:** All of the patients had a prompt response to anakinra, with disappearance of symptoms and normalization of acute-phase reactant levels,

including SAA. In all pediatric patients, anakinra was withdrawn after 15 days of treatment. After a few days (mean 5.6 days [range 3-8]) a disease relapse occurred, which dramatically responded to reintroduction of anakinra. During the following period of observation (mean 11.4 months [range 4-20 months]), the patients did not experience episodes of fever or other disease-related clinical manifestations. Levels of acute-phase reactants remained in the normal range. No major adverse reactions or severe infections were observed.

CONCLUSION: Continuous treatment with anakinra effectively controlled both the clinical and laboratory manifestations in patients with TRAPS and prevented disease relapses.

DOI: 10.1002/art.23475

PMID: 18438813 [Indexed for MEDLINE]

3731. An Med Interna. 2008 Feb;25(2):93-7.

[Periodic familial fever].

[Article in Spanish]

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The familial periodic fevers are Known as autoinflammatory syndromes. It is important in clinical practice to recognize these uncommon illnesses characterized by recurrent bouts of unspecific systemic symptoms associated to elevation of acute phase reactants without autoantibodies or underlying infection. The clinical suspicion supported on the molecular diagnosis represents a new perspective in relation to treatment and prognosis of these patients.

PMID: 18432368 [Indexed for MEDLINE]

3732. J Pediatr. 2008 May;152(5):742-3; author reply 743. doi: 10.1016/j.jpeds.2007.11.035.

The role of tonsillectomy in management of periodic fever, aphthous stomatitis, pharyngitis, and adenopathy: Unanswered questions.

Spalding SJ, Hashkes PJ.

Comment on

J Pediatr. 2007 Sep;151(3):289-92.

DOI: 10.1016/j.jpeds.2007.11.035

PMID: 18410792 [Indexed for MEDLINE]

3733. J Pediatr. 2008 May;152(5):742; author reply 743. doi: 10.1016/j.jpeds.2007.11.033.

Tonsillectomy for periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome is not always successful.

Ogose T.

Comment on

J Pediatr. 2007 Sep;151(3):289-92.

DOI: 10.1016/j.jpeds.2007.11.033

PMID: 18410791 [Indexed for MEDLINE]

3734. Hum Mutat. 2008 Jun;29(6):803-8. doi: 10.1002/humu.20720.

The infevers autoinflammatory mutation online registry: update with new genes and functions.

Milhavet F(1), Cuisset L, Hoffman HM, Slim R, El-Shanti H, Aksentijevich I, Lesage S, Waterham H, Wise C, Sarrauste de Menthier C, Touitou I.

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Infervers (Internet Fevers; <http://fmf.igh.cnrs.fr/ISSAID/infervers>), a website dedicated to mutations responsible for hereditary autoinflammatory diseases, was created in 2002 and has continued to evolve. This new version includes eight genes; six were already present: MEFV, MVK, TNFRSF1A, NLRP3, NOD2, PSTPIP1, and two are new, LPIN2 and NLRP7. Currently, Infervers contains over 540 sequence variants. Several new database functions were recently instituted. The website now accepts confidential data and complex alleles. For each gene, a newly created menu offers: 1) a tabular list of the variants that can be sorted by several parameters; 2) a gene graph providing a schematic representation of the variants along the gene; 3) statistical analysis of the data according to the phenotype, alteration type, and location of the mutation in the gene; 4) the cDNA and gDNA sequences of each gene, showing the nucleotide changes along the sequence, with a color-based code highlighting the gene domains, the first ATG, and the termination codon; and 5) a "download" menu making all tables and figures available for the users, which, except for the gene graphs, are all automatically generated and updated upon submission of the variants. Finally, the entire database was curated to comply with the HUGO Gene Nomenclature Committee (HGNC) and HGVS nomenclature guidelines, and wherever necessary, an informative note was provided. Infervers has already proven useful for the scientific community with a mean number of visits per month of 200 in 2002 and 800 in 2007, and its new design will lead to a more comprehensive comparative analysis and interpretation of auto-inflammatory sequence variants.

DOI: 10.1002/humu.20720

PMID: 18409191 [Indexed for MEDLINE]

3735. Eur J Pediatr. 2008 Dec;167(12):1421-5. doi: 10.1007/s00431-008-0685-2. Epub 2008 Apr 12.

TNF receptor-associated periodic syndrome (TRAPS): description of a novel TNFRSF1A mutation and response to etanercept.

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TRAPS is the most common of the autosomal dominant periodic fever syndromes. It is caused by mutations in the TNFRSF1A gene, which encodes for the type 1 TNF-receptor (TNFR1). We describe here a Brazilian patient with TRAPS associated to a novel TNFRSF1A de novo mutation and the response to anti-TNF therapy. The patient is a 9-year-old girl with recurrent fevers since the age of 3 years, usually lasting 3 to 7 days, and recurring every other week. These episodes are associated with mild abdominal pain, nausea, vomiting and generalized myalgia. Recurrent conjunctivitis and erysipela-like skin lesions in the lower limbs also occur. Laboratory studies show persistent normocytic normochromic anemia, thrombocytosis, elevated erythrocyte sedimentation rate and C-reactive protein. IgD levels are normal. Mutational screening of TNFRSF1A revealed the association of a novel C30F mutation with the common R92Q low-penetrance mutation. The R92Q mutation is seen in 5% of the general population and is associated with an atypical inflammatory phenotype. The patient had a very good response to etanercept, with cessation of fever and normalization of inflammatory markers. Our report expands the spectrum of TNFRSF1A mutations associated with TRAPS, adding further evidence for possible additive effects of a low-penetration R92Q and cysteine residue mutations, and confirms etanercept as an efficacious treatment alternative.

DOI: 10.1007/s00431-008-0685-2

PMID: 18408954 [Indexed for MEDLINE]

3736. Med Princ Pract. 2008;17(3):255-7. doi: 10.1159/000117803. Epub 2008 Apr 10.

An unusual association between familial mediterranean fever and IgM nephropathy.

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OBJECTIVE: To report a case with the diagnosis of IgM nephropathy and familial Mediterranean fever (FMF).

CLINICAL PRESENTATION AND INTERVENTION: A 9-year-old boy was admitted to our hospital with recurrent abdominal pain since the age of 4 years. Laboratory investigations revealed a sedimentation rate of 88 mm/h, C-reactive protein: 83.2 mg/l (0-10 mg/l), white blood cell count: 12,700/mm(3), fibrinogen: 622 mg/dl (200-400 mg/dl) and serum amyloid A: 186 mg/l (0-5.8 mg/l). Urinalysis revealed +2 proteinuria. A 24-hour urinary protein excretion was 12 mg/m(2)/h. M694V homozygous mutation was identified in exon 10. Percutaneous renal biopsy showed mesangial cell proliferation and increased mesangial matrix in the glomeruli, without amyloid accumulation. Immunofluorescence study showed IgM (+1) and C1q (+1) deposits. Treatment with 1 mg/day colchicine was started. Six weeks later, proteinuria had disappeared and the patient was asymptomatic.

CONCLUSION: This case illustrates the unusual association of FMF with non-amyloid glomerulopathy. Glomerular diseases such as IgM nephropathy may be seen as a manifestation of FMF.

(c) 2008 S. Karger AG, Basel

DOI: 10.1159/000117803

PMID: 18408398 [Indexed for MEDLINE]

3737. Georgian Med News. 2008 Mar;(156):105-11.

Familial Mediterranean Fever in Armenian population.

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Familial Mediterranean Fever (FMF) is an inherited, recessively transmitted inflammatory condition usually occurred in populations from Mediterranean descent (Armenian, Arab, Jewish, Greek, Turkish and Italian populations). Identification of MEFV gene mutations has been of tremendous help for early diagnosis of most cases. The frequency of FMF is different. The prevalence of heterozygous carriers of one of the mutations of MEFV gene is as high as 1 in 5 healthy individuals in Armenia. Genetic testing of this rare Mendelian disorder (MIM no 249100) is efficient for early and prenatal diagnosis of the disease, especially for atypic cases, for carrier screening and pregnancy planning since certain mutations have

been shown to have significant correlation with renal amyloidosis (RA), the most severe possible manifestation of FMF. Also genetic testing is very important for colchicine therapy correction. Twelve MEFV mutations are identified in 7000 Armenian FMF patients. Investigation of MEFV mutations in FMF patients (heterozygotes, homozygotes and compound heterozygotes) in comparison with healthy individuals has revealed the most frequent mutations and genotypes, and the information was received about the heterozygous carriers and genotype-phenotype correlation. In heterozygote carriers the most prevalent and severe cases are caused by the presence of a single M694V mutation. Our results could confirm that the MEFV gene analysis provides the first objective diagnostic criterion for FMF (characterisation of the two MEFV mutated alleles in more than 90% of the patients). Molecular testing is also used to screen the MEFV gene for mutations in patients with a clinical suspicion of FMF. We also demonstrated the unfavourable prognostic value of the M694V homozygous genotype, and provided the first molecular evidence for incomplete penetrance and pseudo-dominant transmission of the disease. Overall, these data, which confirm the involvement of the MEFV gene in the development of FMF, should be essential in clinical practice, leading to new ways of management and treatment of FMF patients.

PMID: 18403822 [Indexed for MEDLINE]

3738. Rev Med Interne. 2008 Dec;29(12):994-9. doi: 10.1016/j.revmed.2008.01.022. Epub 2008 Apr 9.

[What's new in autoinflammatory diseases?].

[Article in French]

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PURPOSE: The concept of auto-inflammation was initially coined to define the



group of mendelian disorders characterized by recurrent inflammatory symptoms. The core of this group mainly consists of hereditary recurrent fevers, which has been lately enlarged to other inflammatory mendelian disorders as well as to some sporadic diseases with a genetic component relevant to innate immunity.

CURRENT KNOWLEDGE AND KEY POINTS: Cryopyrin, the product of the CIAS1/PYPPAF1/NALP3/NLRP gene, whose mutations underline some mendelian syndromes (Mückle-Wells and chronic infantile neurological cutaneous and articular (CINCA), familial cold urticaria) can now be considered as a major factor of the regulation of interleukin-1 production within the multiprotein complex called inflammasome. This discovery has lit up our view of innate immunity.

FUTURE PROSPECTS AND PROJECTS: The contribution of the innate immunity mechanisms in inflammatory disorders have led to a new look to the current nosology of this vast group of diseases and to suggest a classification with two poles. The first would be defined by the predominance of auto-inflammation, whereas in the second one auto-immunity predominates.

DOI: 10.1016/j.revmed.2008.01.022

PMID: 18403063 [Indexed for MEDLINE]

3739. Rev Med Suisse. 2008 Feb 27;4(146):529-32.

[Periodic fever in children: keep in mind the PFAPA syndrome].

[Article in French]

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The autoinflammatory diseases should be considered in the differential diagnosis of recurrent fever in childhood. These diseases are characterized by inflammatory episodes without an evident cause. Some of these diseases, like the Familial Mediterranean Fever, have a genetic origin and need a chronic treatment to avoid severe complications on the long term. PFAPA syndrome is the most frequent cause of recurrent fever and is diagnosed based on unspecific criteria. The treatment is still controversial. One dose of Prednisone is able to interrupt the flare and

tonsillectomy may induce a remission in the majority of the cases.

PMID: 18402405 [Indexed for MEDLINE]

3740. Chest. 2008 Apr;133(4):999-1001. doi: 10.1378/chest.07-1736.

Unilateral lymphocytic pleuritis as a manifestation of familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease affecting predominantly populations surrounding the Mediterranean basin. It is the most prevalent hereditary periodic fever syndrome characterized mainly by recurrent and short attacks of fever and serositis (pleuritis, arthritis, peritonitis).

Unilateral polymorphonuclear exudative pleuritis associated with fever has been reported as the solitary manifestation of the first FMF attack, in < 10% of patients. This case study describes a 30-year-old Greek man with recurrent episodes of lymphocytic exudative pleuritis associated with fever. After a thorough workup (clinical criteria and molecular genetic testing identifying homozygosity polymorphisms of the FMF gene), the diagnosis of FMF was established. Treatment with colchicine, 2 mg/d, eliminated FMF attacks. To our knowledge, this is the first well-documented case report of a patient with FMF presenting with a lymphocytic exudative pleural effusion.

DOI: 10.1378/chest.07-1736

PMID: 18398120 [Indexed for MEDLINE]

3741. Joint Bone Spine. 2008 May;75(3):295-8. doi: 10.1016/j.jbspin.2007.09.011. Epub 2008 Apr 3.

# Circulating adrenomedullin levels in ankylosing spondylitis and Familial Mediterranean Fever.

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**INTRODUCTION:** Adrenomedullin (AM) is a 52-amino acid peptide with vasorelaxant properties. Apart from its roles on vascular tonus, AM can also contribute to inflammatory events. Plasma AM levels were elevated in connective tissue diseases and vasculitic disorders. Ankylosing spondylitis (AS) is a chronic inflammatory disease of the spine initiating in the sacroiliac joints. Familial Mediterranean Fever (FMF) is a hereditary disorder characterized by self-limiting acute attacks of fever and the presence of sustained subclinical inflammation in the attack-free periods. In this study, we investigated plasma AM levels in patients with AS and patients with FMF.

**METHODS:** Twenty AS patients with active disease manifestations (mean age: 41.6 $\pm$ 10.9 years, female/male: 7/13), 28 FMF patients with acute attack (mean age: 27.4 $\pm$ 10.7 years, female/male: 17/11), and 26 healthy controls (mean age: 39.9 $\pm$ 5.5 years, female/male: 16/10) were enrolled in this study. AM levels were also measured in 11 FMF patients 2 months after the cessation of their attacks. AM levels of those 11 patients during their FMF attacks and attack-free periods were also compared.

**RESULTS:** Median plasma AM levels were 23.86 (17.24-40.09) pmol/mL, 27.33 (17.24-38.52) pmol/mL, and 26.11 (17.05-37.42) pmol/mL in AS patients, FMF patients with acute attack, and healthy controls, respectively ( $p>0.05$ ). AM levels were also similar in the attack-free periods of FMF patients [26.35 (24.35-34.14) pmol/mL]. There was no correlation between plasma AM levels and C-reactive protein, or between plasma AM levels and erythrocyte sedimentation rate.

**CONCLUSIONS:** AM does not seem to have any role in the pathogenesis of AS and FMF. Previous reports of elevated levels of AM in connective tissue disorders and vasculitic diseases are probably disease specific, and AM does not seem to be a common component of inflammatory rheumatic disorders.

PMID: 18394945 [Indexed for MEDLINE]

3742. Med Clin (Barc). 2008 Mar 29;130(11):429-38.

[Hereditary systemic autoinflammatory diseases. Part II: cryopyrin-associated periodic syndromes, pediatric systemic granulomatosis and PAPA syndrome].

[Article in Spanish]

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Hereditary systemic autoinflammatory diseases result from a genetically-based dysregulated inflammatory process, and are clinically characterized by recurrent or persistent systemic inflammatory episodes, which typically occur in the absence of infectious, neoplastic or autoimmune etiology. Elucidation of their molecular basis has enabled the use of genetic analyses to achieve an accurate and definitive diagnosis, and to establish a tailored treatment. The present review is the second and last part of an updated and comprehensive overview of hereditary systemic autoinflammatory diseases, and will introduce persistent, non-periodic autoinflammatory diseases, such as: a) the group of cryopyrin-associated periodic syndromes (CAPS), which includes familial cold-induced autoinflammatory syndrome (FCAS), Muckle-Wells syndrome, and CINCA-NOMID syndrome; b) the group of pediatric systemic granulomatosis, which includes both Blau syndrome and early-onset sarcoidosis, and c) the pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA) syndrome.

PMID: 18394369 [Indexed for MEDLINE]

3743. Mol Biol Rep. 2009 Apr;36(4):757-60. doi: 10.1007/s11033-008-9240-5. Epub 2008 Apr 4.

The spectrum of FMF mutations and genotypes in the referrals to molecular genetic laboratory at Kirikkale University in Turkey.

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Familial Mediterranean Fever (FMF) is an autosomal recessive genetic disorder characterised by recurrent and self-limited abdominal pain, synovitis and pleuritis. MEFV gene mutations are responsible for the disease and its protein product, pyrin or marenostrin, plays an essential role in the regulation of the inflammatory reactions. MEFV gene contains 10 exons and most of the mutations have been found on the last exon. Up to date, 152 mutations and polymorphisms have been reported in where V726A, M694V, M694I, M680I and E148Q are the most common mutations. In this study, MEFV allele frequencies of 136 individuals (60 from Pediatrics, 76 from Internal Medicine) have been evaluated, and compared with each other. Asymptomatic individuals with FMF family history (4 from Pediatrics, 6 from Internal Medicine) were excluded from the analysis. The prominent mutations indicated in the Pediatrics group are V726A, M694V and M680I (G/C) and with the allele frequency of 0.06, 0.05 and 0.04 respectively while they were E148Q, M694V, M680I (G/C) in the Internal Medicine group with the allele frequency of 0.12, 0.08 and 0.04. The E148Q mutation is significantly overrepresented in the adult referrals ( $P = 0.02$ ). Mutation on both alleles was observed in only 12% of cases. Overall mutation frequency was low, seen in 26.2% (66/252). However, when only diagnosed patients were analyzed it is 72.7% (16/22). It is also interesting that 63% of individuals are female that there may be sex influence on FMF phenotype.

DOI: 10.1007/s11033-008-9240-5

PMID: 18389382 [Indexed for MEDLINE]

3744. Rheumatology (Oxford). 2008 Jul;47(7):946-51. doi: 10.1093/rheumatology/ken118. Epub 2008 Apr 3.

Autoinflammatory diseases: an update of clinical and genetic aspects.

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To review clinical manifestations and genetic features of the autoinflammatory diseases, a group of rare, genetically defined diseases which have been newly grouped into a coherent whole. We performed a literature review using the keywords 'periodic fever syndrome', 'autoinflammatory disease' and 'therapy'. All relevant original and review articles in English were reviewed. A case report of each autoinflammatory disease was excerpted from the literature and presented. This review summarizes the clinical manifestations, genetic analysis and therapy of FMF, TNF-alpha receptor-associated periodic fever syndrome, hyperimmunoglobulinaemia D periodic fever syndrome and cryopyrin-associated periodic fever syndrome. These diseases have periodic fever, are hereditary and recurrent, with elevated acute-phase reactants. Differentiating features of these disorders are tabulated. Autoinflammatory diseases have some communalities in their presentation although they represent a relatively diverse group of genetically associated diseases.

DOI: 10.1093/rheumatology/ken118

PMID: 18388145 [Indexed for MEDLINE]

3745. Turk J Gastroenterol. 2008 Mar;19(1):64-8.

A rare cause of ascites: Familial Mediterranean fever.

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Familial Mediterranean fever is an autosomal recessive disorder characterized by sporadic, paroxysmal attacks of fever and serosal inflammation. In Familial Mediterranean fever, peritoneal effusion during abdominal attacks is usually mild, is not detected by clinical evaluation, and disappears during clinical

remission. Chronic ascites has rarely been described in patients with Familial Mediterranean fever. Genetic analysis is highly specific and sensitive for diagnosis of Familial Mediterranean fever. All of the four cases discussed in our study had no benign or malignant pathology that could explain the ascites. They had suffered from repetitive periods of fever and ascites since childhood. Genetic analysis of these four cases revealed that one was M694V/M694V homozygote, one was M694V/? heterozygote, and the other two were M694V/V726A compound heterozygote. Ascites regressed with colchicine therapy. Since Familial Mediterranean fever is common our country, it should be kept in mind in the differential diagnosis in patients with ascites of unknown etiology.

PMID: 18386244 [Indexed for MEDLINE]

3746. Joint Bone Spine. 2008 May;75(3):280-5. doi: 10.1016/j.jbspin.2007.05.021. Epub 2008 Mar 28.

Assessment of aortic wall stiffness in patients with Familial Mediterranean Fever.

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**INTRODUCTION:** To evaluate aortic wall stiffness and its relation between the aortic stiffness and the left ventricular function in patients with Familial Mediterranean Fever (FMF).

**METHODS:** The study population was composed of 31 patients with FMF in attack-free period (12 men, 19 women; mean age: 36+/-7 years) and 27 healthy subjects (10 men, 17 women; mean age: 34+/-7 years) who had volunteered to participate. Aortic stiffness indices, aortic strain and distensibility, were calculated from the aortic diameters measured by echocardiography and blood pressure obtained by sphygmomanometry.

**RESULTS:** There were significant differences between the control and the patient group in aortic strain (mean (SD), 7.23+/-2.14 versus 4.91+/-1.66%, p=0.01) and distensibility (4.02+/-1.42 versus 2.84+/-1.46, 10(-6)cm(2)dyn(-1), p=0.001).

Although there was no correlation between the aortic stiffness parameters and the left ventricular function parameters, there were significant negative correlations between the disease duration and aortic strain index ( $r=-0.29$ ,  $p<0.001$ ), and between the disease duration and distensibility ( $r=-0.32$ ,  $p<0.001$ ).

CONCLUSION: Aortic stiffness measurements were found abnormal in patients with FMF. We have also demonstrated that there were significant correlations between aortic stiffness parameters and disease duration.

DOI: 10.1016/j.jbspin.2007.05.021

PMID: 18375166 [Indexed for MEDLINE]

3747. J Dtsch Dermatol Ges. 2008 Aug;6(8):626-31. doi: 10.1111/j.1610-0387.2008.06627.x. Epub 2008 Mar 14.

The Schnitzler syndrome: chronic urticaria and monoclonal gammopathy--an autoinflammatory syndrome?

[Article in English, German]

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Schnitzler syndrome describes the simultaneous occurrence of monoclonal gammopathy and chronic urticaria with at least two additional minor symptoms (arthralgia, bone pain, fever of uncertain origin, hepato- or splenomegaly, lymphadenopathy, increased erythrocyte sedimentation rate, leukocytosis/thrombocytosis or increased bone density). Schnitzler syndrome is not wellknown and very likely under-recognized. Comprehensive diagnostic examinations are necessary to rule out other diseases, especially those of hematologic origin. Close interdisciplinary collaboration is mandatory. The etiology of Schnitzler syndrome is unclear, but the rapid response to the interleukin-1 receptor inhibitor anakinra underlines the pivotal role which the proinflammatory cytokine interleukin-1 may play in the pathophysiology of this potentially autoinflammatory disorder.



DOI: 10.1111/j.1610-0387.2008.06627.x

PMID: 18371052 [Indexed for MEDLINE]

3748. J Clin Immunol. 2008 May;28 Suppl 1:S73-83. doi: 10.1007/s10875-008-9178-3. Epub 2008 Mar 27.

Diagnosis and management of autoinflammatory diseases in childhood.

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**INTRODUCTION:** Autoinflammatory diseases are a group monogenic inflammatory conditions characterized by an early onset during childhood.

**DISCUSSION:** Under the term "periodic fevers" are gathered some monogenic diseases (familial Mediterranean fever, mevalonate kinase deficiency, and tumor necrosis factor receptor-associated syndrome) characterized by periodic or recurrent episodes of systemic inflammation causing fever often associated with rash, serositis (peritonitis, pleuritis), lymphadenopathy, arthritis, and other clinical manifestations. Systemic reactive (AA) amyloidosis may be a severe long-term complication. Cryopyrinopathies are a group of conditions associated to mutations of the gene Cryopyrin that are responsible for a spectrum of diseases (familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and chronic infantile neurological cutaneous and articular syndrome) characterized by a chronic or recurrent systemic inflammation variably associated with a number of clinical features, such as urticarial-like rash, arthritis, sensorineural deafness, and central nervous system and bone involvement. Other disorders are dominated by the presence of sterile pyogen abscesses prevalently affecting the skin, joints, and bones (pyogenic disorders). These include pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome, and Majeed syndrome. Finally, some diseases, such as Blau's syndrome, are characterized by the appearance of typical noncaseating granulomatous inflammation affecting the joints, skin, and uveal tract (granulomatous disorders). In the present review, we will focus on the clinical presentation of these disorders in childhood and report on the available therapeutic strategies.

DOI: 10.1007/s10875-008-9178-3

PMID: 18368292 [Indexed for MEDLINE]

3749. Turk J Pediatr. 2008 Jan-Feb;50(1):40-4.

Familial Mediterranean fever in northwest of Iran (Ardabil): the first global report from Iran.

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Familial Mediterranean fever (FMF), which is the prototype of the hereditary periodic fever syndromes, is common in the countries around the Mediterranean Sea. Considering its geographical position in the northwest of Iran, with its population of Turkish origin and its vicinity to the Mediterranean Sea, the incidence of FMF should be high in Ardabil. The goal of this study was to introduce FMF as a disease with significant outbreak in this area. Based on the Tel-Hashomer criteria, patients suffering from FMF were collected from private clinics together with the medical records of adult and pediatric rheumatology clinics. Of 112 total patients determined, 74 were studied. All of the patients were interviewed and completed a questionnaire. Familial Mediterranean fever was common among children under 18 years (76%), and it was more common in males than females (M/F 1.17). Abdominal pain was the most common complaint (74%) and abdominal pain and fever (95% and 84%, respectively) were the main clinical symptoms. The average duration of pain was 12-72 hours and the average recovery (attack-free period) was from one week to one month (63.5%). The majority of the patients had hospital admission for diagnostic work-up (85%) and some (32%) had undergone surgical operation erroneously; 92% of the patients had taken medications with incorrect diagnosis; and 20% had positive familial history of FMF. Fifty percent of the patients' parents were first-degree relatives and in 59.5% delay in diagnosis was more than three years. It seems that FMF is more common in the Northwest of Iran than previously thought, although physicians are not familiar with it. The common age for manifestation of this disease is under

18 years and its presentation after the age of 40 years is very rare.

PMID: 18365590 [Indexed for MEDLINE]

3750. *Pediatr Int.* 2008 Apr;50(2):208-12. doi: 10.1111/j.1442-200X.2008.02554.x.

Genotype-phenotype correlation in children with familial Mediterranean fever in a Turkish population.

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**BACKGROUND:** The aim of the present study was not only to review clinical and demographic features of child-onset familial Mediterranean fever (FMF) patients but also to investigate whether there is a phenotype-genotype correlation in the same patient population.

**METHODS:** The medical records of 102 patients with FMF were retrospectively reviewed. Patients were classified into three groups according to mutations: group 1, Met694Val-Met694Val (homozygote); group 2, Met694Val-other; and group 3, other-other. These groups were compared with regard to gender, age of onset, age of diagnosis, time interval between disease onset and diagnosis, fever, abdominal pain, arthritis, chest pain, erysipelas-like erythema, edema, amyloidosis, number of attacks per year before and after treatment, consanguinity, severity score, response of colchicines treatment, and family history of FMF and amyloidosis.

**RESULTS:** The presence of M694V homozygote was found to be associated with amyloidosis. Homozygosity for M694V was found in 46 patients (45%).

**CONCLUSIONS:** M694V homozygosity is associated with phenotype II and amyloidosis compared to other common genotypes in patients with FMF. Despite current knowledge on FMF, prospective clinical studies with large numbers of patients and different ethnic groups will help us to clarify this considerable disease.

DOI: 10.1111/j.1442-200X.2008.02554.x

PMID: 18353061 [Indexed for MEDLINE]

3751. J Clin Immunol. 2008 May;28 Suppl 1:S84-9. doi: 10.1007/s10875-008-9179-2. Epub 2008 Mar 20.

Autoinflammatory diseases: mimics of autoimmunity or part of its spectrum? Case presentation.

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**INTRODUCTION:** Autoinflammatory diseases are very rare diseases presenting within a wide clinical spectrum. Recognition of the main clinical features are challenging due to overlapping or mimicking with autoimmune diseases.

**DISCUSSION:** A case series is reviewed to illustrate typical and atypical features and the difficulties of these diagnoses in the low prevalence areas--a typical unrecognized case of familial Mediterranean fever (FMF) in a youngster, an atypical adult case with overlapping of FMF with Behçet disease, and an early presentation of FMF in infant presenting with inflammatory colitis, as well as the overlapping features within the cryopirin diseases spectrum in an 8-year-old boy who presented with systemic onset arthritis.

**CONCLUSION:** These cases may represent examples of a very puzzling relationship among disorders of innate and adaptive immune systems and inflammation.

DOI: 10.1007/s10875-008-9179-2

PMID: 18351446 [Indexed for MEDLINE]

3752. Clin Rheumatol. 2008 Sep;27(9):1135-9. doi: 10.1007/s10067-008-0879-z. Epub 2008 Mar 20.

Is there an association between familial Mediterranean fever and celiac disease?

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Familial Mediterranean fever (FMF) and celiac disease (CD) shares some clinical features such as abdominal pain, diarrhea, arthralgia, and arthritis. Furthermore, both diseases are related to several inflammatory disorders. Based on these analogies, we have investigated whether there is any relationship between CD and FMF. The study had two groups. Group I: 50 children with FMF were questioned and examined for the evidence of CD, serum immunoglobulin A (IgA) levels, antigliadin antibodies (AGA) IgA, AGA IgG, and anti-endomysial antibodies (EMA) IgA were tested, and intestinal biopsy was performed when necessary. Group II: 17 children with CD were evaluated for the presence of clinical and laboratory features of FMF and mutation analysis for MEFV gene was performed to all of them. Six predominant mutations (p.M694V, p.M680I, p.M694I, p.V726A, p.K695R, p.E148Q) in the MEFV gene were studied. The results were as follows-group I: three patients had diarrhea, six had abdominal pain, one had positive AGA IgA, six had AGA IgG, and one had EMA IgA. Intestinal biopsy was performed in one patient who was normal, so none of the patients with FMF were diagnosed as CD and group II: none of the patients with CD had complaints consistent with FMF. Four of the 17 patients (23.5%) were found to carry MEFV mutations. Three of them had heterozygous p.E148Q mutation and one of them had heterozygous p.M680I mutation. None of the FMF patients had CD. MEFV mutation frequency in patients with CD was similar to the normal population in Turkey. Our study did not reveal any association between CD and FMF.

DOI: 10.1007/s10067-008-0879-z

PMID: 18351429 [Indexed for MEDLINE]

3753. Reumatizam. 2007;54(2):11-23.

[Pediatric rheumatic diseases--per aspera ad astra].

[Article in Croatian]

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Progress in the field of pediatric rheumatology has been extraordinary; subspecialty is accepted as essential, vital, indispensable and distinct from adult rheumatology. It is clear that arthritis in children is more heterogeneous than RA. Although there are similarities between the inflammatory arthritides occurring in adults and children, RA and JIA appear to be distinct phenotypically with exception for the older child with RF-positive polyarticular arthritis. Progress in molecular biology has enabled us to diagnose those children earlier, and treat them more efficaciously with variety of drugs and biologic agents. In recent years a new group of hereditary autoinflammatory disorders has emerged. These rare syndromes are characterized by recurrent episodes of seemingly unprovoked, intermittent inflammation. In the near future we will be able to distinguish various subtypes of autoimmune/autoinflammatory diseases earlier in the course, have a better understanding of the biomarkers and other prognostic factors, and most importantly treat them earlier with extended set of various new exciting drugs and biological therapy.

PMID: 18351134 [Indexed for MEDLINE]

3754. Arch Dermatol. 2008 Mar;144(3):392-402.

Autoinflammatory diseases: clinical and genetic advances.

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We conducted a literature review to investigate the recent advances in genetics, molecular biology, clinical manifestations, and therapy of 7 inherited diseases that are characterized by seemingly unprovoked inflammation. These autoinflammatory diseases include familial Mediterranean fever; tumor necrosis factor receptor-associated periodic syndrome; hyperimmunoglobulinemia D with periodic fever syndrome; pyogenic arthritis, pyoderma gangrenosum, and acne syndrome; and the 3 cryopyrinopathies: neonatal-onset multisystem inflammatory

disease/chronic infantile neurologic cutaneous and arthropathy syndrome, familial cold autoinflammatory syndrome, and Muckle-Wells syndrome. Recent identification of the susceptibility genes for autoinflammatory diseases has broadened the clinical spectrum as well as the molecular basis of these diseases. The cryopyrinopathies represent a continuum of diseases associated with mutations in the cold-induced autoinflammatory syndrome 1 (CIAS1) gene that encodes cryopyrin. Cryopyrin and pyrin (protein mutated in familial Mediterranean fever) belong to the family of PYRIN domain-containing proteins. Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome is associated with mutations in the gene that encodes for CD2-binding protein 1 (CD2BP1), which binds pyrin. Recent studies have shown that activation of the interleukin 1beta pathway is a common mechanism in the pathogenesis of autoinflammatory diseases, further unifying these diseases. Recent advances in genetics and molecular biology have advanced our understanding of the pathogenesis of autoinflammatory diseases. Understanding autoinflammatory diseases will further our knowledge of cutaneous as well as systemic inflammation. Anakinra, a recombinant human interleukin 1 receptor antagonist, is a promising new biologic agent for the treatment of cryopyrinopathies as well other autoinflammatory diseases, such as tumor necrosis factor receptor-associated periodic syndrome and hyperimmunoglobulinemia D with periodic fever syndrome.

PMID: 18347298 [Indexed for MEDLINE]

3755. An Pediatr (Barc). 2008 Feb;68(2):143-5.

[Tumor necrosis factor receptor-associated periodic syndrome].

[Article in Spanish]

Velasco Sánchez D(1), Antón López J, Ros Viladoms JB, Yagüe Ribes J, Arostegui Gorospe JI.

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Tumoral necrosis factor receptor-associated periodic syndrome (TRAPS) is an

autosomal dominantly inherited disease belonging to the hereditary periodic fever syndromes, which are the main subgroup among systemic autoinflammatory diseases. TRAPS is characterized by prolonged and recurrent inflammatory attacks associated with fever and an acute phase reaction. Articular, cutaneous, ocular and abdominal symptoms may also be present. We describe the case of a 4-year-old boy with recurrent inflammatory episodes, fever and cutaneous symptoms who was diagnosed with TRAPS. We review the clinical and laboratory findings, genetic diagnosis, and treatment approach in this disease.

PMID: 18341881 [Indexed for MEDLINE]

3756. Inflamm Bowel Dis. 2008 Sep;14(9):1313. doi: 10.1002/ibd.20424.

Familial mediterranean fever gene (MEVF) mutations in Crohn's disease in a Mediterranean area.

Renda MC, Civitavecchia G, Fabiano C, Sammarco P, Cottone M.

DOI: 10.1002/ibd.20424

PMID: 18340637 [Indexed for MEDLINE]

3757. Mod Rheumatol. 2008;18(2):203-7. doi: 10.1007/s10165-008-0033-4. Epub 2008 Mar 14.

A case of periodic-fever-syndrome-like disorder with lipodystrophy, myositis, and autoimmune abnormalities.

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A 24-year-old Japanese woman had been suffering from a periodic fever since 10 months of age. She developed deformities in her fingers, with severe atrophy of



subcutaneous adipose tissue, myositis, and frostbitten hands. She showed elevated C-reactive protein, creatine kinase, and gamma-globulin. She was also positive for antinuclear, anti-DNA, anti-SS-B, and anti-U1RNP antibodies. Her myositis was similar to amyopathic dermatomyositis rather than juvenile dermatomyositis. Although consanguineous marriage of her parents and early onset of disease suggested her disease as a hereditary disorder with periodic fever, her clinical feature and laboratory tests were unlike any known periodic fever syndromes. Her disease was regarded as a unique type of periodic-fever-syndrome-like disorder with autoimmune abnormalities.

DOI: 10.1007/s10165-008-0033-4

PMID: 18340505 [Indexed for MEDLINE]

3758. Nefrologia. 2008;28(1):93-8.

[Systemic AA amyloidosis induced by benign neoplasms].

[Article in Spanish]

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Amyloidosis is a systemic disorder characterized by the extracellular tissue deposition of insoluble, toxic aggregates in bundles of beta-sheet fibrillar proteins. These deposits are typically identified on the bases of their apple-green birefringence under a polarized light microscope after staining with Congo red, and by the presence of rigid, nonbranching fibrils 8 to 10 nm in diameter on electron microscopy. The type of amyloid fibril unit can be further defined by immunohistology or by immunoelectron microscopy. It has been described at least 25 different human protein precursors of amyloid fibrils, which will describe its corresponding amyloid disease. The most common types of amyloidosis are AL (primary) and AA (secondary) types; the former, is the most frequent and is due to deposition of proteins derived from immunoglobulin light chain fragments, occurring alone or in association with multiple myeloma. The later (AA), is caused by deposition of fibrils composed of fragments of the acute phase

reactant serum amyloid A (SAA) and complicates chronic diseases with ongoing or recurring inflammation, namely; rheumatoid arthritis (RA), juvenile chronic polyarthritis, ankylosing spondylitis, familial periodic fever syndromes (Familial Mediterranean Fever), chronic infections and furthermore, some neoplasms (mainly renal cell carcinoma and Hodgkin's disease). Despite its less frequent association, some benign neoplasms can subsequently complicate to AA amyloidosis, therefore, an early diagnose and successful treatment may lead indeed, to regression of the amyloid disease. Herein, we present two cases of AA amyloidosis, both of them caused by 2 different benign neoplasms: 1. A 34 year-old woman, after chronic oral contraceptive use, developed an hepatic adenoma (fig. 1) which finally lead to AA amyloidosis with primary kidney presentation (pure nephrotic syndrome) (table 1). Post-surgical complications yield to acute renal failure from which unfortunately could not be recovered. After being on hemodialysis therapy during 10 months she received a first renal allograft without any complication. 2. A 20 year old woman, was diagnosed of AA amyloidosis after a renal biopsy (fig. 2) because of nephrotic syndrome (table 1). Further investigation lead to the finding of a hialyne-vascular type Castleman's disease located in the retroperitoneum (fig. 2). Despite surgical resection and medical treatment (colchicine) she developed progressive renal failure requiring initialization of hemodialysis therapy. After 6 years being on hemodialysis, she received a first renal allograft which is currently functioning after one year of follow- up. Although other chronic inflammatory diseases complicate more frequently to AA amyloidosis, benign tumors have to be taken into account as a potential ethiological cause for secondary amyloidosis.

PMID: 18336138 [Indexed for MEDLINE]

3759. J Cell Physiol. 2008 Sep;216(3):595-602. doi: 10.1002/jcp.21435.

Pyrin, product of the MEFV locus, interacts with the proapoptotic protein, Siva.

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Mutations in pyrin cause the autoinflammatory disorder familial Mediterranean fever (FMF), a syndrome characterized by sporadic and unpredictable attacks of fever and localized severe pain. Currently, it is not clear how attacks are triggered, nor why they spontaneously resolve after 2 or 3 days. In fact, the cellular function of the pyrin protein and the molecular underpinnings of its malfunction in FMF have so far eluded clear definition. The identification of pyrin-interacting proteins has the potential to increase our understanding of the cellular networks in which pyrin functions. Previous reports have established that pyrin interacts with the apoptotic protein ASC, the cytoskeletal adaptor protein PSTPIP1, the inflammatory caspase, Caspase-1 and certain forms of the cytosolic anchoring protein 14-3-3. Here, we report that pyrin also interacts with Siva, a pro-apoptotic protein first identified for its interaction with the cytosolic tail of CD27, a TNF family receptor. The interaction between pyrin and Siva involves the C-terminal B30.2/rfp/SRPY domain of pyrin and exon 1 of Siva. We show that Siva and pyrin are indeed co-expressed in human neutrophils, monocytes, and synovial cells. Furthermore, using a novel protein/protein interaction assay, we demonstrate that pyrin can recruit Siva to ASC specks, establishing a potential platform for intersection of ASC and Siva function. Finally, we show that pyrin modulates the apoptotic response to oxidative stress mediated by Siva. Thus, the Siva-pyrin interaction may be a potential target for future therapeutic strategies.

DOI: 10.1002/jcp.21435

PMID: 18330885 [Indexed for MEDLINE]

3760. Clin Exp Rheumatol. 2008 Jan-Feb;26(1):13-7.

MEFV mutation analysis of familial Mediterranean fever in Japan.

Tomiyama N(1), Higashiuesato Y, Oda T, Baba E, Harada M, Azuma M, Yamashita T, Uehara K, Miyazato A, Hatta K, Ohya Y, Iseki K, Jinno Y, Takishita S.

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BACKGROUND: Familial Mediterranean fever (FMF) is an autosomal recessive disease

characterized by recurrent attacks of fever with serosal inflammation. FMF gene (MEFV) mutations have been identified primarily in patients from Mediterranean populations. Although several clinical cases have been reported in Japan, there have been few reports to date on mutation analysis. We studied FMF patients and their relatives to examine the clinical and genetic features of this disease in the Japanese population.

**METHODS:** Twelve Japanese FMF patients who met the Tel Hashomer criteria and a total of 17 relatives from 5 of 10 families underwent molecular genetic studies to detect MEFV mutations. The characteristics of these Japanese FMF patients and geno-phenotypical correlations were examined.

**RESULTS:** Almost all of our patients had been suffering for a long time from fever of unknown origin and one patient also had systemic amyloidosis. In our 12 FMF patients, we detected the substitutions E84K, L110P, E148Q, R761H and M694I. We also newly diagnosed 2 relatives as having FMF based on clinical symptoms and the existence of FMF mutations. One patient was homozygous for E148Q, the patient with systemic amyloidosis was a homozygote for M694I and 4 patients from 3 families were compound heterozygotes for E148Q and M694I. Three patients in one family were compound heterozygotes for E148Q, L110P and M694I. There were 3 patients who were heterozygous for E84K, L110P-E148Q or M694I and had no other nucleotide changes in the exons of MEFV. On the other hand, 2 relatives who had never experienced symptoms of FMF were homozygous for L110P-E148Q as well as compound heterozygous for E148Q/E148Q-R761H. E148Q and M694I were the most frequently detected substitutions in our study.

**CONCLUSIONS:** MEFV mutations occur in Japanese FMF patients though FMF is rare in Japan. The identification of MEFV mutations could be a reliable diagnostic test for FMF. The results of genetic analyses on 14 Japanese FMF patients in this study revealed that E148Q and M694I are frequent alleles.

PMID: 18328141 [Indexed for MEDLINE]

3761. Expert Opin Investig Drugs. 2008 Mar;17(3):349-59. doi: 10.1517/13543784.17.3.349

The future of the IL-1 receptor antagonist anakinra: from rheumatoid arthritis to adult-onset Still's disease and systemic-onset juvenile idiopathic arthritis.

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**BACKGROUND:** IL-1 receptor antagonist (IL-1Ra) is a naturally occurring IL-1RI-binding molecule that blocks the biologic effects of the proinflammatory cytokine IL-1. A recombinant form of human IL-1Ra, anakinra (Kineret), has been approved for use in rheumatology initially to manage rheumatoid arthritis (RA) patients that are refractory to more conventional forms of treatment.

**OBJECTIVE:** This review summarizes the experience with anakinra in the treatment of patients with rheumatic diseases emphasizing its beneficial effects in novel applications.

**METHODS:** English-language trials of anakinra were searched using MEDLINE and abstracts from rheumatology scientific meetings.

**RESULTS/CONCLUSIONS:** In the treatment of patients with RA anakinra is effective but inferior to TNF-alpha blocking agents. Over the last few years it has become increasingly evident that anakinra is highly effective and safe in patients with systemic-onset juvenile idiopathic arthritis, adult-onset Still's disease, hereditary autoinflammatory syndromes, Schnitzler's syndrome and recently in gouty attacks.

DOI: 10.1517/13543784.17.3.349

PMID: 18321234 [Indexed for MEDLINE]

3762. Ann Allergy Asthma Immunol. 2008 Feb;100(2):170. doi:  
10.1016/S1081-1206(10)60428-0.

Adult-onset periodic fever, aphthous stomatitis, pharyngitis, and adenitis.

Cavuoto M, Bonagura VR.

DOI: 10.1016/S1081-1206(10)60428-0

PMID: 18320921 [Indexed for MEDLINE]

3763. Genet Test. 2008 Mar;12(1):125-7. doi: 10.1089/gte.2007.0068.

Different intrafamilial clinical presentation of FMF mutation carriers.

Chalevelakis G(1), Apostolakis I, Koliou X, Apessos A, Kyriakopoulou V, Vrakidou E, Vasilopoulou A, Lamnisou K, Nasioulas G.

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Familial Mediterranean fever (FMF) is a heterogeneous disorder; at present, it is diagnosed using only genetic methods. In the current study, we performed molecular analysis in two families presenting with FMF. In the first family, we report two brothers with a common genotype (M694V/V726A) but with different clinical presentation. In the second family, we identified the M694V and K695R mutations in a presymptomatic carrier.

DOI: 10.1089/gte.2007.0068

PMID: 18318646 [Indexed for MEDLINE]

3764. Joint Bone Spine. 2008 May;75(3):370-2. doi: 10.1016/j.jbspin.2007.10.004. Epub 2008 Jan 18.

Early suppression of familial Mediterranean fever attacks by single medium dose methyl-prednisolone infusion.

Erken E, Ozer HT, Bozkurt B, Gunesacar R, Erken EG, Dinkci S.

DOI: 10.1016/j.jbspin.2007.10.004

PMID: 18313967 [Indexed for MEDLINE]

3765. Arthritis Rheum. 2008 Mar;58(3):864-8. doi: 10.1002/art.23261.

Anakinra improves sensory deafness in a Japanese patient with Muckle-Wells syndrome, possibly by inhibiting the cryopyrin inflammasome.

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Comment in

Arthritis Rheum. 2008 Dec;58(12):3970; author reply 3970-1.

Muckle-Wells syndrome (MWS) is a dominantly inherited autoinflammatory syndrome. Patients with MWS have a mutation in *CIAS1*, the gene encoding cryopyrin, a component of the inflammasome that regulates the processing of interleukin-1beta (IL-1beta). In this report we describe an 8-year-old Japanese girl with MWS who had symptoms of periodic fever, urticarial rash, conjunctivitis, arthropathy, and sensory deafness. Laboratory analysis of the patient's serum showed abnormally high concentrations of C-reactive protein, serum amyloid A, and IL-1beta, and she had a heterozygous mutation in the *CIAS1* gene, with C-to-T transversion at nucleotide position 778, encoding an arginine-to-tryptophan mutation at position 260 (R260W). Mononuclear cells (MNCs) isolated from the patient secreted large amounts of IL-1beta, without stimulation, and were highly sensitive to muramyl dipeptide and lipopolysaccharide. After treatment with anakinra, laboratory results normalized, and clinical symptoms, including sensory deafness, disappeared, while MNCs appeared to remain activated. Thus, our case suggests that anakinra possibly affects the cryopyrin inflammasome and markedly improves the clinical and laboratory manifestations of MWS.

DOI: 10.1002/art.23261

PMID: 18311804 [Indexed for MEDLINE]

3766. Genet Test. 2008 Mar;12(1):171-4. doi: 10.1089/gte.2007.0085.

Comparison of the results of PCR-RFLP and reverse hybridization methods used in molecular diagnosis of FMF.

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Familial Mediterranean fever (FMF) is characterized by recurrent fever,

serositis, and arthritis. Due to the abundance of mutations and clinical heterogeneity of the disease, different screening methods have been developed. In this study, we aimed to compare our findings of mutations determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) with reverse hybridization (RH) methods. In 152 of 263 patients (57.79%) different mutations were determined with RH. Allelic frequencies were E148Q 6.84%, M680I(G/C) 3.61%, M694V 20.91%, V726A 7.03%, P369S 1.33%, F479L 0.19%, M680I(G/A) 0.76%, M694I 0.57%, K695R 0.57%, A744S 0.38%, R731H 0.38%, and del1692 0%. Frequent mutations were also confirmed by PCR-RFLP. There were no conflicting results between the two methods. Four of these genotypes were homozygous for a single mutation, 15 were heterozygous for two mutations, 8 were heterozygous for a single mutation, 1 was heterozygous for three mutations, and 1 was homozygous for one mutation and heterozygous for another mutation. It has been reported that analytical sensitivity of RH is 97%. We did not find a discrepancy between the two methods. In 21 patients, we detected additional mutations with RH. This finding was regarded as an advantage of RH, and we concluded that this assay is a useful method for detection of first stage FMF mutation screening.

DOI: 10.1089/gte.2007.0085

PMID: 18307385 [Indexed for MEDLINE]

3767. J Genet. 2007 Dec;86(3):293-5.

ABCC6 is unlikely to be a modifier gene for familial Mediterranean fever severity.

Chassaing N(1), Touitou I, Cattan D, Calvas P.

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PMID: 18305351 [Indexed for MEDLINE]

3768. Isr Med Assoc J. 2008 Jan;10(1):69-72.



Colchicine for the prevention of recurrent pericarditis.

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The most troublesome complication of acute pericarditis is recurrent episodes of pericardial inflammation, which occur in 15-32% of cases. It was recently found that viral infection has a major role, but in many cases the cause is unknown. The optimal method for prevention has not been fully established; accepted modalities include non-steroidal anti-inflammatory drugs, corticosteroids, immunosuppressive agents, and pericardiectomy. Based on the proven efficacy of colchicine in familial Mediterranean fever, several small and large-scale international clinical trials have shown the beneficial effect of colchicine therapy in preventing recurrent pericarditis. Indeed, colchicine-treated patients consistently display significantly fewer recurrences, longer symptom-free periods, and even when attacks occur they are weaker and shorter in nature. It was also found that pretreatment with corticosteroids substantially attenuates the efficacy of colchicine, as evidenced by significantly more recurrence episodes and longer therapy periods. Colchicine is a safe and effective modality for the treatment and prevention of recurrent pericarditis, especially as an adjunct to other modalities, since it provides a sustained benefit superior to all current modalities. The safety profile seems superior to other drugs such as corticosteroids and immunosuppressive drugs.

PMID: 18300579 [Indexed for MEDLINE]

3769. Ren Fail. 2008;30(2):187-91. doi: 10.1080/08860220701810364.

The relationship between the MEFV genotype, clinical features, and cytokine-inflammatory activities in patients with familial mediterranean fever.

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Familial Mediterranean Fever (FMF) is an autosomal recessive disease characterized by periodic attacks of fever and polyserositis. The effects of the MEFV genotype differences on clinical picture and inflammatory activity have not been well documented. The aim of this study was to investigate levels of conventional inflammation markers, procalcitonin, interleukin levels, TNF-alpha, and C5a levels in patients with FMF who had different MEFV genotypes and compare them with those of healthy subjects. The study consisted of 41 patients with FMF (F/M: 23/18), and 31 healthy subjects (F/M: 18/13). Tests were performed during the attack-free period. White-blood cell count, CRP and IL-8 levels were higher in patients with FMF than in healthy subjects ( $p < 0.05$ ) and also higher in M680I carriers than in the patients with M694V allele carriers. However, ESR, fibrinogen, procalcitonin, IL-6, C5a, TNF-alpha, and IgD levels were not significantly different between patients and healthy subjects ( $p > 0.05$ ). Arthralgia or arthritis was significantly higher in M694V carriers than in non-M694V carriers ( $p < 0.05$ ). It is concluded that the clinical features and inflammatory-cytokine activities were higher in patients with FMF during the attack-free period than in healthy subjects, and the different genotype might be related to different clinical pictures.

DOI: 10.1080/08860220701810364

PMID: 18300119 [Indexed for MEDLINE]

3770. Z Rheumatol. 2008 Mar;67(2):151-6. doi: 10.1007/s00393-007-0254-5.

[New aspects of the pathogenesis of gout. Danger signals, autoinflammation and beyond].

[Article in German]

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Gout is caused by monosodium urate (MSU) crystal-induced inflammation of the joints and periarticular tissues. MSU crystals activate the NOD-like receptor (NLR) NALP3, which functions as a pattern recognition receptor (PRR). Activated NALP3 mediates interleukin-1 $\beta$  (IL-1 $\beta$ ) generation from its inactive pro-form, resulting in the activation of further cells and an IL-8-mediated neutrophil influx into the joint. Based on these new findings on the pathophysiology of gout, an open pilot study has recently demonstrated successful treatment of gout with the soluble IL-1R antagonist anakinra in 10 patients. The physiological role of MSU crystals might be that of a danger signal in peripheral tissues, where they stimulate dendritic cell maturation. The role of PRRs such as the NLR is underlined by NALP3 mutations causing hereditary autoinflammatory syndromes and NOD2 polymorphisms as genetic risk factors for Crohn's disease. In addition to the recognition of danger-associated molecular patterns (e.g. MSU), PRRs confer autoantigen recognition and activation of the innate and adaptive immune system in autoimmune diseases. Detection of RNA and DNA-containing immune complexes by toll-like receptors inducing B-cell activation in systemic lupus erythematosus and of proteinase 3 by the protease-activated receptor-2 inducing dendritic cell maturation in Wegener's granulomatosis have recently been reported.

DOI: 10.1007/s00393-007-0254-5

PMID: 18299853 [Indexed for MEDLINE]

3771. J Cell Mol Med. 2008 Sep-Oct;12(5A):1502-16. doi: 10.1111/j.1582-4934.2008.00292.x. Epub 2008 Feb 24.

Caspases as therapeutic targets.

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The development of small molecules to modulate caspase activity offers a novel therapeutic strategy in the treatment of apoptosis-related and inflammatory diseases. Caspases are key mediators of apoptosis and inflammation; deregulation of their activation or expression can lead to the development of conditions such

as neurodegenerative and autoinflammatory disorders. This review details the different caspase-associated disorders while focusing on caspase-1 inhibition as a potential therapeutic strategy. Problems facing the development of effective and safe caspase therapeutics will also be addressed.

DOI: 10.1111/j.1582-4934.2008.00292.x

PMCID: PMC3918066

PMID: 18298652 [Indexed for MEDLINE]

3772. FEMS Immunol Med Microbiol. 2008 Apr;52(3):370-8. doi: 10.1111/j.1574-695X.2008.00385.x. Epub 2008 Feb 22.

Heightened endotoxin susceptibility of monocytes and neutrophils during familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is a relapsing autoinflammatory disorder, caused by various mutations in the MEFV gene, which encodes a protein called pyrin, expressed in neutrophils and activated monocytes. Induction of monocyte endotoxin tolerance is observed in FMF patients during attack, whereas monocytes from patients in the attack-free period failed to induce lipopolysaccharide tolerance and exhibited heightened sensitivity to bacterial endotoxin. In this study, we demonstrated that impaired lipopolysaccharide tolerance induction in attack-free FMF patients correlates with both increased lipopolysaccharide-induced proinflammatory cytokine synthesis polarization and a different time-course pattern of lipopolysaccharide-induced changes on monocytic surface expression of CD14 and CD11b coreceptors. We found that this pattern is characterized either by delayed turnover of CD14 or increased surface retention of CD11b receptors on monocytes during stimulation with lipopolysaccharide. In addition, enhancement of lipopolysaccharide-induced apoptosis of neutrophils was observed in FMF patients, and was confirmed based on the fact that neutrophils from FMF patients previously unexposed to *Salmonella enteritidis* exhibited heightened susceptibility to the lipopolysaccharide of this pathogen similar to

that of patients infected with this species.

DOI: 10.1111/j.1574-695X.2008.00385.x

PMID: 18294193 [Indexed for MEDLINE]

3773. Inflamm Res. 2008 Feb;57(2):65-74. doi: 10.1007/s00011-007-7074-6.

Engaging anti-inflammatory mechanisms and triggering inflammatory effector apoptosis during Familial Mediterranean Fever attack.

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**OBJECTIVE:** To investigate endotoxin-induced tolerance, intracellular cytokine synthesis polarization and monocyte apoptosis during Familial Mediterranean Fever (FMF).

**METHODS:** Lipopolysaccharide (LPS)-induced tolerance, intracellular cytokine synthesis and monocyte apoptosis were determined in FMF patients by flow cytometry using whole blood cell culture technique.

**RESULTS:** Endotoxin homo- and cross-tolerance, detected as the percentage of TNF-alpha synthesizing monocytes, developed in whole blood preparations of patients in attack period, but not during remission. The induction of anti-inflammatory cytokine synthesis polarization and enhancement of iodine-lithium-alpha-dextrin- and LPS-induced monocyte apoptosis was observed in FMF patients during the attack, whereas monocytes from patients in remission period exhibited proinflammatory cytokine polarization and resistance to the repeated LPS-induced apoptosis. Colchicine induced anti-inflammatory cytokine synthesis and caused down-modulation of monocyte apoptosis, whereas cytokines did not alter LPS-induced monocyte apoptosis.

**CONCLUSION:** The self-limited nature of attacks during FMF may represent periods of inflammation resolution compensatory to continued sub-clinical inflammation during the remission.

DOI: 10.1007/s00011-007-7074-6

PMID: 18288456 [Indexed for MEDLINE]

3774. Curr Opin Rheumatol. 2008 Jan;20(1):66-75. doi: 10.1097/BOR.0b013e3282f1bf4b.

The spectrum of autoinflammatory diseases: recent bench to bedside observations.

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**PURPOSE OF REVIEW:** The autoinflammatory diseases are a group of conditions that include the hereditary fever syndromes, and result from upregulated innate immune responses. The discovery of the genetic basis for these conditions led to the description of novel intracellular receptors for infectious and noninfectious danger signals. This article focuses on recent progress in our understanding of autoinflammatory syndromes, and how insights into these conditions have triggered the exploration of the role of innate immunity in common rheumatologic diseases.

**RECENT FINDINGS:** New models for the pathogenesis of several autoinflammatory syndromes have been proposed, including the role of pyrin and cryopyrin in regulating inflammation. Robust evidence has emerged that IL-1beta oversecretion is pivotal in cryopyrin-associated periodic syndromes, and that IL-1 inhibition ameliorates the clinical features of these syndromes. Monosodium urate crystals stimulate IL-1beta secretion via cryopyrin, which led to the addition of gout to the spectrum of autoinflammatory diseases.

**SUMMARY:** Advances in our understanding of the autoinflammatory diseases have led to renewed interest in the innate immune system, and its role in the pathogenesis of more common rheumatic diseases.

DOI: 10.1097/BOR.0b013e3282f1bf4b

PMCID: PMC4565798

PMID: 18281860 [Indexed for MEDLINE]

3775. Adv Drug Deliv Rev. 2008 Apr 29;60(7):830-40. doi: 10.1016/j.addr.2007.12.003. Epub 2007 Dec 31.

Intracellular pattern-recognition receptors.

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The last ten years of research in the field of innate immunity have been incredibly fertile: the transmembrane Toll-like receptors (TLRs) were discovered as guardians protecting the host against microbial attacks and the emerging pathways characterized in detail. More recently, cytoplasmic sensors were identified, which are capable of detecting not only microbial, but also self molecules. Importantly, while such receptors trigger crucial host responses to microbial insult, over-activity of some of them has been linked to autoinflammatory disorders, hence demonstrating the importance of tightly regulating their actions over time and space. Here, we provide an overview of recent findings covering this area of innate and inflammatory responses that originate from the cytoplasm.

DOI: 10.1016/j.addr.2007.12.003

PMID: 18280002 [Indexed for MEDLINE]

3776. Digestion. 2008;77(1):35-7. doi: 10.1159/000116724. Epub 2008 Feb 15.

A disease must be considered in the differential diagnosis of ascites: familial Mediterranean fever.

Bektaş M, Altan M, Kutlay S, Goren D, Soykan I, Korkut E, Cetinkaya H, Ozden A.

DOI: 10.1159/000116724

PMID: 18277074 [Indexed for MEDLINE]

3777. Amyloid. 2008 Mar;15(1):49-53. doi: 10.1080/13506120701815456.

Familial Mediterranean fever gene mutations in the Southeastern region of Turkey and their phenotypical features.

Pasa S(1), Altintas A, Devecioglu B, Cil T, Danis R, Isi H, Bayan K, Tuzun Y, Ecer S, Batun S, Ayyildiz O.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent inflammatory attacks of serosal membranes. Several studies have focused on the differences between frequency of the mutations and their phenotypical manifestations. The aim of this study was to evaluate whether or not this phenotypical variation is associated with the existence of particular mutations. Twelve MEFV (Mediterranean fever) gene mutations were investigated in 119 patients suffering from FMF. Heterozygote M694V (21/119), heterozygote E148Q (21/119), homozygote M694V (17/119) and heterozygote V726A (12/119) mutations were the most common mutations. Patients were grouped according to the presence of the M694V mutation: group I was M694V/M694V, group II was M694V/others, and group III was other/other. Mean severity scores for the groups were 13.94 +/- 4.10, 10.79 +/- 3.01 and 8.31 +/- 2.26, respectively. There were statistically significant differences between the mean severity scores of groups I and II ( $p = 0.029$ ), groups I and III ( $p < 0.0001$ ), and groups II and III ( $p < 0.0001$ ). Diagnosis of amyloidosis was established in four (23%) patients of group I, and three (8%) patients of group II, but in none of the patients in group III. There was also a statistically significant difference between groups I and III ( $p = 0.046$ ), but not between groups II and III ( $p = 0.083$ ) and groups I and II ( $p = 0.317$ ) in terms of amyloidosis development. In conclusion, we found a higher disease severity score and higher prevalence of amyloidosis in FMF patients who were M694V mutation carriers. Many ethnic groups live in Anatolia and more ethnic origin-based studies are needed to determine the real effect of these mutations on disease severity and amyloidosis.

DOI: 10.1080/13506120701815456

PMID: 18266121 [Indexed for MEDLINE]

3778. Transplant Proc. 2008 Jan-Feb;40(1):308-9. doi: 10.1016/j.transproceed.2007.11.012.



A renal transplant recipient with delayed gastric emptying in amyloidosis due to familial Mediterranean fever improved with erythromycin: a case report.

Saglam F(1), Celik A, Cavdar C, Sifil A, Atila K, Kaya GC, Bora S, Gulay H, Camsari T.

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Patients with systemic amyloidosis often have symptoms related to impaired gastrointestinal motility due to delayed gastric emptying, which results from autonomic nerve or smooth muscle infiltration with amyloid. There is no current report about gastric delaying secondary to amyloidosis due to familial Mediterranean fever. In this report, we have described a renal transplant recipient with delayed gastric emptying secondary to amyloidosis due to familial Mediterranean fever, which improved with erythromycin treatment.

DOI: 10.1016/j.transproceed.2007.11.012

PMID: 18261613 [Indexed for MEDLINE]

3779. J Rheumatol. 2008 Feb;35(2):357-8.

Dramatic improvement following interleukin 1beta blockade in tumor necrosis factor receptor-1-associated syndrome (TRAPS) resistant to anti-TNF-alpha therapy.

Sacré K, Brihaye B, Lidove O, Papo T, Pocidalo MA, Cuisset L, Dodé C.

PMID: 18260167 [Indexed for MEDLINE]

3780. Cytokine Growth Factor Rev. 2008 Feb;19(1):41-52. doi: 10.1016/j.cytogfr.2007.10.004.

Dendritic cells and cytokines in human inflammatory and autoimmune diseases.

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Dendritic cells (DCs) produce cytokines and are susceptible to cytokine-mediated activation. Thus, interaction of resting immature DCs with TLR ligands, for example nucleic acids, or with microbes leads to a cascade of pro-inflammatory cytokines and skewing of T cell responses. Conversely, several cytokines are able to trigger DC activation (maturation) via autocrine, for example TNF and plasmacytoid DCs, and paracrine, for example type I IFN and myeloid DCs, pathways. By controlling DC activation, cytokines regulate immune homeostasis and the balance between tolerance and immunity. The increased production and/or bioavailability of cytokines and associated alterations in DC homeostasis have been implicated in various human inflammatory and autoimmune diseases. Targeting these cytokines with biological agents as already is the case with TNF and IL-1 represents a success of immunology and the coming years will expand the range of cytokines as therapeutic targets in autoinflammatory and autoimmune pathology.

DOI: 10.1016/j.cytogfr.2007.10.004

PMCID: PMC2413068

PMID: 18258476 [Indexed for MEDLINE]

3781. J Cutan Med Surg. 2008 Jan-Feb;12(1):8-16.

Use of anakinra (Kineret) in the treatment of familial cold autoinflammatory syndrome with a 16-month follow-up.

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**BACKGROUND:** The susceptibility gene for familial cold autoinflammatory syndrome (FCAS) has been mapped to chromosome 1q44 and a point mutation determined to be present in all affected members of a large Canadian kindred. Anakinra (Kineret)

is known to block IL-1 receptor and in the few patients with FCAS in whom it has been used, it has been shown to provide relief for this lifelong disability.

OBJECTIVE: To demonstrate the efficacy and safety of anakinra (Kineret) in FCAS.

METHODS: Eight affected family members aged 29 to 77 years received anakinra 100 mg subcutaneously daily for 4 weeks preceded and followed by a 2-week control period.

RESULTS: The treatment was rapidly effective paralleled by the immediate fall of the C-reactive protein and serum amyloid A protein. The only significant side effect was an injection-site reaction in 50%, which declined in the follow-up period. The effect was sustained in all who continued to use the treatment at 4 and 16 months of follow-up.

CONCLUSION: This is the first treatment of FCAS that is completely effective while it is used.

DOI: 10.2310/7750.2008.07050

PMID: 18258152 [Indexed for MEDLINE]

3782. Proc Natl Acad Sci U S A. 2008 Feb 5;105(5):1614-9. doi: 10.1073/pnas.0708616105. Epub 2008 Jan 29.

Mutations in NALP12 cause hereditary periodic fever syndromes.

Jéru I(1), Duquesnoy P, Fernandes-Alnemri T, Cochet E, Yu JW, Lackmy-Port-Lis M, Grimpel E, Landman-Parker J, Hentgen V, Marlin S, McElreavey K, Sarkisian T, Grateau G, Alnemri ES, Amselem S.

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NALP proteins, also known as NLRPs, belong to the CATERPILLER protein family involved, like Toll-like receptors, in the recognition of microbial molecules and the subsequent activation of inflammatory and immune responses. Current advances in the function of NALPs support the recently proposed model of a disease continuum bridging autoimmune and autoinflammatory disorders. Among these diseases, hereditary periodic fevers (HPFs) are Mendelian disorders associated with sequence variations in very few genes; these variations are mostly missense mutations whose deleterious effect, which is particularly difficult to assess, is

often questionable. The growing number of identified sporadic cases of periodic fever syndrome, together with the lack of discriminatory clinical criteria, has greatly hampered the identification of new disease-causing genes, a step that is, however, essential for appropriate management of these disorders. Using a candidate gene approach, we identified nonambiguous mutations in NALP12 (i.e., nonsense and splice site) in two families with periodic fever syndromes. As shown by means of functional studies, these two NALP12 mutations have a deleterious effect on NF-kappaB signaling. Overall, these data identify a group of HPFs defined by molecular defects in NALP12, opening up new ways to manage these disorders. The identification of these first NALP12 mutations in patients with autoinflammatory disorder also clearly demonstrates the crucial role of NALP12 in inflammatory signaling pathways, thereby assigning a precise function to this particular member of an emerging family of proteins whose putative biological properties are currently inferred essentially through in vitro means.

DOI: 10.1073/pnas.0708616105

PMCID: PMC2234193

PMID: 18230725 [Indexed for MEDLINE]

3783. Ann Allergy Asthma Immunol. 2007 Dec;99(6):517-21. doi: 10.1016/S1081-1206(10)60380-8.

Familial Mediterranean fever gene and protection against asthma.

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**BACKGROUND:** Asthma is an inflammatory airway disease caused by interaction between susceptibility genes and diverse environmental factors. In Israel, asthma seems to be familial and more severe in patients of Iraqi Jewish descent. On the other hand, asthma is less frequent in individuals with familial Mediterranean fever, an autoinflammatory disease prevalent in the Iraqi Jewish community and linked to mutations in the familial Mediterranean fever gene, designated MEFV.

**OBJECTIVES:** To explore a possible role for mutated MEFV in the reduced

susceptibility to asthma and to determine its expression in Israeli subjects of Iraqi origins.

**METHODS:** Using a case-control approach, we studied the presence of the 3 most common MEFV mutations (M694V, V726A, and E148Q) in DNA samples from 75 patients with asthma and 45 asymptomatic first-degree relatives, all of Iraqi Jewish origin. The severity of asthma was evaluated using a published severity score.

**RESULTS:** Eleven patients with asthma and 14 of their relatives carried 1 or 2 mutations in the MEFV gene, a carrier rate significantly lower in patients with asthma than in their first-degree relatives and in ethnically matched healthy individuals ( $P < .03$  and  $P < .003$ , respectively). Carriers of MEFV mutations had less severe disease, compared with noncarriers ( $P < .002$ ).

**CONCLUSION:** These findings suggest that MEFV mutations may have a protective effect in the pathogenesis of asthma.

DOI: 10.1016/S1081-1206(10)60380-8

PMID: 18219832 [Indexed for MEDLINE]

3784. Urologe A. 2008 Mar;47(3):345-7. doi: 10.1007/s00120-007-1617-x.

[Infiltrating perineal and scrotal inflammation: rare cutaneous manifestation of familial Mediterranean fever or acne inversa?].

[Article in German]

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Familial Mediterranean fever (FMF) can present cutaneous symptoms. In the reported case, infiltrating perineal and scrotal inflammation were attributed to FMF and treated by systemic medication with colchicine. The poor outcome of this conservative approach and pathognomonic axillary dermatological findings allowed the diagnosis of acne inversa to be made. Knowledge of this clinical picture possibly including genital manifestations is crucial, as early excision of all affected regions is the therapy of choice that enables healing.

DOI: 10.1007/s00120-007-1617-x  
PMID: 18210069 [Indexed for MEDLINE]

3785. Hautarzt. 2008 Aug;59(8):653-5. doi: 10.1007/s00105-007-1451-5.

[First manifestation of psoriasis vulgaris in tumor necrosis factor receptor-associated periodic syndrome during treatment with etanercept].

[Article in German]

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Drugs antagonizing tumor necrosis factor (TNF) alpha have been increasingly and successfully used in the treatment of psoriasis vulgaris and psoriatic arthritis. We report a patient with TNF receptor 1-associated periodic syndrome (TRAPS) who received TNF-alpha antagonist etanercept. A month later, the patient developed for the first time generalized psoriasis vulgaris. This paradoxical phenomenon has been reported sporadically in patients receiving TNF-alpha antagonists for other inflammatory diseases. The cause of psoriasis induced by TNF-alpha antagonists is still obscure.

DOI: 10.1007/s00105-007-1451-5  
PMID: 18210001 [Indexed for MEDLINE]

3786. Semin Arthritis Rheum. 2008 Oct;38(2):161-2. doi: 10.1016/j.semarthrit.2007.10.009. Epub 2008 Jan 14.

Protracted febrile myalgia syndrome in a patient with familial Mediterranean fever homozygous for the E148Q mutation.

Soylu A, Kasap B, Türkmen M, Ulgenalp A, Uzuner N, Kavukçu S.

DOI: 10.1016/j.semarthrit.2007.10.009

PMID: 18191992 [Indexed for MEDLINE]

3787. Scand J Rheumatol. 2008 Jan-Feb;37(1):75-6. doi: 10.1080/03009740701691491.

Two pathogenic CIAS1 mutations and plasma cytokine profile in a Finnish patient with familial cold autoinflammatory syndrome responsive to anakinra.

Kaipiainen-Seppänen O, Punnonen K, van Gijn ME, Mononen T.

DOI: 10.1080/03009740701691491

PMID: 18189199 [Indexed for MEDLINE]

3788. Int J Immunogenet. 2008 Feb;35(1):33-6. doi: 10.1111/j.1744-313X.2007.00730.x.

Analysis of vascular endothelial growth factor gene 936 C/T polymorphism in patients with familial Mediterranean fever.

Gunesacar R(1), Erken E, Ozer HT, Bozkurt B, Dinkci S, Deveci D.

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Vascular endothelial growth factor (VEGF) is a cytokine that promotes endothelial cell proliferation, leucocyte chemotaxis and expression of adhesion molecules and is a major mediator of vascular permeability. It has been demonstrated that VEGF directly activates neutrophils and it could promote acute recruitment of leucocytes. It is known that neutrophils are the major cell population involved in acute inflammation in familial Mediterranean fever (FMF) and the role of VEGF in these cells may be crucial. The aim of this study was to investigate whether the 936 C/T functional polymorphism of the VEGF gene is associated with susceptibility to FMF and its relationship with the main clinical features of the disease. Polymerase chain reaction-restriction fragment length polymorphism technique was used to determine 936 C/T polymorphism within the VEGF gene in 75 patients with FMF and 122 non-related healthy controls. Genotype and allele frequencies of the VEGF 936 C/T polymorphism between patients with FMF and healthy control groups were not significantly different (OR = 0.74, 95% CI =

0.40-1.37,  $P = 0.335$  for CT genotype; OR = 1.11, 95% CI = 0.67-1.83,  $P = 0.700$ , for T allele). Although VEGF 936 TT genotype was found to be more frequent in patients with FMF than in healthy controls (6.7% vs. 1.6%, respectively), the difference was not significant (OR = 4.28, 95% CI = 0.81-22.67,  $P = 0.108$ ). No associations were found between the studied polymorphism and either the clinical features such as arthritis, abdominal pain, pleuritis, myalgia, arthralgia and erysipelas-like erythema of the disease or the four common studied exon 10 mutations (M694V, M680I, V726A, M694I) of the Mediterranean fever gene. Present results suggest that VEGF gene 936 C/T polymorphism does not seem to be associated with susceptibility to FMF and its clinical manifestations.

DOI: 10.1111/j.1744-313X.2007.00730.x

PMID: 18186798 [Indexed for MEDLINE]

3789. *Pediatr Nephrol.* 2008 Aug;23(8):1233, 1235-7. doi: 10.1007/s00467-007-0677-x. Epub 2008 Jan 9.

Multiple visceral hematomas in a child with familial Mediterranean fever: polyarteritis nodosa.

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A 14-year-old girl was diagnosed with familial Mediterranean fever (FMF) with homozygous for M694V mutation of the MEFV gene and was started on colchicine therapy 4 years before admission to our hospital. She was uncompliant to therapy and was admitted to a local hospital with complaining of fever, malaise, abdominal pain and arthralgia lasting for 2 months. Multiple hypoechogenic mass lesions were detected on liver and kidneys with ultrasonography (US) and diagnosed to be hematomas by laparoscopic examination. She was referred to our hospital because of development of convulsions. On physical examination her blood pressure was 140/90 mmHg and body temperature was 39 degrees C. She was pale and extremely cachectic, with atrophic muscles of the extremities. She had diffuse abdominal tenderness and hepatosplenomegaly. Laboratory investigations revealed a hemoglobin of 9.8 g/dl, white blood cell count 9,900/mm<sup>3</sup>, platelets 213,000/mm<sup>3</sup>,



erythrocyte sedimentation rate (ESR) 112 mm/h, C- reactive protein (CRP) 78 mg/L (normal < 2 mg/L) and fibrinogen 500 mg/dl. Electrolytes, renal and hepatic functions and urinalysis were normal. Examinations of peripheral blood smear and bone marrow aspiration were normal. X-rays of bones and chest showed no pathological finding. Protrombine, partial thromboplastine and bleeding times were normal. Bacterial cultures of blood, urine and stool grew no organisms. Serological tests for hepatitis B and C, cytomegalovirus, salmonella and brucella were negative.

DOI: 10.1007/s00467-007-0677-x

PMID: 18183427 [Indexed for MEDLINE]

3790. Ann Rheum Dis. 2008 Sep;67(9):1292-8. doi: 10.1136/ard.2007.079376. Epub 2008 Jan 7.

Clinical and functional characterisation of a novel TNFRSF1A c.605T>A/V173D cleavage site mutation associated with tumour necrosis factor receptor-associated periodic fever syndrome (TRAPS), cardiovascular complications and excellent response to etanercept treatment.

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**OBJECTIVES:** To study the clinical outcome, treatment response, T-cell subsets and functional consequences of a novel tumour necrosis factor (TNF) receptor type 1 (TNFRSF1A) mutation affecting the receptor cleavage site.

**METHODS:** Patients with symptoms suggestive of tumour necrosis factor receptor-associated periodic syndrome (TRAPS) and 22 healthy controls (HC) were screened for mutations in the TNFRSF1A gene. Soluble TNFRSF1A and inflammatory cytokines were measured by ELISAs. TNFRSF1A shedding was examined by stimulation of peripheral blood mononuclear cells (PBMCs) with phorbol 12-myristate 13-acetate followed by flow cytometric analysis (FACS). Apoptosis of PBMCs was studied by stimulation with TNFalpha in the presence of cycloheximide and annexin

V staining. T cell phenotypes were monitored by FACS.

RESULTS: TNFRSF1A sequencing disclosed a novel V173D/p.Val202Asp substitution encoded by exon 6 in one family, the c.194-14G>A splice variant in another and the R92Q/p.Arg121Gln substitution in two families. Cardiovascular complications (lethal heart attack and peripheral arterial thrombosis) developed in two V173D patients. Subsequent etanercept treatment of the V173D carriers was highly effective over an 18-month follow-up period. Serum TNFRSF1A levels did not differ between TRAPS patients and HC, while TNFRSF1A cleavage from monocytes was significantly reduced in V173D and R92Q patients. TNFalpha-induced apoptosis of PBMCs and T-cell senescence were comparable between V173D patients and HC.

CONCLUSIONS: The TNFRSF1A V173D cleavage site mutation may be associated with an increased risk for cardiovascular complications and shows a strong response to etanercept. T-cell senescence does not seem to have a pathogenetic role in affected patients.

DOI: 10.1136/ard.2007.079376

PMID: 18180277 [Indexed for MEDLINE]

3791. Clin Genet. 2008 Feb;73(2):146-51. doi: 10.1111/j.1399-0004.2007.00945.x. Epub 2007 Dec 19.

Mutations in the familial Mediterranean fever gene of patients with IgA nephropathy and other forms of glomerulonephritis.

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Glomerulonephritis, particularly IgA nephropathy (IgAN), seems to be more common in familial Mediterranean fever (FMF), an inherited disease caused by mutations in the MEiterranean FeVer gene (MEFV). The present study is aimed to determine, in populations not suffering from FMF, whether carriage of MEFV mutations may modify or precipitate IgAN and other forms of primary glomerulonephritis (PGN).

Forty patients with biopsy proven IgAN and 40 with PGN were surveyed for the presence of the three most common MEFV mutations (M694V, V726A and E148Q), using

polymerase chain reaction amplification and restriction enzyme analysis. The rate of MEFV mutations in the patients was related to the expected carrier rate in the general population of the same ethnic extraction. The effect of mutation carriage on the disease course was determined in the IgAN patient group. The frequency of MEFV mutations in IgAN or PGN was comparable to that found in ethnically adjusted general population ( $p = 0.1$  and  $0.5$ , respectively). Carriage of mutated MEFV was not associated with the course and severity of the disease or findings in kidney biopsy and urine analysis. In a population, mostly of Jewish extraction, MEFV mutations do not seem to predispose to the development of IgAN and other forms of PGN or affect the phenotype.

DOI: 10.1111/j.1399-0004.2007.00945.x

PMID: 18177471 [Indexed for MEDLINE]

3792. Clin Genet. 2008 Feb;73(2):152-9. doi: 10.1111/j.1399-0004.2007.00948.x. Epub 2007 Dec 29.

Familial Mediterranean Fever in Crete: a genetic and structural biological approach in a population of 'intermediate risk'.

Fragouli E(1), Eliopoulos E, Petraki E, Sidiropoulos P, Aksentijevich I, Galanakis E, Kritikos H, Repa A, Fragiadakis G, Boumpas D, Goulielmos GN.

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Familial Mediterranean Fever (FMF) is an autosomal, recessively inherited disease, characterized by recurrent and short attacks of fever with serosal inflammation that are caused by mutations in MEFV gene that encodes pyrin protein. To date, more than 70 disease-associated mutations have been identified, almost all of them representing missense nucleotide changes. FMF is very common among patients with Mediterranean ancestry, although the exact prevalence is not yet known, Greeks are considered to be at 'intermediate risk'. In the present study, we studied FMF patients in natives of Crete, a population sharing a common genetic and cultural background. The spectrum of MEFV gene mutations in 71 patients as well as 158 healthy controls was studied by performing a molecular analysis focused on the 12 most frequent FMF-associated mutations. We found that

59 of 71 (83.1%) FMF patients had at least one MEFV mutation, five patients were homozygotes and 54 heterozygotes for FMF-associated mutations. No mutations were detected in 12 patients (16.9%). As in high-risk populations, common MEFV mutations were found in Cretan FMF patients, with the M694V being the most penetrant. M694V and M694I mutations were associated with severe phenotypes, with many patients presenting with uncommon clinical manifestations such as erysipelas-like erythema or renal disturbances. Of interest, 20 (37%) of our heterozygous FMF patients presented with a severe phenotype. Population genetics analysis showed an FMF carrier frequency in healthy Cretan population of approximately 6% (1:17) and places Cretans closer to the Western rather than Eastern populations of the Mediterranean basin. Finally, we constructed a three-dimensional model showing the interaction of the PRYSPRY domain of pyrin with caspase-1 onto which we mapped MEFV mutations, classified according to disease severity. In this model, the 'flexible loops' of caspase-1 appear to have no access to some positions that have been previously associated with mild disease, suggesting that alternative pathogenic pathways leading to FMF need to be explored.

DOI: 10.1111/j.1399-0004.2007.00948.x

PMID: 18177465 [Indexed for MEDLINE]

3793. Rheumatology (Oxford). 2008 Mar;47(3):309-10. doi: 10.1093/rheumatology/kem318. Epub 2008 Jan 3.

New CIAS1 mutation and anakinra efficacy in overlapping of Muckle-Wells and familial cold autoinflammatory syndromes.

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**OBJECTIVES:** Muckle-Wells syndrome (MWS) and familial cold autoinflammatory syndrome (FCAS) are rare periodic fevers associated with CIAS1 mutations. A third entity, the chronic infantile neurological, cutaneous, articular (CINCA) syndrome was also recently associated with mutation in the same gene. A phenotypic and

genotypic continuum seems to exist from the most benign (FCAS) to the most severe forms (CINCA). Although a CIAS1 mutation can be associated with two different phenotypes.

**METHODS:** We report a family of three patients exhibiting the MWS and FCAS phenotypes. These phenotypes were associated with a novel missense mutation in CIAS1.

**RESULTS:** Anakinra controlled inflammatory flares in the three patients.

**CONCLUSIONS:** FCAS, MWS and CINCA could be different phenotype expressions of the same disease.

DOI: 10.1093/rheumatology/kem318

PMID: 18174231 [Indexed for MEDLINE]

3794. Rheumatol Int. 2008 Jun;28(8):793-6. doi: 10.1007/s00296-007-0515-2. Epub 2008 Jan 3.

Exposition to chickenpox of two children with autoinflammatory syndromes under treatment with anakinra.

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We report two children with autoinflammatory syndromes treated with anakinra who came in contact with the varicella-zoster virus after being exposed accidentally to infected children: both cases were managed prophylactically with specific antichickenpox intravenous immunoglobulins and anakinra temporary suspension; neither adverse events nor complications related to the natural course of chickenpox were experienced by the two patients. The risk of developing infectious events should be closely monitored, because of the absence of data concerning long-term safety of biological agents in the pediatric age, and prevention strategies should be highly encouraged before they are started.

DOI: 10.1007/s00296-007-0515-2

PMID: 18172653 [Indexed for MEDLINE]

3795. Nat Clin Pract Rheumatol. 2008 Jan;4(1):34-42. doi: 10.1038/ncprheum0681.

Primer: inflammasomes and interleukin 1beta in inflammatory disorders.

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Inflammasomes are large, multimeric protein complexes that link the sensing of microbial products and metabolic stress to the proteolytic processing of prointerleukin (pro-IL)-1beta to its active form. NALP1 and NALP2 are founding members of the Nod-like receptor family. Other Nod-like receptors, including NALP3 and NOD2, which are associated with inflammatory disorders, have also been described. The NALP1 and NALP3 inflammasomes are located in the cytoplasm and can, therefore, detect intracellular infection through recognition of microbial pathogen-associated molecular patterns. The inflammasome pathways cooperate with Toll-like receptor pathways to mediate a rapid and appropriate response to pathogens and genotoxic stress. Mutations in both pyrin and NALP3 components of inflammasomes are associated with innate-immune-mediated diseases (familial Mediterranean fever and the 'cryopyrinopathies'), and aberrant IL-1beta processing has been reported in several autoinflammatory conditions, including Muckle-Wells syndrome, chronic infantile neurologic, cutaneous and articular syndrome/neonatal onset multisystem inflammatory disease, and gout. The effectiveness of IL-1beta blockade in treating many of these conditions has transformed the understanding and management of these disorders and also highlighted the role of aberrant IL-1beta signaling in other conditions, such as adult-onset Still's disease and systemic juvenile idiopathic arthritis.

DOI: 10.1038/ncprheum0681

PMID: 18172447 [Indexed for MEDLINE]

3796. Arthritis Rheum. 2008 Jan;58(1):273-83. doi: 10.1002/art.23123.

Abnormal tumor necrosis factor receptor I cell surface expression and NF-kappaB activation in tumor necrosis factor receptor-associated periodic syndrome.

Nedjai B(1), Hitman GA, Yousaf N, Chernajovsky Y, Stjernberg-Salmela S, Pettersson T, Ranki A, Hawkins PN, Arkwright PD, McDermott MF, Turner MD.

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Comment in

Arthritis Rheum. 2008 Jul;58(7):2213-4; author reply 2214-5.

**OBJECTIVE:** Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is an autosomal-dominant autoinflammatory condition caused by mutations in the TNFRSF1A gene. The cellular mechanisms by which mutations in this gene trigger inflammation are currently unclear. Because NF-kappaB is the major intracellular signaling component inducing secretion of proinflammatory cytokines, we sought to determine whether differences in the clinical phenotype of patients with TRAPS may be attributable to variable effects of TNFRSF1A mutations on TNFRI expression, localization, or NF-kappaB activity.

**METHODS:** Peripheral blood mononuclear cells were obtained from patients (following informed consent), and cellular nuclear and cytosolic fractions were generated by subcellular fractionation. Localization of IkappaBalpha and NF-kappaB was determined by Western blotting of the resultant fractions. NF-kappaB subunit activity was determined by enzyme-linked immunosorbent assay analysis and confirmed by electrophoretic mobility shift assay. Subcellular localization of TNFRI was determined by immunofluorescence confocal microscopy or by immunoblotting following affinity isolation of plasma membrane by subcellular fractionation.

**RESULTS:** Cells from patients with the fully penetrant C73R mutation had marked activation of the proinflammatory p65 subunit of NF-kappaB. In contrast, cells from patients with the low-penetrant R92Q mutation displayed high levels of DNA binding by the p50 subunit, an interaction previously linked to repression of inflammation. Interestingly, although cells from patients with the C73R mutation have no TNFRI shedding defect, there was nonetheless an unusually high concentration of functional TNFRI at the plasma membrane.

**CONCLUSION:** High levels of TNFRI at the cell surface in patients with the C73R mutation hypersensitizes cells to stimulation by TNF, leading to increased NF-kappaB p65 subunit activation and an exaggerated proinflammatory response.

DOI: 10.1002/art.23123

PMID: 18163488 [Indexed for MEDLINE]

3797. J Med Liban. 2008 Jan-Mar;56(1):35-41.

An overview of familial Mediterranean fever with emphasis on pyrin and colchicine.

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Familial Mediterranean fever (FMF) is the earliest known autoinflammatory disease, characterized by symptoms such as arthritis, peritonitis, pleuritis, erysipelas-like erythema, and most importantly amyloidosis. This disease is very common in populations of the Mediterranean area, and due to its high carrier frequency and occurrence rate in these populations, it has been the focus of much research work. Such research has allowed greater insights into the genetics of FMF, leading to the discovery of the responsible gene in 1997 and the determination of mutations and their effect on the phenotype of patients, as well as the interactions and roles of the pyrin protein, which seems to have various roles in regulation of innate immunity, inflammation, and apoptosis. Colchicine has been used as preventive treatment since 1972, and recent studies have allowed the determination of its mode of action.

PMID: 19534089 [Indexed for MEDLINE]

3798. Mol Cell Biol. 2008 Mar;28(5):1841-50. Epub 2007 Dec 26.

ATP binding by monarch-1/NLRP12 is critical for its inhibitory function.

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The recently discovered nucleotide binding domain-leucine rich repeat (NLR) gene family is conserved from plants to mammals, and several members are associated with human autoinflammatory or immunodeficiency disorders. This family is defined by a central nucleotide binding domain that contains the highly conserved Walker A and Walker B motifs. Although the nucleotide binding domain is a defining feature of this family, it has not been extensively studied in its purified form. In this report, we show that purified Monarch-1/NLRP12, an NLR protein that negatively regulates NF-kappaB signaling, specifically binds ATP and exhibits ATP hydrolysis activity. Intact Walker A/B motifs are required for this activity. These motifs are also required for Monarch-1 to undergo self-oligomerization, Toll-like receptor- or CD40L-activated association with NF-kappaB-inducing kinase (NIK) and interleukin-1 receptor-associated kinase 1 (IRAK-1), degradation of NIK, and inhibition of IRAK-1 phosphorylation. The stable expression of a Walker A/B mutant in THP-1 monocytes results in increased production of proinflammatory cytokines and chemokines to an extent comparable to that in cells in which Monarch-1 is silenced via short hairpin RNA. The results of this study are consistent with a model wherein ATP binding regulates the anti-inflammatory activity of Monarch-1.

DOI: 10.1128/MCB.01468-07

PMCID: PMC2258772

PMID: 18160710 [Indexed for MEDLINE]

3799. Mod Rheumatol. 2008;18(1):57-9. Epub 2007 Dec 22.

Familial Mediterranean fever in three Japanese patients, and a comparison of the frequency of MEFV gene mutations in Japanese and Mediterranean populations.

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We report on three Japanese patients (two families) with familial Mediterranean fever (FMF), a rare disease in the Far East. Two of the patients (siblings with definite FMF) were heterozygous for both E148Q and M694I, and the remaining patient (with probable FMF and no family history of the disease) was heterozygous for both P369S and R408Q. Although the M694I mutation is less common among Mediterranean populations, it was present in 22 (76%) of 29 Japanese patients with FMF (previously reported cases). We therefore investigated the allele frequency of M694I in the healthy Japanese population, as well as other FMF-causing mutations in exon 10 (M680I, M694V, and V726A) and polymorphisms (E148Q, P369S, and R408Q) of the Mediterranean fever gene (MEFV). The allele frequencies of disease-causing mutations, even M694I, were  $<0.001$ . While those of E148Q, P369S, and R408Q were 0.23, 0.057, and 0.054, respectively. Because of the low allele frequencies of disease-causing mutations, FMF is an extremely rare disease among Japanese individuals. However, FMF is an important component of hereditary autoinflammatory syndrome, and a diagnosis of FMF is crucial for the choice of treatment, because of the benefit of colchicine therapy.

DOI: 10.1007/s10165-007-0003-2

PMID: 18097735 [Indexed for MEDLINE]

3800. J Cutan Pathol. 2008 Jan;35(1):70-3.

Acne inversa complicated by squamous cell carcinoma in association with diffuse malignant peritoneal mesothelioma arising in the absence of predisposing factors: a case report.

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Diffuse malignant peritoneal mesothelioma (DMPM) is a relatively rare neoplasm. Risk factors associated with its development include asbestos exposure, chronic irritation or inflammation of the peritoneum, abdominal radiotherapy, familial Mediterranean fever and simian virus 40. A familial segregation of this neoplasia has been reported in small villages of the Cappadocian region of Turkey, and it has been postulated that hereditary factors may predispose to mesothelioma, even

with exposure to small amounts of asbestos. We report a case of DMPM, which apparently occurred in the absence of predisposing factors in a patient with a clinical history characterized by recurrent pre-sacral acne inversa of long duration. The association of this chronic inflammatory disease with DMPM has never been reported. The genetic locus for acne inversa has recently been identified within the 1p21.1-1q25.3 chromosomal region. Interestingly, frequent losses in chromosomal region 1p.21-22 have been found in mesothelioma as well. It is thus tempting to speculate that genetic mutations involving chromosome 1p.21-22 may account for the development of both diseases.

DOI: 10.1111/j.1600-0560.2007.00766.x

PMID: 18095999 [Indexed for MEDLINE]

3801. Ann Rheum Dis. 2008 Nov;67(11):1589-95. Epub 2007 Dec 17.

A novel TNFRSF1A splice mutation associated with increased nuclear factor kappaB (NF-kappaB) transcription factor activation in patients with tumour necrosis factor receptor associated periodic syndrome (TRAPS).

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**OBJECTIVE:** To characterise and investigate the functional consequences of a novel TNFRSF1A splice site mutation causing tumour necrosis factor receptor associated periodic syndrome (TRAPS) in a 16-year-old male patient and his mother.

**METHODS:** Mutational DNA screening was performed in the patient and his mother. Western blotting was used to analyse protein expression levels of TNFR1. A multiplex bead immunoassay was used to quantify serum levels of range of cytokines, and an ELISA-based transcription factor assay to measure nuclear factor (NF)-kappaB transactivation. Serum levels of soluble TNFR1 (sTNFR1) were measured by ELISA and fluorescence-activated cell sorting (FACS) analysis used to measure monocyte TNFR1 cell surface expression.

**RESULTS:** A novel mutation, c.472+1G>A (C158delinsYERSSPEAKPSPHPRG), involving a splice site in intron 4 of TNFRSF1A, was found in the proband and affected mother

leading to a 45 nucleotide insertion of intronic DNA into the mRNA, resulting in an in-frame insertion of 15 amino acids in the mature TNFR1 protein and a deletion of a cysteine residue C129 (158) in cysteine rich domain (CRD)3. The patients had reduced serum sTNFR1 and surface expression levels of TNFR1, with marked increases in pro- and anti-inflammatory cytokine. Their peripheral blood mononuclear cells (PBMC) had increased basal NF-kappaB activation compared with healthy controls and also had increased p50 nuclear expression following tumour necrosis factor (TNF) stimulation compared with PBMC from healthy controls, as well as T50M (T79M) and C88R (C117R) patients with TRAPS and patients with rheumatoid arthritis (RA).

CONCLUSION: A novel, TRAPS causing, TNFRSF1A splice site mutation is associated with decreased sTNFR1 levels, cell surface and whole cell extract expression and increased NF-kappaB transcription factor activation.

DOI: 10.1136/ard.2007.078667

PMID: 18086728 [Indexed for MEDLINE]

3802. J Clin Immunol. 2008 Mar;28(2):134-8. Epub 2007 Dec 15.

Phenotype-genotype analysis of cryopyrin-associated periodic syndromes (CAPS): description of a rare non-exon 3 and a novel CIAS1 missense mutation.

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We describe in this paper the phenotype-genotype analysis of a Brazilian cohort of patients with cryopyrin-associated periodic syndromes (CAPS). Patient 1 presented with an urticarial rash and recurrent fever exacerbated by cold weather, arthritis, and anterior uveitis, thus, receiving a clinical diagnosis of familial cold autoinflammatory syndrome. CIAS1 sequencing identified the T436I mutation, previously associated to a clinical phenotype of chronic infantile neurological cutaneous and articular/neonatal onset multisystem inflammatory disease. Patient 2 developed a papular exanthema with daily fever shortly after birth, frontal bossing, patellae enlargement, and cognitive and motor impairments. Sequencing identified the exceedingly rare G755R CIAS1 mutation in

exon 4. Patient 3 developed skin rash and articular symptoms 6 h after birth, followed by aseptic meningitis. He was found to have the novel C148Y missense mutation in CIAS1. This report expands the spectrum of CIAS1 mutations associated to clinical disease, suggests that the same mutation can be associated with different clinical syndromes, and supports the evidence that CAPS patients should always be screened for mutations outside exon 3.

DOI: 10.1007/s10875-007-9150-7

PMID: 18080732 [Indexed for MEDLINE]

### 3803. RETRACTED ARTICLE

Dig Dis Sci. 2008 Aug;53(8):2079-82. Epub 2007 Dec 15.

Gastric changes following colchicine therapy in patients with FMF.

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Retraction in

Dig Dis Sci. 2009 Dec;54(12):2772.

**BACKGROUND:** Familial Mediterranean fever (FMF) is also called recurrent polyserositis. The salient features of this disease include brief recurrent episodes of peritonitis, pleuritis, and arthritis, which are usually associated with fever. Colchicine is highly effective in the treatment of FMF and in preventing the development of recurrent attacks and amyloidosis, and it is essential to make the correct diagnosis and institute daily therapy with colchicine (0.5-0.6 mg bid). Colchicine is used to treat a variety of conditions but it is known to have gastrointestinal (GI) side effects. In this study, effects of colchicines on the gastrointestinal tract were evaluated in patients with FMF treated with colchicine.

**METHODS:** Biopsies were reviewed from 43 patients attending Ain Shams University Hospital (Egypt) who were diagnosed with FMF and treated with colchicine. One-hundred and twelve GI biopsies, obtained over a 14-year period, were

reviewed. This included biopsies from stomach body (38), stomach antrum (50), and colon (24). In addition, gastric biopsies were reviewed from 17 control patients who did not have FMF and were not on colchicine.

RESULTS: Three patients known to have FMF and on colchicine therapy showed typical histological features of colchicine (metaphase mitoses, epithelial pseudoproliferation, mucin depletion, and frequent apoptosis). These features were seen only in gastric antral biopsies and not in colonic biopsies. None of the control group showed the characteristic morphological features of colchicine toxicity.

CONCLUSION: This is the first report of histological changes seen in the stomach following colchicine therapy. In contrast with previous reports, we did not find any definitive change in the large intestine. Our data show that gastric changes can be encountered in symptomatic patients who have recently had colchicine. If these findings are seen histologically, they merit correlation with the clinical impression and should not be interpreted as toxicity in isolation.

DOI: 10.1007/s10620-007-0132-7

PMID: 18080195 [Indexed for MEDLINE]

3804. Clin Exp Rheumatol. 2007 Sep-Oct;25(5):792.

Coexistence of familial Mediterranean fever and Sjögren's syndrome in a Japanese patient.

Tanaka M, Migita K, Miyashita T, Maeda Y, Nakamura M, Komori A, Ishibashi H, Eguchi K, Kikuchi M, Hirayama K, Yasunami M.

PMID: 18078637 [Indexed for MEDLINE]

3805. Semin Cutan Med Surg. 2007 Sep;26(3):179-87.

A four-year-old boy with fever, rash, and arthritis.

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The triad of fever, rash, and arthritis in a hospitalized child suggests an inflammatory, infectious, or postinfectious process in most cases; however, malignancy must be considered. The most common causes in this age group are inflammatory conditions, including Kawasaki disease, Henoch-Schönlein Purpura, serum sickness-like reaction, and juvenile idiopathic arthritis. Other rarer inflammatory processes can present with this triad of symptoms such as Cryopyrin-related diseases (autoinflammatory disorders), urticarial vasculitis, and systemic lupus erythematosus. We will discuss the differential diagnosis and inpatient management of fever, rash, and arthritis in a young child, focusing on inflammatory conditions. The important features which can help distinguish these conditions include the nature of the rash, associated signs or symptoms, time course of the eruption, and characteristic laboratory and/or histologic findings.

DOI: 10.1016/j.sder.2007.09.001

PMID: 18070685 [Indexed for MEDLINE]

3806. Blood. 2008 Feb 15;111(4):2132-41. Epub 2007 Dec 6.

Disease-associated CIAS1 mutations induce monocyte death, revealing low-level mosaicism in mutation-negative cryopyrin-associated periodic syndrome patients.

Saito M(1), Nishikomori R, Kambe N, Fujisawa A, Tanizaki H, Takeichi K, Imagawa T, Iehara T, Takada H, Matsubayashi T, Tanaka H, Kawashima H, Kawakami K, Kagami S, Okafuji I, Yoshioka T, Adachi S, Heike T, Miyachi Y, Nakahata T.

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Cryopyrin-associated periodic syndrome (CAPS) is a spectrum of systemic autoinflammatory disorders in which the majority of patients have mutations in the cold-induced autoinflammatory syndrome (CIAS)1 gene. Despite having indistinguishable clinical features, some patients lack CIAS1 mutations by conventional nucleotide sequencing. We recently reported a CAPS patient with mosaicism of mutant CIAS1, and raised the possibility that CIAS1 mutations were

overlooked in "mutation-negative" patients, due to a low frequency of mosaicism. To determine whether there were latent mutant cells in "mutation-negative" patients, we sought to identify mutation-associated biologic phenotypes of patients' monocytes. We found that lipopolysaccharide selectively induced necrosis-like cell death in monocytes bearing CIAS1 mutations. Monocyte death correlated with CIAS1 up-regulation, was dependent on cathepsin B, and was independent of caspase-1. Cell death was intrinsic to CIAS1-mutated monocytes, was not mediated by the inflammatory milieu, and was independent of disease severity or anti-IL-1 therapy. By collecting dying monocytes after lipopolysaccharide treatment, we succeeded in enriching CIAS1-mutant monocytes and identifying low-level CIAS1-mosaicism in 3 of 4 "mutation-negative" CAPS patients. Our findings reveal a novel effect of CIAS1 mutations in promoting necrosis-like cell death, and demonstrate that CIAS1 mosaicism plays an important role in mutation-negative CAPS patients.

DOI: 10.1182/blood-2007-06-094201

PMID: 18063752 [Indexed for MEDLINE]

3807. J Rheumatol. 2008 Jan;35(1):106-13. Epub 2007 Dec 1.

MEFV mutations in patients with familial Mediterranean fever in the Black Sea region of Turkey: Samsun experience [corrected].

Yigit S(1), Bagci H, Ozkaya O, Ozdamar K, Cengiz K, Akpolat T.

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Erratum in

J Rheumatol. 2008 Feb;35(2):367.

**OBJECTIVE:** To investigate MEFV mutations among patients with familial Mediterranean fever (FMF), their relatives, and healthy controls in the Black Sea region of Turkey; to compare 3 different MEFV mutation analysis methods; to evaluate the role of MEFV mutations in the diagnosis of FMF; and to investigate the role of M694V in the development of amyloidosis.

**METHODS:** In total, 890 subjects (625 patients, 165 relatives, 100 healthy controls) were included in this prospective study. MEFV mutations were studied



with the amplification refractory mutation system (ARMS; n = 335), polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP; n = 335), and reverse hybridization assay (FMF StripAssay; n = 693).

RESULTS: All methods were used in 79 patients. The ratio of false negativity was about 2% using ARMS compared to PCR-RFLP. The FMF StripAssay was used to investigate 9 more mutations and detected 17 mutations in 14 patients. The M694V/M694V genotype was more common in patients with amyloidosis (37%) compared to patients without amyloidosis (18%) ( $p = 0.009$ ). The frequency of MEFV carriers was 27%. The frequency of individuals having 2 mutations among asymptomatic relatives of FMF patients was 6%.

CONCLUSION: The FMF StripAssay is a reliable and time-saving method. In spite of detection of new mutations and developments in MEFV assay technology, there were patients in whom no mutation was detected. Our data, combined with previous studies, show that patients having M694V/M694V carry a risk for amyloidosis.

PMID: 18061974 [Indexed for MEDLINE]

3808. Infect Dis Clin North Am. 2007 Dec;21(4):1189-211, xi.

Recurrent fevers of unknown origin.

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Recurrent fever of unknown origin is mostly caused by rather rare diseases and many cases remain unexplained. The very limited literature data do not allow one to construct a diagnostic algorithm. A number of general principles should be kept in mind before starting the investigation for this rare subtype of fever of unknown origin.

DOI: 10.1016/j.idc.2007.08.004

PMID: 18061093 [Indexed for MEDLINE]

3809. Ann Rheum Dis. 2008 Nov;67(11):1499-504. Epub 2007 Dec 4.

The metastasis associated protein S100A4: a potential novel link to inflammation and consequent aggressive behaviour of rheumatoid arthritis synovial fibroblasts.

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The metastasis-associated protein S100A4 belongs to the large family of S100 calcium-binding proteins that appear to play regulatory roles in diverse biological activities. Moreover, a prognostic role of S100A4 has been suggested for patients with several types of cancer. Cancer promoting properties for S100A4 have been demonstrated, particularly through its regulation of cell motility, proliferation and apoptosis, as well as by stimulation of angiogenesis and remodelling of the extracellular matrix. Increased expression of S100A4 mRNA has been detected in proliferating synovial fibroblasts in rheumatoid arthritis. Furthermore, strong upregulation of the S100A4 protein in rheumatoid arthritis synovial tissue compared with osteoarthritis and control tissues has been demonstrated recently, especially at sites of joint invasion. Several immune and vascular cells were also identified to be producing S100A4 within the synovium. The local upregulation of S100A4 was accompanied by high plasma and synovial fluid concentrations of the S100A4 protein existing in the bioactive oligomeric form in patients with rheumatoid arthritis. Consistent with data from cancer studies, the extracellular S100A4 oligomer appears to be involved in regulation of several matrix-degrading enzymes and modulation of the transcriptional activation function of the tumour suppressor protein p53 in rheumatoid arthritis synovial fibroblasts. Taken together, one can speculate that increased S100A4 protein in circulation and locally at sites of inflammation, particularly at sites of joint destruction, might be linked to the process of aggressive fibroblast behaviour contributing to the pathogenesis of chronic autoinflammatory diseases such as rheumatoid arthritis.

DOI: 10.1136/ard.2007.079905

PMID: 18056757 [Indexed for MEDLINE]

3810. Rheumatology (Oxford). 2008 Feb;47(2):228-9. Epub 2007 Dec 3.

Comment on: Failure of anti-TNF therapy in TNF receptor 1-associated periodic syndrome (TRAPS).

Siebert S, Amos N, Lawson TM.

Comment on

Rheumatology (Oxford). 2007 Jul;46(7):1211-2.

DOI: 10.1093/rheumatology/kem243

PMID: 18056150 [Indexed for MEDLINE]

3811. Arthritis Rheum. 2007 Dec;56(12):4182-8.

Elevated CD16 expression by monocytes from patients with tumor necrosis factor receptor-associated periodic syndrome.

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**OBJECTIVE:** Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is an inherited autosomal-dominant autoinflammatory condition caused by mutations in the ectodomain of the 55-kd tumor necrosis factor (TNF) receptor superfamily 1A.

Proinflammatory blood monocytes with the phenotype CD14<sup>+</sup>,CD16<sup>+</sup>,HLA-DR<sup>++</sup> are a major source of TNF, and the number of such monocytes is increased during infection and inflammation. The aim of this study was to investigate whether the expression of circulating CD16<sup>+</sup> monocytes is affected in patients with TRAPS.

**METHODS:** Peripheral blood obtained from patients with TRAPS and healthy control subjects was stained with monoclonal antibodies to detect CD14<sup>++</sup>,CD16<sup>-</sup> monocytes and CD14<sup>+</sup>,CD16<sup>+</sup> monocytes, using flow cytometry. Lipopolysaccharide-induced TNF production was measured by intracellular cytokine staining. Activation-induced shedding of CD16 was investigated by treating blood samples with phorbol myristate acetate.

**RESULTS:** The level of CD16 expression by CD14<sup>+</sup>,CD16<sup>+</sup> monocytes, but not their

absolute number, was significantly elevated in patients with TRAPS, even though the patients were not experiencing clinically overt episodes of autoinflammation at the time of sampling. These findings are similar to those for the C-reactive protein levels and erythrocyte sedimentation rates in the same patients. The enhanced level of CD16 expression by monocytes from patients with TRAPS was not attributable to a defect in activation-induced shedding of CD16. The CD14<sup>+</sup>,CD16<sup>+</sup> monocytes were the predominant source of TNF in both patients and healthy control subjects.

**CONCLUSION:** The level of CD16 expression by monocytes was elevated in patients with TRAPS, as a feature of the underlying constitutive inflammation status.

DOI: 10.1002/art.23133

PMID: 18050249 [Indexed for MEDLINE]

3812. Cell. 2007 Nov 30;131(5):873-86.

Trex1 exonuclease degrades ssDNA to prevent chronic checkpoint activation and autoimmune disease.

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Comment in

Cell. 2007 Nov 30;131(5):836-8.

Trex1 is the major 3' DNA exonuclease in mammalian cells, and mutations in the human TREX1 gene can cause Aicardi-Goutières syndrome, characterized by perturbed immunity. Similarly, Trex1(-/-) mice have an autoinflammatory phenotype; however, the mechanism of Trex1-deficient disease is unknown. We report that Trex1, ordinarily associated with the endoplasmic reticulum (ER), relocalizes to the S phase nucleus after gamma irradiation or hydroxyurea treatment. Notably, Trex1-deficient cells show defective G1/S transition and chronic ATM-dependent checkpoint activation, even in the absence of exogenous stress, correlating with persistent single-stranded DNA molecules produced in S phase, which accumulate in the ER. Our data indicate that Trex1 acts on a single-stranded DNA polynucleotide

species generated from processing of aberrant replication intermediates to attenuate DNA damage checkpoint signaling and prevent pathological immune activation.

DOI: 10.1016/j.cell.2007.10.017

PMID: 18045533 [Indexed for MEDLINE]

3813. J Pediatr. 2007 Dec;151(6):675-8. Epub 2007 Aug 28.

Prevalence of the MEFV gene mutations in childhood polyarteritis nodosa.

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**OBJECTIVES:** To test the hypothesis that alterations in the Mediterranean fever (MEFV) gene are a susceptibility factor for the development of polyarteritis nodosa (PAN) we investigated the prevalence of MEFV mutations in patients with PAN without any symptoms of familial Mediterranean fever (FMF).

**STUDY DESIGN:** Pediatric patients with PAN (n = 29) were enrolled in this study. Six predominant mutations (p.M694V, p.M680I, p.M694I, p.V726A, p.K695R, p.E148Q) in the MEFV gene were studied.

**RESULTS:** Fifteen MEFV mutations were identified in 58 chromosomes. Eleven of the 29 patients (38%) were found to carry MEFV mutations. Three (10.3%) of them had homozygous p.M694V mutation, and one of the patients (3.4%) had compound heterozygous mutation (p.V726A/p.E148Q).

**CONCLUSIONS:** Our study confirms that alterations in the MEFV gene are important susceptibility factors for the development of PAN. We believe that mutations in MEFV gene provide a basis for the development of PAN both by forming a proinflammatory state and by possibly giving exaggerated response to streptococcal infections.

DOI: 10.1016/j.jpeds.2007.04.062

PMID: 18035151 [Indexed for MEDLINE]

3814. Ann Rheum Dis. 2007 Nov;66 Suppl 3:iii91-5.

Regulatory T cells and toll-like receptors: regulating the regulators.

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Regulatory T cells (Treg) play a crucial role in maintaining control of leucocytes. Several studies have shown that in vivo Treg depletion results in autoimmune syndromes like thyroiditis, gastritis, diabetes mellitus and colitis, but at the same time, may also result in improved anti-tumour vaccination. Although Treg are recognised to maintain peripheral tolerance in healthy individuals, recent research has shown that Treg also suppress immune responses during infections to prevent tissue damage. How the Treg themselves are regulated is still under investigation. Their suppressive activity must be regulated in order to allow for the effective elimination of pathogens. Until recently, this control of Treg function was found to be through modulation via cytokines or by stimulation via co-stimulatory molecules on antigen-presenting cells. It is now demonstrated, however, that the presence of pathogens can be communicated to Treg directly through toll-like receptors (TLRs). Up until now, Treg have been reported to respond to ligands for TLR2, 4, 5 and 8, and different TLRs can have alternative effects on Treg resulting in more suppression or, in contrast, abrogation of suppression. As TLRs can also recognise endogenous proteins, such as heat shock proteins, it is tempting to speculate on the role of these proteins in modulating Treg function during chronic inflammation. In this review, we will discuss the implications of TLR engagement on Treg and any consequences this may have for chronic autoinflammatory diseases like rheumatoid arthritis (RA).

DOI: 10.1136/ard.2007.078535

PMCID: PMC2095279

PMID: 17934105 [Indexed for MEDLINE]

3815. J Inherit Metab Dis. 2007 Nov;30(6):888-95. Epub 2007 Nov 19.

Deletion of a single mevalonate kinase (Mvk) allele yields a murine model of hyper-IgD syndrome.

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In the current study our objective was to develop a murine model of human hyper-IgD syndrome (HIDS) and severe mevalonic aciduria (MA), autoinflammatory disorders associated with mevalonate kinase deficiency (MKD). Deletion of one Mvk allele (Mvk (+/-)) yielded viable mice with significantly reduced liver Mvk enzyme activity; multiple matings failed to produce Mvk (-/-) mice. Cholesterol levels in tissues and blood, and isoprene end-products (ubiquinone, dolichol) in tissues were normal in Mvk (+/-) mice; conversely, mevalonate concentrations were increased in spleen, heart, and kidney yet normal in brain and liver. While the trend was for higher IgA levels in Mvk (+/-) sera, IgD levels were significantly increased (9-12-fold) in comparison to Mvk (+/+) littermates, in both young (<15 weeks) and older (>15 weeks) mice. Mvk (+/-) animals manifested increased serum TNF-alpha as compared to wild-type littermates, but due to wide variation in levels between individual Mvk (+/-) mice the difference in means was not statistically significant. Mvk (+/-) mice represent the first animal model of HIDS, and should prove useful for examining pathophysiology associated with this disorder.

DOI: 10.1007/s10545-007-0776-7

PMID: 18008182 [Indexed for MEDLINE]

3816. Semin Arthritis Rheum. 2008 Apr;37(5):334-8. Epub 2007 Nov 19.

Common MEFV mutation analysis in Iranian Azeri Turkish patients with familial Mediterranean fever.

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**OBJECTIVES:** To identify the frequency and distribution of familial Mediterranean fever (FMF) gene (MEFV) mutations among Azeri Turkish patients from northwestern Iran.

**METHODS:** One hundred ninety unrelated patients were referred by specialists to the Molecular-Medical Genetic Center of Tabriz. A clinical diagnosis of FMF was made according to published criteria. Mutation screening of the MEFV gene was performed for the 5 most commonly known mutations, namely M694V, V726A, M680I, M694I, and E148Q, by using amplification refractory mutation system for the first 4 and by polymerase chain reaction restriction-digestion testing for E148Q. These methods may also be used as a screening tool within affected families.

**RESULTS:** Of the unrelated patients investigated, 120 (63%) had 1 or 2 mutations. Of those with mutations, 41 were homozygous, 37 were compound heterozygous, and 42 had only 1 identifiable mutation. Of the studied alleles, the most frequent mutation was M694V (28%), followed by V726A (9%), E148Q (7%), M680I (7%), and M694I (1%) mutations.

**CONCLUSIONS:** Our results indicate that the common Mediterranean mutations are frequent in the Azeri Turkish FMF patients but with some differences in the frequency of individual mutations. The high frequency of E148Q in Azeri Turks compared with Mediterranean ethnic groups is rather interesting. The results open the way for further investigations on patients diagnosed as having FMF and in whom no mutations or only 1 mutated allele were found.

DOI: 10.1016/j.semarthrit.2007.08.005

PMID: 18006045 [Indexed for MEDLINE]

3817. Medicine (Baltimore). 2007 Nov;86(6):355-62.

Familial Mediterranean fever and cryptogenic cirrhosis.

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Familial Mediterranean fever (FMF) is a febrile disease characterized by acute, spontaneously resolving episodes of fever and pain caused by serosal inflammation and associated with mutations in the FMF gene, MEFV. Prophylaxis is maintained with colchicine. To our knowledge, no study has yet shown an association between FMF and cirrhosis of the liver. We conducted the current study to describe cryptogenic cirrhosis in FMF and to examine the possible relationship between the 2 entities. Patients with chronic liver disease were retrospectively identified through a computer search of a registry of 6000 patients with FMF followed in the clinics of the National Center for FMF. Data pertaining to FMF phenotype and genotype and characteristics of the liver disease were abstracted from patients' charts. Cryptogenic cause of cirrhosis was determined by exclusion of known causes of liver disease. Nine patients with cryptogenic cirrhosis were identified, comprising 0.15% of the FMF patient population, a rate significantly higher than the rate of 0.015% of cirrhosis of all types expected in the total population of Israel ( $p < 0.000$ ). Most patients had typical FMF, with a normal severity score distribution. The mean daily dose of colchicine was  $1.4 \pm 0.4$  mg, not different from the usual dose. All 7 patients who underwent mutation analysis had 2 mutations. Five of them were homozygous for M694V. Child-Pugh classification was determined in 6 patients at the time of cirrhosis diagnosis, and was classified as A in 4 of them. These findings suggest that MEFV may serve as a modifier gene in cryptogenic cirrhosis. Genetic analysis in patients with cryptogenic cirrhosis unrelated to FMF, particularly patients of a Mediterranean origin, may be warranted in future studies.

DOI: 10.1097/MD.0b013e31815be056

PMID: 18004180 [Indexed for MEDLINE]

3818. Clin Rheumatol. 2008 Jun;27(6):729-32. Epub 2007 Nov 14.

A very frequent mutation and remarkable association of R761H with M694V mutations in Turkish familial Mediterranean fever patients.

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Familial Mediterranean fever (FMF) is an autosomal-recessive disease. It is characterized by recurring fever, abdominal pain, and serositis. The Mediterranean fever (MEFV) gene is localized on 16p13.3 and more than 35 mutations have been described to date. There are some differences in the gene mutations of FMF in the various ethnic groups. The aim of this study is to determine the frequency of the mutations which has been reported comparatively rare, to define the most effective mutation set, and to select the most suitable DNA analysis system for Turkish FMF patients. Mutations in 330 Turkish FMF patients with typical phenotypes from various regions of Turkey were evaluated for the research purposes. These patients were analyzed for six MEFV gene mutations by the NanoChip Molecular Genetics Workstation. The most frequent mutation was M694V, identified in 50.00% of the alleles examined; M680I followed with 14.10% and V726A--9.70%. Consequently, we determined that R761H (n = 23; 3.48%) was the most frequent rare mutations in Turkish FMF patients. Frequency of the rare mutations were R761H (3.48%), E148Q (1.36%), and M694I (1.21%). All of these mutations were in the compound heterozygote state. Our study showed that R761H mutations were higher than it has been reported in literature until now and were mainly associated with M694V. We suggest that mutation R761H should be included in the mutation scanning analysis researches or considered if the patient has M694V/? mutation especially in Turkish FMF patients. Larger serial studies need to be done to investigate the rate and coexistence of these mutations.

DOI: 10.1007/s10067-007-0780-1

PMID: 18000697 [Indexed for MEDLINE]

3819. Clin Exp Rheumatol. 2007 Jul-Aug;25(4 Suppl 45):S119.

Identification of familial Mediterranean fever (FMF) in a Gypsy woman: a case report.

Kovács G, Tarján E, Magyar P, Nagy E, Müzes G, Ben-Chetrit E.

PMID: 17949566 [Indexed for MEDLINE]

3820. Clin Exp Rheumatol. 2007 Jul-Aug;25(4 Suppl 45):S114-7.

Protracted febrile myalgia in children and young adults with familial Mediterranean fever: analysis of 15 patients and suggested criteria for working diagnosis.

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**OBJECTIVES:** To present an analysis of patients with protracted febrile myalgia (PFM), a rarely reported manifestation of familial Mediterranean fever (FMF), and propose clinical criteria for working diagnosis.

**METHODS:** A multicenter retrospective cohort study of children with PFM was performed. Clinical and laboratory data were obtained by medical record review.

**RESULTS:** The study group included 15 patients with PFM. PFM occurred as the presenting sign of FMF in 33%. FMF was diagnosed clinically in all and by genetic analysis in 93%. M694V allelic involvement was noted in 93% of the patients. PFM occurred at a mean age of 9 +/- 3.4 years and was characterized by severe generalized muscle pain in all patients and fever in 71%. Mean duration up to diagnosis was 15.5 +/- 6 days. Mean erythrocyte sedimentation rate was 104 +/- 26 mm/h; mean C-reactive protein was 15.4 +/- 6.3 mg%. Creatine kinase was normal. Treatment included corticosteroids (4 patients) and nonsteroidal anti-inflammatory drugs (NSAIDs) (9 patients) with a symptomatic relief achieved at a mean of 7.7 +/- 4.3 days and 5 +/- 3.8 days, respectively ( $p = 0.14$ ) (mean severity score 3 and 2.2, respectively,  $p = 0.075$ ). Symptomatic relief in 2 untreated patients was achieved at a mean of 45.5 days.

**CONCLUSION:** Based on our data, we propose criteria for working diagnosis including: severe disabling myalgia of at least 5 days in a young patient with FMF, associated with fever, elevated levels of inflammatory markers and presence of at least one M694V mutation.

PMID: 17949564 [Indexed for MEDLINE]

3821. Clin Exp Rheumatol. 2007 Jul-Aug;25(4 Suppl 45):S93-5.

Overlap syndrome between FMF and TRAPS in a patient carrying MEFV and TNFRSF1A mutations.

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Comment in

Clin Exp Rheumatol. 2008 Jul-Aug;26(4 Suppl 50):S128-9; author reply S129.

**OBJECTIVE:** Familial Mediterranean Fever (FMF) and TNF-Receptor Associated Periodic Syndrome (TRAPS) are two inheritable inflammatory disorders. They share some clinical manifestations but their treatments are different. We present here the case of an overlap syndrome of FMF and TRAPS in a patient carrying a mutation in both the MEFV and TNFRSF1A genes.

**CASE REPORT:** A 20-year-old woman of Mediterranean origin had suffered since childhood from attacks of fever and arthritis, with skin and ophthalmic manifestations. The initial diagnosis was FMF. The symptoms responded poorly to colchicine but regressed with steroids. Genetic analysis revealed a homozygous M694V mutation in MEFV and a heterozygous R92Q mutation in TNFRSF1A. We discuss the complexity of this combined FMF-TRAPS phenotype.

**CONCLUSION:** This case shows that mutations in MEFV and TNFRSF1A can occur together in a single patient, a condition that may modify its response to treatment. It would be interesting to evaluate the role of the R92Q mutation in TNFRSF1A in patients of Mediterranean origin with FMF unresponsive to colchicine.

PMID: 17949559 [Indexed for MEDLINE]

3822. Clin Exp Rheumatol. 2007 Jul-Aug;25(4 Suppl 45):S16-20.

Plasma and platelet serotonin levels in familial Mediterranean fever.

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**OBJECTIVE:** Familial Mediterranean fever (FMF) is the most common auto-inflammatory syndrome with exaggerated acute phase and inflammatory response. After revealing the MEFV gene mutation with the finally disturbed end product pyrin, some of the mechanisms were explained. However it is still unknown what triggers or ends these periodical attacks. Moreover, the treatment of up to 30% of the patients, that are resistant to colchicine is still a problem. In this study we investigated the role of serotonin in colchicine-resistant FMF patients.

**METHODS:** Twenty-four FMF patients (male/female: 15/9) and 32 age- and sex-matched healthy controls (male/female: 17/15) were included into the study. Patients were subdivided into two groups. Thirteen had FMF attacks despite regular colchicine (colchicine-resistant group), other 11 had disease under control with colchicine for at least 6-months. Sampling was done both during the attack and ten days after its cessation. Plasma and platelet serotonin levels and acute phase reactants were studied in patients and controls.

**RESULTS:** Colchicine-resistant patients had plasma serotonin (5-HT) levels of  $7.85 \pm 1.0$  nmol/l during acute attacks which significantly reduced to the levels of  $6.3 \pm 0.6$  nmol/l ( $p < 0.001$ ), after 10 days of acute attacks and these levels were significantly lower than those of attack-free patients' and controls' ( $10.7 \pm 0.2$  nmol/l and  $10.1 \pm 0.3$  nmol/l, respectively). Platelet 5-HT level was  $6.4 \pm 0.3$  nmol/10(9) platelets during acute attack, and this level was increased to  $9.8 \pm 0.5$  nmol/10(9) platelets on the 2(nd) sampling, 10 days after the cessation of the acute attack ( $p < 0.001$ ). They were both significantly higher than those of attack-free FMF patients ( $5.9 \pm 0.1$  nmol/10(9) platelets) and healthy controls ( $5.7 \pm 0.3$  nmol/10(9) platelets). There was a negative correlation between plasma and platelet 5-HT levels ( $r = -0.77$ ,  $p < 0.001$ ).

**CONCLUSION:** Changes in plasma and platelet 5-HT levels may be related to the disturbances in 5-HT transport mechanisms or may also be attributed to the potential role of serotonin in the inflammatory cascade. Last but not least, serotonin may have a role in the pathogenesis of FMF.

PMID: 17949546 [Indexed for MEDLINE]

3823. Clin Exp Rheumatol. 2007 Jul-Aug;25(4 Suppl 45):S6-8.

Pyrin and cryopyrin--similar domain sequence but opposite inflammatory consequence.

Berkun Y, Ben-Chetrit E.

PMID: 17949543 [Indexed for MEDLINE]

3824. Rev Clin Esp. 2007 Nov;207(10):508-9.

[The spectrum of familial Mediterranean fever].

[Article in Spanish]

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Familial mediterranean fever (FMF) is a disease whose importance in recent years is reappearing thanks to the advances in molecular genetics. The diagnosis is established by symptoms, presence of inflammatory episodes of fever and serositis, family background and genetic study. Identification of the most prevalent mutations of the MEFV gene may confirm atypical or incomplete forms of FMS that are difficult to recognize based on the classical major and minor criteria. Knowledge of this more extensive clinical spectrum makes it possible to have a new diagnostic and therapeutic perspective based on the treatment of colchicine and secondary prevention of AA amyloidosis.

PMID: 17988598 [Indexed for MEDLINE]

3825. Allergy. 2007 Dec;62(12):1349-58.

Periodic fever syndromes: a diagnostic challenge for the allergist.

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Cincinnati, OH 41017, USA.

The objective was to present a case of periodic fever with aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA), summarize the medical literature on PFAPA, review the differential diagnosis and suggest a diagnostic approach to periodic fevers in children. A PubMed search was conducted for all case reports and series of patients with PFAPA. The references of these papers yielded further case reports. Review articles or large case series were used for sources of information regarding the other periodic fever and autoinflammatory syndromes. All cases reported as PFAPA were included in the review, even though a few of the cases may not have been accurately diagnosed. The periodic fever and autoinflammatory syndromes of childhood are a group of diseases that cause repeated febrile illnesses with various associated symptoms. Except for PFAPA, each of these diseases is caused by a known genetic mutation. Effective treatment options and long-term prognosis varies among these syndromes. Children with periodic fever or autoinflammatory syndromes sometimes present to an Allergy/Immunology clinic for immunologic evaluation. It is important for the Allergy/Immunology specialist to be familiar with the clinical presentation, diagnostic approach and treatment of these conditions.

DOI: 10.1111/j.1398-9995.2007.01534.x

PMID: 17983370 [Indexed for MEDLINE]

3826. Cytokine. 2008 Feb;41(2):71-8. Epub 2007 Nov 5.

Regulation of IL-17 production in human lymphocytes.

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The discovery of a new lineage of helper T cells that selectively produces interleukin (IL)-17 has provided exciting new insights into immunoregulation, host defense and the pathogenesis of autoimmune diseases. Although the factors that promote murine Th17 differentiation have been intensively examined, there has been much less information on the regulation of this cytokine in human T cells. IL-17 is readily produced by human memory T cells, which we now know exhibit distinct patterns of chemokine receptor expression and may differentiate in response to selective pathogens. Recently it has been shown that IL-1, IL-6 and IL-23 are important in driving human Th17 differentiation. However, TGFbeta-1 which is important for the differentiation of murine Th17 cells and inducible regulatory T cells (iTregs), is reportedly not required and even inhibits for human Th17 differentiation. In addition, human Th17 cells also produce other proinflammatory cytokines. Further characterization of the transcription regulation of human IL-17 expression, and the epigenetic regulation of human IL17 locus should improve our understanding the lineage commitment of human Th17 cells. Targeting the production and action of this cytokine is also likely to be beneficial therapeutically for autoinflammatory and autoimmune diseases.

DOI: 10.1016/j.cyto.2007.09.009

PMID: 17981475 [Indexed for MEDLINE]

3827. Adv Immunol. 2007;96:41-101.

Regulation of interferon-gamma during innate and adaptive immune responses.

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Interferon-gamma (IFN-gamma) is crucial for immunity against intracellular pathogens and for tumor control. However, aberrant IFN-gamma expression has been



associated with a number of autoinflammatory and autoimmune diseases. This cytokine is produced predominantly by natural killer (NK) and natural killer T (NKT) cells as part of the innate immune response, and by Th1 CD4 and CD8 cytotoxic T lymphocyte (CTL) effector T cells once antigen-specific immunity develops. Herein, we briefly review the functions of IFN-gamma, the cells that produce it, the cell extrinsic signals that induce its production and influence the differentiation of naïve T cells into IFN-gamma-producing effector T cells, and the signaling pathways and transcription factors that facilitate, induce, or repress production of this cytokine. We then review and discuss recent insights regarding the molecular regulation of IFN-gamma, focusing on work that has led to the identification and characterization of distal regulatory elements and epigenetic modifications with the IFN-gamma locus (*Ifng*) that govern its expression. The epigenetic modifications and three-dimensional structure of the *Ifng* locus in naïve CD4 T cells, and the modifications they undergo as these cells differentiate into effector T cells, suggest a model whereby the chromatin architecture of *Ifng* is poised to facilitate either rapid opening or silencing during Th1 or Th2 differentiation, respectively.

DOI: 10.1016/S0065-2776(07)96002-2

PMID: 17981204 [Indexed for MEDLINE]

3828. *Biochim Biophys Acta*. 2007 Dec;1774(12):1536-43. Epub 2007 Oct 4.

Transport proteins PotD and Crr of *Escherichia coli*, novel fusion partners for heterologous protein expression.

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The *Escherichia coli* proteome response to the stressor GdnHCl was analyzed through 2-dimensional gel electrophoresis (2-DE). We identified PotD (spermidine/putrescine-binding periplasmic protein) and Crr [glucose-specific phosphotransferase (PTS) enzyme IIA component] as a stress-responsive protein. Even under a stress situation where the total number of soluble proteins decreased by about 10%, 3.5- and 2.2-fold increase was observed in the synthesis

of PotD and Crr, respectively. As fusion partners, PotD and Crr dramatically increased the solubility of many aggregation-prone heterologous proteins [e.g. human minipro-insulin (mp-INS), human epidermal growth factor (EGF), human prepro-ghrelin (ppGRN), human interleukin-2(hIL-2), human activation induced cytidine deaminase (AID), human glutamate decarboxylase (GAD(448-585)), *Pseudomonas putida* cutinase (CUT), human ferritin light chain (hFTN-L), human granulocyte colony-stimulating factor (G-CSF), and cold autoinflammatory syndrome1 protein (NALP3) Nacht domain (NACHT)] in the *E. coli* cytoplasm. Presumably PotD and Crr were very effective in shielding interactive surfaces of heterologous proteins associated with non-specific protein-protein interactions leading to the formation of inclusion bodies most likely due to intrinsic high folding efficiency, chaperone-like activity, or a combination of both factors. Both the stress-induced proteins were well suited for the production of a biologically active fusion mutant of *P. putida* cutinase that can be expected to be of biotechnological and commercial interest.

DOI: 10.1016/j.bbapap.2007.09.012

PMID: 17974510 [Indexed for MEDLINE]

3829. Eur J Clin Invest. 2007 Nov;37(11):912-4.

Anakinra in two adolescent female patients suffering from colchicine-resistant familial Mediterranean fever: effective but risky.

Gattringer R, Lagler H, Gattringer KB, Knapp S, Burgmann H, Winkler S, Graninger W, Thalhammer F.

DOI: 10.1111/j.1365-2362.2007.01868.x

PMID: 17973784 [Indexed for MEDLINE]

3830. Eur J Immunol. 2007 Nov;37 Suppl 1:S34-45.

Historical insights into cytokines.

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Cytokines affect nearly every biological process; these include embryonic development, disease pathogenesis, non-specific response to infection, specific response to antigen, changes in cognitive functions and progression of the degenerative processes of aging. In addition, cytokines are part of stem cell differentiation, vaccine efficacy and allograft rejection. This short insight focuses on the milestones in cytokine biology and how the various and often contradictory activities of these small, non-structural proteins affected the fields of inflammation and immunology. Multiple biological properties or pleiotropism is the hallmark of a cytokine. Today, the term "cytokine" encompasses interferons, the interleukins, the chemokine family, mesenchymal growth factors, the tumor necrosis factor family and adipokines. As of this writing, 33 cytokines are called interleukins, but many are part of families of related but distinct gene products. There are certainly over 100 separate genes coding for cytokine-like activities, many with overlapping functions and many still unexplored. Also discussed in this overview are the failures and successes of cytokines as therapeutic targets. A recent advance in the field has been that of differential cytokine production, which can be used to classify human disease as being "autoimmune" or "autoinflammatory" thus impacting on therapeutic interventions.

DOI: 10.1002/eji.200737772

PMCID: PMC3140102

PMID: 17972343 [Indexed for MEDLINE]

3831. Liver Int. 2008 Jan;28(1):140-2. Epub 2007 Oct 25.

Acute hepatitis in a patient with familial Mediterranean fever.

Migita K(1), Abiru S, Tanaka M, Ito M, Miyashita T, Maeda Y, Koga T, Nakamura M, Komori A, Yatsushashi H, Ida H, Eguchi K, Hirayama K, Yasunami M, Ishibashi H.

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Familial Mediterranean fever (FMF) is a hereditary syndrome characterized by recurrent episodes of fever and serositis. In this report, we describe a Japanese patient with FMF and Sjögren's syndrome, in whom acute elevations of transaminase occurred. The histological findings from the liver biopsy specimens demonstrated a nonspecific hepatitis, with liver cell necrosis and interlobular inflammatory cell invasion, without the presence of interface hepatitis or bile duct injury. This case underscores the possibility that MEFV mutations contribute to hepatic inflammation, as seen in this case, by way of an alteration of the pyrin function.

DOI: 10.1111/j.1478-3231.2007.01598.x

PMID: 17971092 [Indexed for MEDLINE]

3832. Tunis Med. 2007 Nov;85(11):913-9.

Usefulness of video-capillaroscopy in clinical practice: systematic review of indications and results in rheumatology and in non-rheumatic disorders.

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**BACKGROUND:** Nailfold video-capillaroscopy (VCP) is nowadays worldwide considered as one of the best diagnostic noninvasive imaging technique able to study microcirculation in vivo.

**AIM:** To review the applications of VCP in the clinical practice and its results in rheumatic and non-rheumatic diseases.

**METHODS:** Review of literature

**RESULTS:** The possibility of managing the imaging, by means of dedicated software able to characterize quantitative and qualitative data, represents another relevant property of VCP. This technique is very useful at the identification of microvascular involvement in many rheumatic diseases, particularly in systemic sclerosis and related disorders. At the same time, VCP has been showed valuable in many other extra-rheumatic diseases. The authors review the applications of VCP in the clinical practice and its results in rheumatic and non-rheumatic

diseases.

PMID: 19166140 [Indexed for MEDLINE]

3833. Arthritis Rheum. 2007 Nov;56(11):3805-13.

NOD2 gene-associated pediatric granulomatous arthritis: clinical diversity, novel and recurrent mutations, and evidence of clinical improvement with interleukin-1 blockade in a Spanish cohort.

Aróstegui JI(1), Arnal C, Merino R, Modesto C, Antonia Carballo M, Moreno P, García-Consuegra J, Naranjo A, Ramos E, de Paz P, Rius J, Plaza S, Yagüe J.

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**OBJECTIVE:** Blau syndrome and early-onset sarcoidosis are NOD2 gene-associated chronic autoinflammatory diseases characterized by skin rash, arthritis, and/or eye involvement, with noncaseating granulomata as their pathologic hallmark. This study was undertaken to describe the expanded clinical phenotype, treatment outcomes, and NOD2 gene mutation analysis in a Spanish cohort with pediatric granulomatous arthritis, a chronic disease resembling Blau syndrome/early-onset sarcoidosis.

**METHODS:** Clinical, laboratory, and treatment data on the 12 patients in the cohort were obtained through direct interviews. NOD2 gene analysis was performed in a central laboratory, by bidirectional sequencing. Cytokine levels were measured using the human Flex-Set cytokine bead array.

**RESULTS:** The classic Blau syndrome/early-onset sarcoidosis triad of skin rash, arthritis, and recurrent uveitis was identified in 5 patients (41.7%), whereas 7 patients (58.3%) presented with fewer than 3 of the classic features. Novel atypical manifestations such as persistent fever and myocardopathy were also observed. NOD2 analysis revealed 1 heterozygous mutation in each patient, and familial studies confirmed its full penetrance. Of the 12 cases, 58.3% were sporadic, due to de novo mutations. Four different missense mutations on exon 4 were detected. Two of them (R334W and R334Q) were recurrent mutations and were found in 77.8% of the Spanish families, whereas the other 2 (C495Y and R587C)

were novel. In the patient who received anakinra treatment, all clinical inflammatory symptoms improved and plasma cytokine levels normalized.  
CONCLUSION: These findings indicate that the expanding clinical heterogeneity of the disease (that is, the presentation of incomplete forms of the classic triad and atypical manifestations) and the high prevalence of sporadic cases should alert clinicians to the possible genetic basis of the condition and support the inclusion of DNA analysis as a diagnostic test. The positive response to anakinra observed in 1 patient suggests a new potential therapeutic approach that merits further investigation, and suggests that the pathogenesis of pediatric granulomatous arthritis may involve interleukin-1-mediated events.

DOI: 10.1002/art.22966

PMID: 17968944 [Indexed for MEDLINE]

3834. Arthritis Rheum. 2007 Nov;56(11):3879-80; author reply 3880.

Periodic fever and apoptosis of accumulated neutrophils in familial mediterranean fever: comment on the article by Touitou et al.

Yasui K, Yamazaki T.

Comment in

Arthritis Rheum. 2008 Jun;58(6):1883-4; author reply 1884.

Comment on

Arthritis Rheum. 2007 May;56(5):1706-12.

DOI: 10.1002/art.23032

PMID: 17968916 [Indexed for MEDLINE]

3835. Amyloid. 2007 Dec;14(4):271-5.

Analysis of SAA1 gene polymorphisms in the Greek population: rheumatoid arthritis and FMF patients relative to normal controls. Homogeneous distribution and low incidence of AA amyloidosis.

Mavragani CP(1), Yiannakouris N, Zintzaras E, Melistas L, Ritis K, Skopouli FN.

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**OBJECTIVE:** To address whether or not the rarity of amyloidosis in Greek patients with rheumatoid arthritis (RA) is related to specific alleles of single nucleotide polymorphisms (SNPs) in the 5'-flanking region and the exon 3 of the SAA1 gene.

**METHODS:** The genotypes of the -13T/C SNP in the 5'-flanking region of the SAA1 gene and the two SNPs within exon 3 of SAA1 (2995C/T and 3010C/T polymorphisms) were determined in 88 Greek patients with RA, 14 patients with familial Mediterranean fever (FMF) and 110 healthy controls. Linkage disequilibrium and haplotype frequencies involving -13T/C, 2995C/T and 3010C/T in these populations were tested and estimated, respectively.

**RESULTS:** The genotypic distribution and allelic frequencies were similar in all groups tested. SNPs 2995 and 3010 were in linkage disequilibrium for all study populations ( $p < 0.05$ ), whereas SNP -13 was not in linkage disequilibrium with either 2995 or 3010 ( $p > \text{or} = 0.05$ ). Two major haplotypes presented in all patients with RA and FMF and controls: -13C; 2995T; 3010C (-13C; alpha) and -13C; 2995C; 3010T (-13C; beta). The -13T allele was linked with the gamma haplotype in Greek patients with RA and controls. The frequency of the -13T allele was found to be very rare in all groups tested.

**CONCLUSIONS:** In conclusion, the rarity of the putative amyloidogenic -13T allele in Greek populations may be related to low prevalence of AA amyloidosis development in Greek RA patients.

DOI: 10.1080/13506120701614008

PMID: 17968686 [Indexed for MEDLINE]

3836. Rheumatology (Oxford). 2007 Dec;46(12):1865-6. Epub 2007 Oct 29.

Comment on: Failure of anti-TNF therapy in TNF receptor 1-associated periodic syndrome (TRAPS).

Drewe E, Powell RJ, McDermott EM.

Comment on

Rheumatology (Oxford). 2007 Jul;46(7):1211-2.

DOI: 10.1093/rheumatology/kem231

PMID: 17967816 [Indexed for MEDLINE]

3837. Free Radic Biol Med. 2008 Feb 1;44(3):386-93. Epub 2007 Oct 10.

Oxidative DNA damage in polymorphonuclear leukocytes of patients with familial Mediterranean fever.

Kirkali G(1), Tunca M, Genc S, Jaruga P, Dizdaroglu M.

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Familial Mediterranean fever (FMF) is an autosomal recessively inherited disorder characterized by recurrent, inflammatory self-limited episodes of fever and other symptoms. This disease is caused by more than 25 mutations in the gene MEFV. During fever attacks, there is a substantial influx of polymorphonuclear leukocytes into the affected tissues. Attack-free periods are accompanied by the up-regulation of neutrophil and monocyte phagocytic activity and oxidative burst. These facts led us to hypothesize that oxidative damage by free radicals to DNA may accumulate in FMF patients. To test this hypothesis, we investigated oxidative DNA damage in polymorphonuclear leukocytes of FMF patients during the attack-free period in comparison with FMF-free control individuals. DNA was isolated from polymorphonuclear leukocytes of 17 FMF patients and 10 control individuals. DNA samples were analyzed by liquid chromatography/mass spectrometry and gas chromatography/mass spectrometry to measure the levels of various typical oxidatively induced products of DNA. We show, for the first time, that FMF patients accumulate statistically significant levels of these lesions in their DNA when compared to FMF-free control individuals. This work suggests that the persistent oxidative stress with excess production of free radicals in FMF patients may lead to accumulation of oxidative DNA damage. Defective DNA repair may also contribute to this phenomenon, perhaps due to mutations in the MEFV gene. The accumulation of mutagenic and cytotoxic DNA lesions may contribute to increased mutations and apoptosis in FMF patients, thus to worsening of the disease and well-being of the patients. Future research should deal with



prevention of oxidative DNA damage and apoptosis in FMF patients, and also the elucidation of a possible role of DNA repair in this disease.

DOI: 10.1016/j.freeradbiomed.2007.09.020

PMID: 17967429 [Indexed for MEDLINE]

3838. Mol Cell. 2007 Oct 26;28(2):214-27.

Pyrin activates the ASC pyroptosome in response to engagement by autoinflammatory PSTPIP1 mutants.

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The molecular mechanism by which mutations in the cytoskeleton-organizing protein PSTPIP1 cause the autoinflammatory PAPA syndrome is still elusive. Here, we demonstrate that PSTPIP1 requires the familial Mediterranean fever protein pyrin to assemble the ASC pyroptosome, a molecular platform that recruits and activates caspase-1. We provide evidence that pyrin is a cytosolic receptor for PSTPIP1. Pyrin exists as a homotrimer in an autoinhibited state due to intramolecular interactions between its pyrin domain (PYD) and B-box. Ligation by PSTPIP1, which is also a homotrimer, activates pyrin by unmasking its PYD, thereby allowing it to interact with ASC and facilitate ASC oligomerization into an active ASC pyroptosome. Because of their high binding affinity to pyrin's B-box, PAPA-associated PSTPIP1 mutants were found to be more effective than WT PSTPIP1 in inducing pyrin activation. Therefore, constitutive ligation and activation of pyrin by mutant PSTPIP1 proteins explain the autoinflammatory phenotype seen in PAPA syndrome.

DOI: 10.1016/j.molcel.2007.08.029

PMCID: PMC2719761

PMID: 17964261 [Indexed for MEDLINE]

3839. Arch Dermatol Res. 2008 Jan;300(1):19-26. Epub 2007 Oct 25.

Relationship between periodontal findings and specific polymorphisms of interleukin-1alpha and -1beta in Turkish patients with Behçet's disease.

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Genetic factors predispose individuals to Behçet's disease (BD) and periodontal disease. IL-1 has been implicated in the pathogenesis of both BD and periodontal disease. The relationship between periodontitis and pathogenesis of BD has not yet been determined. Since IL-1 has been implicated in the pathogenesis of both BD and periodontal disease, we aimed to investigate the possible relation of the periodontal scores and SNPs of IL-1alpha-889C/T, IL-1beta-511C/T, and IL-1beta+3962T/C with BD compared to healthy controls (HC) and recurrent aphtous stomatitis (RAS). A total of 155 Turkish individuals were enrolled in this study. The periodontal status of all subjects was evaluated according to the WHO community periodontal index of treatment needs. For genotyping, CTS-PCR-SSP was employed. IL-1alpha-889C allele was significantly higher in BD patients ( $p = 0.03$ ) and RAS ( $p = 0.02$ ) compared to HC. The frequency of IL-1beta+3962T allele was significantly higher in RAS patients compared to HC ( $p = 0.015$ ). Male gender ( $p = 0.04$ ), age ( $p = 0.02$ ) and carrying IL-1beta-511T allele ( $p = 0.01$ ) were found to be a significant risk factors for higher periodontal scores in Turkish population. We can speculate that susceptibility to the development of periodontal disease could be influenced by IL-1 SNPs. Periodontitis-induced autoinflammatory response also may play a role in the development/severity of BD and RAS via IL-1 gene alteration.

DOI: 10.1007/s00403-007-0794-1

PMID: 17960403 [Indexed for MEDLINE]

3840. Neth J Med. 2007 Oct;65(9):318-24.

Familial Mediterranean fever: clinical, molecular and management advancements.

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Comment in

Neth J Med. 2008 Jun;66(6):261; author reply 261.

Familial Mediterranean fever (FMF), the most frequent of the periodic fever syndromes, is an autosomal recessive disease, predominantly affecting people of Mediterranean descent. The disease is caused by mutations in the MEFV gene, encoding the pyrin protein thought to be associated with the interleukin-1 related inflammation cascade. The condition manifests as attacks of serositis, commonly involving the abdomen, chest or joints, typically accompanied by fever and elevated acute phase reactants. Attacks subside spontaneously within one to three days, without residue. Continuous treatment with colchicine, at a daily dose of 1 to 2 mg, reduces attack frequency, duration and intensity in the majority of patients, and also prevents the development of secondary amyloidosis, the most dreaded complication of the disease. In this communication we review the current state of the art in the diagnosis and care of FMF patients, starting with the presentation of a typical case.

PMID: 17954950 [Indexed for MEDLINE]

3841. Joint Bone Spine. 2007 Dec;74(6):544-50. Epub 2007 Sep 20.

Auto inflammatory syndromes: Diagnosis and treatment.

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Hereditary recurrent fevers are rare genetic diseases characterized by apparently spontaneous attacks of inflammation. They include familial Mediterranean fever (FMF); tumor necrosis factor (TNF) receptor periodic syndrome (TRAPS); hyperimmunoglobulinemia D syndrome (HIDS); and hereditary periodic fevers related to mutations in the CIAS1 (cold induced autoinflammatory syndrome 1) gene, such as Muckle-Wells syndrome, familial cold urticaria, and CINCA/NOMID (chronic infantile neurological cutaneous and articular/neonatal-onset multisystemic inflammatory disease). Musculoskeletal manifestations are common. They may occur as features of the acute inflammatory attacks or persist for longer periods. Among them, the most common include arthritis of the large and medium-sized joints in FMF and CINCA, arthralgia in HIDS, and myalgia or pseudo-fasciitis in TRAPS. The outcome is usually favorable, although joint destruction may develop in CINCA or at the hip in FMF. The recurrent bouts of fever and accompanying clinical manifestations suggest the diagnosis, which can be confirmed by genetic testing. Among differential diagnoses, infection should be considered routinely. The treatment of the inflammatory attacks is nonspecific. New pathophysiological insights have led to the development of promising maintenance treatments designed to reduce the number and severity of the inflammatory attacks and to diminish the risk of secondary amyloidosis.

DOI: 10.1016/j.jbspin.2007.07.005

PMID: 17950649 [Indexed for MEDLINE]

3842. J Immunol. 2007 Nov 1;179(9):5644-8.

Cutting edge: Modulation of intestinal autoimmunity and IL-2 signaling by sphingosine kinase 2 independent of sphingosine 1-phosphate.

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Sphingosine kinase (Sphk) phosphorylates sphingosine into sphingosine-1-phosphate (S1P), but its recently identified isoform Sphk2 has been suggested to have

distinct subcellular localization and substrate specificity. We demonstrate here that, surprisingly, Sphk2(-/-) CD4(+) T cells exhibit a hyperactivated phenotype with significantly enhanced proliferation and cytokine secretion in response to IL-2 as well as reduced sensitivity to regulatory T cell-mediated suppression in vitro, apparently independent of effects upon S1P. Such findings appear to reflect a requirement for Sphk2 to suppress IL-2 signaling because, in Sphk2(-/-) CD4(+) T cells, IL-2 induced abnormally accentuated STAT5 phosphorylation and small interfering RNA knockdown of STAT5 abrogated their hyperactive phenotype. This pathway physiologically modulates autoinflammatory responses, because Sphk2(-/-) T cells induced more rapid and robust inflammatory bowel disease in scid recipients. Thus, Sphk2 regulates IL-2 pathways in T cells, and the modulation of Sphk2 activity may be of therapeutic utility in inflammatory and/or infectious diseases.

PMID: 17947634 [Indexed for MEDLINE]

3843. Rheumatology (Oxford). 2007 Nov;46(11):1718-22. Epub 2007 Oct 15.

Unique spectrum of MEFV mutations in Iranian Jewish FMF patients--clinical and demographic significance.

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**OBJECTIVES:** To determine the spectrum of mutations in the Mediterranean fever gene (MEFV) of Iranian Jews with familial Mediterranean fever (FMF) and to analyse their clinical manifestations.

**METHODS:** FMF patients with both parents of Iranian-Jewish (IJ) extraction or with one IJ parent (IJ-other, 10 of each) were characterized for clinical manifestations, and the B30.2 (PRYSPRY) domain of their MEFV was sequenced for mutations.

**RESULTS:** Only one rare mutation, R653H, and one new mutation, G632S were present in the IJ group (in 2/10 patients), whereas the new, and common mutations were present in the IJ-other patients (8/10 patients). The new mutation was traced

thrice to an IJ ancestor, and although carried asymptotically by family members, it was over-represented in the patients (3/28 unrelated IJ alleles) compared non-affected IJ subjects (1/126 alleles,  $P = 0.03$ ) or with non-Jewish Iranians (0/108 alleles,  $P = 0.001$ ). The mutation was associated with a distinct phenotype regarding sites involved in the attack ( $P = 0.001$ ), mild severity, sole expression of febrile episodes ( $P = 0.01$ ) and a male bias ( $P = 0.01$ ). In two 3D PRYSPRY models the G632S mutation was localized to a surface loop and close to a putative binding site.

CONCLUSIONS: Iranian Jews with FMF have a unique spectrum of mutations including a newly described mutation with a non-typical phenotype.

DOI: 10.1093/rheumatology/kem228

PMID: 17938136 [Indexed for MEDLINE]

3844. Rheum Dis Clin North Am. 2007 Aug;33(3):585-623.

Auto-inflammatory fever syndromes.

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Republished from

Pediatr Clin North Am. 2005 Apr;52(2):577-609, vii.

Human autoinflammatory diseases (except for PFAPA) are a heterogeneous group of genetically determined diseases characterized by seemingly unprovoked inflammation in the absence of autoimmune or infective causes (Table 2). The last decade has witnessed tremendous advances in the understanding of these disorders. These advances have allowed therapeutic interventions resulting in improvement in the short-term and long-term morbidity of all of these diseases. Future research into the molecular mechanisms underlying these inflammatory diseases should lead to a better understanding of inflammatory diseases in general and, it is hoped, to better and more targeted therapies.

DOI: 10.1016/j.rdc.2007.07.009

PMID: 17936178

3845. Ann Rheum Dis. 2007 Nov;66(11):1545-6.

Effective treatment of a colchicine-resistant familial Mediterranean fever patient with anakinra.

Kuijk LM, Govers AM, Frenkel J, Hofhuis WJ.

DOI: 10.1136/ard.2007.071498

PMCID: PMC2111630

PMID: 17934085 [Indexed for MEDLINE]

3846. Ann Rheum Dis. 2007 Nov;66(11):1541.

Coexistent MEFV and CIAS1 mutations manifesting as familial Mediterranean fever plus deafness.

Singh-Grewal D, Chaitow J, Aksentijevich I, Christodoulou J.

DOI: 10.1136/ard.2007.075655

PMCID: PMC2111617

PMID: 17934081 [Indexed for MEDLINE]

3847. MMWR Morb Mortal Wkly Rep. 2007 Oct 12;56(40):1050-2.

Deaths from intravenous colchicine resulting from a compounding pharmacy error--Oregon and Washington, 2007.

Centers for Disease Control and Prevention (CDC).

Colchicine for injection has been available in the United States since the 1950s. Although not approved by the Food and Drug Administration (FDA), intravenous (IV) colchicine has been an accepted treatment for acute gout symptoms. Several additional IV uses have been studied, including treatment of familial Mediterranean fever, pericarditis, primary biliary cirrhosis, amyloidosis, and

Behçet's syndrome. More recently, outpatient use of IV administration for chronic back pain has been advocated by alternative medicine providers but is not an accepted practice. Colchicine has well-known toxicities that limit its safe therapeutic use. IV doses that exceed the standard single-use therapeutic dose of 2--4 mg per episode of gout have resulted in life-threatening toxicity. In March 2007, two persons from Washington and Oregon died after receiving IV colchicine for back pain from an alternative medicine clinic in Oregon. This report describes the investigation, which determined that a measuring error by a Texas compounding pharmacy resulted in a fatal colchicine concentration that was eight times greater than the recognized standard level. A subsequent review of medical records revealed that a third death from colchicine toxicity in a patient treated at the Oregon clinic also occurred in March and likely was associated with the same compounding error. These deaths highlight the potential risk from use of IV colchicine for back pain and the possibly fatal consequences of measuring errors in compounding pharmacy products.

PMID: 17932481 [Indexed for MEDLINE]

3848. Clin Exp Dermatol. 2008 Jan;33(1):1-9. Epub 2007 Oct 9.

Cryopyrin-associated periodic syndromes and autoinflammation.

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Autoinflammatory syndromes are a distinct class of inherited diseases of cytokine dysregulation with important cutaneous features. Several disorders, including familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome and neonatal onset multisystem inflammatory disorder (NOMID), are associated with mutations in a common gene, CIAS-1. These disorders are now believed to represent related conditions along a spectrum of disease severity, in which FCAS is the mildest and NOMID is the most severe phenotype. Patients typically present with lifelong atypical urticaria with systemic symptoms, with potential for developing end-organ damage due to chronic inflammation. Advances in the understanding of the genetic basis of these syndromes have also revealed cytokine signalling



molecules that are critical to normal regulation of inflammatory pathways. The dramatic response of these syndromes to anakinra, an interleukin (IL)-1 antagonist, highlights the important role of IL-1 cytokine signalling in the pathogenesis of this rare but fascinating class of diseases.

DOI: 10.1111/j.1365-2230.2007.02540.x

PMID: 17927785 [Indexed for MEDLINE]

3849. Clin Rheumatol. 2008 Jun;27(6):689-94. Epub 2007 Oct 10.

The evaluation of carotid intima-media thickness in children with familial Mediterranean fever.

Peru H(1), Altun B, Doğan M, Kara F, Elmaci AM, Oran B.

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The aim is to investigate whether pediatric familial Mediterranean fever (FMF) patients have an increased risk of premature atherosclerosis and to determine the possible strength of association between atherosclerosis and Mediterranean fever (MEFV) gene mutation gene type. Demographic characteristics and MEFV mutations were defined in 49 children diagnosed with FMF (26 female, 23 male; mean age, 10.71 +/- 3.69 years). Twenty-six age-, sex-, and body-mass-index-matched healthy children constituted the control group. We evaluated the blood counts and acute-phase proteins during attack-free periods. Mean C-reactive protein (CRP), serum amyloid-A (SAA), homocysteine (Hcy), lipoprotein-a (Lp-a), and common carotid artery intima-media thickness (CCA-IMT) were 10.75 +/- 15.29 vs 4.03 +/- 1.20, 23.22 +/- 41.94 vs 3.53 +/- 1.04, 10.36 +/- 3.36 vs 8.64 +/- 3.15, 20.84 +/- 23.89 vs 8.56 +/- 7.48, and 0.038 +/- 0.007 vs 0.032 +/- 0.004, respectively, and significantly higher than the mean values of control group ( $p < 0.05$ ). However, no correlation was found between CCA-IMT and CRP, SAA, Hcy, and Lp-a. Twenty-nine patients had M694V mutation, and 13 patients had other mutations. There was no correlation between CCA-IMT and MEFV mutation subgroups. In conclusion, because of the nature of the disease, FMF patients should be considered to have an increased risk of early vascular alteration and atherosclerosis. For this reason, CCA-IMT measurement can be recommended as a

noninvasive and early diagnostic method.

DOI: 10.1007/s10067-007-0764-1

PMID: 17926078 [Indexed for MEDLINE]

3850. J Clin Rheumatol. 2007 Oct;13(5):300-1.

Generalized nonspecific pustular lesions in Tietze's syndrome.

Karabudak O(1), Nalbant S, Ulusoy RE, Dogan B, Harmanyeri Y.

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DOI: 10.1097/RHU.0b013e3181581e1b

PMID: 17921807 [Indexed for MEDLINE]

3851. Ann Rheum Dis. 2008 Oct;67(10):1382-9. Epub 2007 Oct 5.

Inflammasomes and rheumatic diseases: evolving concepts.

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The realisation that the production of inflammatory cytokines in inflammatory rheumatic diseases may be induced by non-infectious endogenous signals has encouraged researchers to explore mechanisms of innate immunity and their contribution to the pathogenesis of these diseases. The nucleotide-binding and oligomerisation domain (NOD)-like receptors (NLRs) sense pathogens, products of damaged cells or endogenous metabolites and could potentially be involved in the initiation, amplification and progression of the inflammatory response in rheumatic diseases. NLRs are involved in the regulation of innate immune

responses with some of them promoting the activation of inflammatory caspases within multiprotein complexes, called inflammasomes. A typical inflammasome consists of a sensor, an NLR protein, an adaptor protein such as ASC (for apoptosis-associated speck-like protein containing a caspase recruitment domain (CARD)) and an effector protein that is a caspase that activates pro-inflammatory cytokines such as interleukin (IL)1 $\beta$  and IL18. Recent data suggest a role of the inflammasome in the pathogenesis of autoinflammatory as well as inflammatory rheumatic diseases such as juvenile chronic arthritis, adult onset Still disease, rheumatoid arthritis and gout. Modulation of these pathways may be a potential therapeutic target for inflammatory rheumatic diseases.

DOI: 10.1136/ard.2007.078014

PMID: 17921182 [Indexed for MEDLINE]

3852. Ann N Y Acad Sci. 2007 Sep;1110:201-8.

Genetics and new treatment modalities for familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is the most common of a rare group of disorders collectively termed familial hereditary periodic fever syndromes, also known as autoinflammatory syndromes. FMF is clinically characterized by intermittent bouts of fever with peritonitis and abdominal pain, pleuritis, arthritis, or erysipelas-like rashes. Amyloidosis due to chronic inflammation progressing to renal failure is one of the most serious potential complications of this disease. Individuals with FMF have identifiable genetic defects in the Mediterranean fever (MEFV) gene, which codes for the protein pyrin. Pyrin normally blunts neutrophil-mediated inflammation, likely via interleukin-1 (IL-1) downregulation, but is defective in FMF. Potential treatments include colchicine, with case reports of benefits with catecholamine blockade (prazosin), tumor necrosis factor (TNF) antagonism (etanercept, thalidomide), and IL-1 receptor blockade (anakinra).

DOI: 10.1196/annals.1423.022

PMID: 17911435 [Indexed for MEDLINE]

3853. Rev Invest Clin. 2007 May-Jun;59(3):212-8.

[Non-surgical acute abdomen as a clinical expression of Mediterranean famililal fever].

[Article in Spanish]

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PMID: 17910414 [Indexed for MEDLINE]

3854. Recenti Prog Med. 2007 Sep;98(9):457-70.

[Autoinflammatory syndromes: inborn errors of natural immunity].

[Article in Italian]

Colina M(1), Govoni M, De Leonardis F, Bernardi S, Volpinari S, Limpido G, Trotta F.

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The notion of autoinflammatory diseases delineates a heterogenous group of genetic pathologies characterized by spontaneous periodic systemic inflammation in the absence of infectious or autoimmune causes. The general hypothesis is that the innate immune response in these patients is wrongly tuned, being either too

sensitive to minor stimuli or turned off too late. Clinical pictures of these disorders are characterized by high spiking fever associated with involvement of musculo-skeletal system, tegumentary apparatus and serosas. Although inflammatory syndromes are considered rare, they may represent a model in order to unravel some aspects of the innate immune system and of the inflammatory cascade.

PMID: 17902572 [Indexed for MEDLINE]

3855. Reumatismo. 2007 Jul-Sep;59(3):244-61.

[Biological therapy with TNF-inhibitors in pediatric rheumatology. Review of the literature and personal experience].

[Article in Italian]

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The therapeutic approach to JIA is sometimes very troublesome and progression to erosive polyarthritis may occur in all JIA categories. Only Methotrexate has shown efficacy and safety in a large controlled trial. Nevertheless, in many cases, drug resistance or intolerance has led to try other therapeutic options, with still debatable results. Therefore, there has been space, in the last few years, for new therapies as the TNF-inhibitors. This therapeutic approach has shown a dramatic clinical benefit in active polyarticular refractory JIA: the rate and rapidity of response have exceeded those of all other studied DMARDs. Preliminary data show that they are efficacious also for other pediatric rheumatic disease (spondyloarthropathies, autoimmune uveitis, dermatomyositis, Kawasaki syndrome and some autoinflammatory diseases). TNF-inhibitors in JIA have demonstrated a favourable benefit-to-risk profile. However, as their use has increased worldwide, some unusual, usually not serious, adverse events have emerged. Severe infections, including TB, and deaths have been reported. Long-lasting active disease, systemic disease, concurrent and previous immunosuppressive therapies, all contribute to risk of infection and other

serious AEs. Given the evidence that TNF has a primary role in the pathogenesis of JIA, particularly in joint destruction, neutralizing this cytokine early, within the window of opportunity, could halt or delay progression of joint damage and debilitating consequences of the disease. Thus, for JIA patients whose disease is not quickly controlled with MTX, TNF blockers may be considered as first-line treatment, although long-term safety data still need to be established.

PMID: 17898886 [Indexed for MEDLINE]

3856. Mol Pharmacol. 2007 Dec;72(6):1402-5. Epub 2007 Sep 25.

Go it alone no more--P2X7 joins the society of heteromeric ATP-gated receptor channels.

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Comment on

Mol Pharmacol. 2007 Dec;72(6):1447-56.

P2X receptors (P2XR) function as ATP-gated nonselective ion channels permeable to Na<sup>+</sup>, K<sup>+</sup>, and Ca<sup>2+</sup>, and they are expressed in a wide range of excitable, epithelial/endothelial, and immune effector cell types. The channels are trimeric complexes composed of protein subunits encoded by seven different P2XR genes expressed in mammalian and other vertebrate genomes. Current genetic, biochemical, and/or physiological evidence indicates that the extended family of functional P2X receptors includes six homomeric channels composed of P2X1, P2X2, P2X3, P2X4, P2X5, or P2X7 subunits and six heteromeric channels that involve subunit pairings of P2X1/P2X2, P2X1/P2X4, P2X1/P2X5, P2X2/P2X3, P2X2/P2X6, or P2X4/P2X6. Thus, all P2XR subtypes--with the salient exception of P2X7R--have previously been implicated in the assembly of heteromeric ATP-gated ion channels that can comprise unique pharmacological targets in different tissues. The assumed "go-it alone" function of the P2X7R has important implications because

agents that target this particular receptor have been proposed as useful therapeutics in various autoinflammatory diseases or amelioration of inflammatory pain. However, this assumption and the interpretations based on it now require reevaluation in light of a new report in this issue of *Molecular Pharmacology* (p. 1447) that provides convincing biochemical and electrophysiological evidence for the existence of P2X4/P2X7 heteromeric receptors.

DOI: 10.1124/mol.107.042077

PMID: 17895406 [Indexed for MEDLINE]

3857. *J Autoimmun.* 2007 Dec;29(4):272-80. Epub 2007 Sep 21.

Regulatory T cells in the prevention of mucosal inflammatory diseases: patrolling the border.

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Regulatory T (Treg) cells are important contributors to the maintenance of immune tolerance in the periphery, and deficiency of Tregs is associated with various immunopathic diseases. Murine models of autoimmune and autoinflammatory disorders have helped to elucidate how Tregs are involved in these diseases. A feature in common between human and mice that lack one or another of the key Treg subsets is the occurrence of mucosal inflammation. The relatively fragile mucosal surface represents a complex system that is normally well equipped to ward off harmful pathogens yet at the same time is inhibitory to destructive inflammatory responses to biologically needed (probiotic) microorganisms, or other common environmental antigens e.g. nutrients. We here discuss the importance of Tregs in maintaining tolerance at mucosal surfaces and the outcomes of deficiency of Treg function. The intestinal tract and its inflammatory diseases provide the "point of departure" for discussion, but similar considerations could apply to other mucosal linings exposed to the environment such as other members of the digestive system. However, the lungs, bile ducts, urogenital tract and other mucosal surfaces are susceptible to poorly understood inflammatory states that possibly

depend on dysfunction of Treg cells. Finally there are now potential therapies predicated on reconstitution of effective function of Treg cells.

DOI: 10.1016/j.jaut.2007.07.021

PMCID: PMC2692919

PMID: 17889505 [Indexed for MEDLINE]

3858. N Engl J Med. 2007 Sep 13;357(11):1153; author reply 1153-4.

Eprodisate in AA amyloidosis.

Manenti L, Tansinda P, Vaglio A.

Comment on

N Engl J Med. 2007 Jun 7;356(23):2361-71.

N Engl J Med. 2007 Jun 7;356(23):2349-60.

DOI: 10.1056/NEJMc071922

PMID: 17855678 [Indexed for MEDLINE]

3859. Trends Mol Med. 2007 Sep;13(9):381-8. Epub 2007 Sep 5.

From inflammasomes to fevers, crystals and hypertension: how basic research explains inflammatory diseases.

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Pattern-recognition receptors, such as Toll-like receptors and NOD-like receptors (NLRs), are able through the recognition of pathogen-associated molecular patterns and danger-associated molecular patterns to sense microbe-dependent and microbe-independent danger and thereby initiate innate immune responses. In some autoinflammatory conditions, abnormalities in NLR signaling pathways are involved in pathogenesis, as exemplified by NOD2 mutations associated with Crohn's



disease. Some other NLRs are components of the inflammasome, a caspase-1- and prointerleukin-1 $\beta$ -activating complex. Clinical and experimental studies are beginning to reveal the central role of the inflammasome in innate immunity. Here, we focus on monogenic hereditary inflammatory diseases, such as Muckle-Wells syndrome, which are associated with mutations in proteins that modulate the activity of the inflammasome, and on some multifactorial disorders, such as Type 2 diabetes and hypertension.

DOI: 10.1016/j.molmed.2007.07.005

PMID: 17822957 [Indexed for MEDLINE]

3860. Semin Immunopathol. 2007 Sep;29(3):303-13. Epub 2007 Sep 6.

The NLR network and the immunological disease continuum of adaptive and innate immune-mediated inflammation against self.

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The nucleotide-binding domain, leucine-rich repeat containing family (NLR) network has provided pivotal genetic and molecular insights into diseases that were hitherto regarded as autoimmune. The NLR-related disorders include rare monogenic autoinflammatory diseases collectively termed cryopyrin-associated periodic syndromes, Crohn's disease which is a common polygenic disease and also an association at the mechanistic level with gout and pseudogout. Unlike the classical autoimmune diseases where disease immunopathogenesis is played out primarily in the primary and secondary lymphoid organs, the immunopathogenesis of the NLR-related disorders is played out in the tissues where inflammation arises. As the genetic mutations or molecular cascades associated with the NLR-related disorders have a widespread cellular distribution, it has been somewhat enigmatic why these disorders attack certain territories, but not others. This implies that tissue-specific factors in the target organs themselves contribute to disease expression. Such examples include the high abundance of NOD2 expressing cells in the part of the gut most typically afflicted by Crohn's disease and the

preferential deposition of crystals in the joints to where inflammation localises in gout and pseudogout. The NLR network is associated principally with increases in TNF or IL-1 production, both of which are key players in innate immunity. Therefore, the NLR network identifies at the genetic and molecular level a robust paradigm for innate immune activation against self. This tissue-specific-factor-associated inflammation is the diametric opposite of classical autoimmunity. Of note, the MHC class-I-associated diseases including psoriasis (HLA-Cw6) and ankylosing spondylitis (HLA-B27) show striking clinical overlaps with Crohn's disease and also some rare monogenic diseases. Thus, the NLR innate immune pathway allows the full spectrum of inflammation against self to be viewed along an immunological disease continuum with autoantibody-associated disease at one end, innate immune diseases at the other and MHC class-I-related disorders as an intermediate.

DOI: 10.1007/s00281-007-0084-1

PMID: 17805542 [Indexed for MEDLINE]

3861. Rheumatology (Oxford). 2007 Oct;46(10):1597-600. Epub 2007 Sep 5.

Diagnostic value of serum immunoglobulinaemia D level in patients with a clinical suspicion of hyper IgD syndrome.

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**OBJECTIVE:** The hyperimmunoglobulinaemia D and periodic fever syndrome (HIDS) was originally defined by the presence of a high serum level of immunoglobulin D associated with recurrent fever. Since the discovery of the mevalonate kinase gene (MVK) gene encoding the mevalonate kinase enzyme, most patients with a clinical diagnostic of HIDS are now found to have a mevalonate kinase deficiency based on metabolic and genetic data. We aimed to assess the value of a high IgD serum level for the diagnosis of HIDS in a cohort of patients with a phenotype of recurrent fever, and to characterize patients with a high IgD serum level without mevalonate kinase mutation.

**METHODS:** Main clinical and biological data of 50 patients who presented with clinical signs compatible with HIDS have been prospectively registered on a

standard form. Clinical data have been analysed according the IgD serum level and the presence of MVK mutation.

**RESULTS:** The metabolic and genetic data establishing the diagnosis of HIDS correlated in all cases. In this series of 50 patients, the sensitivity of a high IgD value for the diagnosis of HIDS is 0.79. In five patients with MVK mutation, IgD levels were found to be in the normal range. Likelihood ratios indicate that IgD measurement is not relevant for the diagnostic of HIDS. Most patients with a high serum IgD level and no MVK mutation have no definite diagnosis.

**CONCLUSION:** The clinical relevance of the IgD measurement for the diagnosis of MKD in our population appears as poor, as reflected by likelihood ratios which are both close to 1.

DOI: 10.1093/rheumatology/kem200

PMID: 17804452 [Indexed for MEDLINE]

3862. Scand J Rheumatol. 2007 Jul-Aug;36(4):307-10.

Serum macrophage migration inhibitory factor (MIF) in the intercritical phase of hereditary periodic fevers and its relationship with the MIF-173G/C polymorphism.

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**OBJECTIVES:** To examine the association of the -173 single-nucleotide G/C polymorphism of the macrophage migration inhibitory factor gene (MIF) and serum macrophage migration inhibitory factor (MIF) concentrations in a group of Italian patients with hereditary periodic fevers (HPF), tested during a symptom-free phase of their disease.

**METHODS:** Genomic DNA for MIF and serum MIF were evaluated in 22 patients with HPF and compared with healthy controls of the same ethnic group. The MIF-173G/C polymorphism was genotyped using polymerase chain reaction (PCR) and visualized by ethidium bromide staining. Serum MIF levels were measured by enzyme-linked immunosorbent assay (ELISA).

**RESULTS:** MIF-173\*C allele frequency and MIF serum concentrations were

significantly higher in patients with HPF than in controls, with no statistically significant difference between familial Mediterranean fever (FMF) and hyperimmunoglobulinaemia D/periodic fever syndrome (HIDS) and no correlation with specific MIF genotypes.

CONCLUSIONS: The MIF-173\*C allele was found more frequently in patients with HPF than in controls and MIF serum concentrations were considerably elevated in attack-free phases, suggesting a persistent state of subclinical cytokine activation with MIF involvement in the autoinflammatory cascade.

DOI: 10.1080/03009740701218816

PMID: 17763209 [Indexed for MEDLINE]

3863. Nat Clin Pract Rheumatol. 2007 Sep;3(9):512-20.

Primer: the practical use of biological markers of rheumatic and systemic inflammatory diseases.

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The assessment of systemic inflammation by means of laboratory tests often complements the results of medical examination. Traditionally, the erythrocyte sedimentation rate and leukocytosis with left shift are diagnostic markers for inflammatory and infectious diseases. The levels of acute-phase proteins--especially C-reactive protein--are used to assess both the presence of inflammation and any response to treatment. The determination of C-reactive protein levels may be advised in three types of pathological situation: infection, acute or chronic inflammation, and evaluation of metabolic risk. Procalcitonin is useful as a marker of sepsis and severe infection. The concentration of serum amyloid A predicts the chances of survival of patients with secondary (AA) amyloidosis. Ferritin and its glycosylated form are of interest in the study of specific diseases such as adult-onset Still's disease. Markers of cartilage and bone turnover are complementary to these markers of inflammation. Although cytokine serum levels are transiently crucial to the generation of inflammation, their usefulness in the clinic is still under

investigation. Serum concentrations of cytokine inhibitors or soluble cytokine receptors, as well as the clinical response of patients to treatment with cytokine antagonists, might generate important information for monitoring autoinflammatory diseases.

DOI: 10.1038/ncprheum0572

PMID: 17762850 [Indexed for MEDLINE]

3864. Curr Opin Rheumatol. 2007 Sep;19(5):492-8.

Autoinflammatory bone disorders.

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**PURPOSE OF REVIEW:** This review provides an update on clinical, genetic, and immunologic aspects of the autoinflammatory bone disorders.

**RECENT FINDINGS:** Chronic noninfectious inflammation of the bone is a clinical feature of both chronic recurrent multifocal osteomyelitis and (to a lesser degree) cherubism. The genes responsible for Majeed syndrome (LPIN2), murine chronic multifocal osteomyelitis (pstpip2), and cherubism (SH3BP2 and possibly PTPN11) have been identified. Murine models of both chronic recurrent multifocal osteomyelitis and cherubism have demonstrated that the bone inflammation is mediated by hematopoietically derived cells and can occur in the absence of a functioning adaptive immune system. As the immunologic defects become better defined, the cells of the myeloid lineage are emerging as the primary players.

**SUMMARY:** Chronic multifocal osteomyelitis and cherubism are hereditary chronic inflammatory disorders in which bone is the primary inflammatory target. Recent genetic and immunologic discoveries demonstrate involvement of the innate immune system, which places these entities in the category of autoinflammatory disorders.

DOI: 10.1097/BOR.0b013e32825f5492

PMID: 17762617 [Indexed for MEDLINE]

3865. Anticancer Drugs. 2007 Jul;18(6):733-5.

Adjuvant chemotherapy with 5-fluorouracil in a patient with colorectal cancer and Familial Mediterranean Fever.

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Colorectal cancer is a common malignancy often requiring adjuvant chemotherapy. Familial Mediterranean Fever is a chronic hereditary disease which is relatively prevalent in the Middle East and is associated with recurrent episodes of serosal, synovial or cutaneous inflammations. The aim of this paper was to describe a patient with Familial Mediterranean Fever who received fluorouracil-based adjuvant chemotherapy for colorectal cancer. A 56-year-old man with Familial Mediterranean Fever and amyloidosis was referred for evaluation and treatment following surgery for colorectal cancer. In light of his relatively young age, good general state of health and apparently well-controlled Familial Mediterranean Fever, he was treated with chemotherapy consisting of four cycles of 5-fluorouracil and leucovorin. The patient's clinical course during chemotherapy was unremarkable except for one minor attack of Familial Mediterranean Fever. The patient's follow-up was notable for periodic fluctuations in serum carcinoembryonic antigen levels, up to 4-fold of normal. The Familial Mediterranean Fever remained stable. Although our patient showed a good tolerability of treatment, the administration of chemotherapy to patients with Familial Mediterranean Fever raises several concerns. These include a potential deterioration in the Familial Mediterranean Fever status owing to chemotherapy-induced stress, the potential effect of Familial Mediterranean Fever or its treatment on the tolerability of chemotherapy and an overlapping toxicity of the drugs used to treat the two diseases. An increase in serum carcinoembryonic antigen in this setting may be related to the underlying pathophysiologic mechanism of Familial Mediterranean Fever but does not necessarily indicate disease recurrence. Clinicians should be aware of these issues considering the recent worldwide increase in colorectal cancer.

DOI: 10.1097/CAD.0b013e32803a46ea

PMID: 17762405 [Indexed for MEDLINE]

3866. J Dermatol. 2007 Sep;34(9):601-18.

Autoinflammatory syndromes with a dermatological perspective.

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The term autoinflammatory syndromes describes a distinct group of systemic inflammatory diseases apparently different from infectious, autoimmune, allergic and immunodeficient ones. Originally, it was almost synonymous with clinically defined hereditary periodic fever syndromes, including familial Mediterranean fever, hyper immunoglobulin D syndrome with periodic fever and tumor necrosis factor receptor-associated periodic syndrome. Similar but distinct periodic fever syndromes accompanied by urticarial rash, familial cold autoinflammatory syndrome, Muckle-Wells syndrome and chronic infantile neurological cutaneous articular syndrome, have all been reportedly associated with CIAS1 mutations and are collectively called cryopyrin-associated periodic syndromes. Consequently, the concept of autoinflammatory syndromes has been spread to contain other systemic inflammatory diseases: rare hereditary diseases with or without periodic fevers, such as pyogenic sterile arthritis, pyoderma gangrenosum and acne syndrome, Blau syndrome and chronic recurrent multifocal osteomyelitis, and the more common collagen disease-like diseases, such as Behcet's disease, Crohn's disease, sarcoidosis and psoriatic arthritis. These diseases are all caused by or associated with mutations of genes regulating innate immunity and have common clinical features accompanied with activation of neutrophils and/or monocytes/macrophages. In this review, major autoinflammatory syndromes are summarized and the pathophysiology of related skin disorders is discussed in association with dysregulated innate immune signaling.

DOI: 10.1111/j.1346-8138.2007.00342.x

PMID: 17727363 [Indexed for MEDLINE]

3867. J Pediatr. 2007 Sep;151(3):289-92. Epub 2007 Jun 14.

A randomized, controlled trial of tonsillectomy in periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome.

Renko M(1), Salo E, Putto-Laurila A, Saxen H, Mattila PS, Luotonen J, Ruuskanen O, Uhari M.

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Comment in

J Pediatr. 2008 May;152(5):742; author reply 743.

J Pediatr. 2008 May;152(5):742-3; author reply 743.

J Pediatr. 2008 Aug;153(2):298.

**OBJECTIVE:** We carried out a prospective, randomized, controlled trial to clarify the effect of tonsillectomy on the clinical course of periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome.

**STUDY DESIGN:** Twenty-six consecutive children (mean age 4.1 years) with at least 5 PFAPA attacks were recruited from 3 tertiary care pediatric hospitals during 1999-2003 and randomly allocated to tonsillectomy or follow-up alone. They were all followed up with symptom diaries for 12 months. Tonsillectomy was allowed after 6 months in the control group if the attacks recurred.

**RESULTS:** Six months after randomization all 14 children in the tonsillectomy group and 6/12 children in the control group (50%) were free of symptoms (difference 50%, 95% confidence interval 23% to 75%,  $P < .001$ ). Tonsillectomy was performed on 5/6 of the patients in the control group who still had symptoms after 6 months. The remaining unoperated child in the control group had recurrences of the fever episodes throughout the follow-up, but the symptoms became less severe, and the parents did not choose tonsillectomy.

**CONCLUSION:** Tonsillectomy appeared to be effective for treating PFAPA syndrome. The fever episodes ceased without any intervention in half of the control subjects. We conclude that although the mechanisms behind this syndrome are unknown, tonsillectomy can be offered as an effective intervention for children with PFAPA.

DOI: 10.1016/j.jpeds.2007.03.015

PMID: 17719940 [Indexed for MEDLINE]



3868. Joint Bone Spine. 2007 Dec;74(6):571-6. Epub 2007 Aug 21.

The inflammasome, autoinflammatory diseases, and gout.

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IL-1beta is a cytokine with major roles in inflammation and innate immune responses. IL-1beta is produced as an inactive proform that must be cleaved within the cell to generate biologically active IL-1beta. The enzyme caspase-1 catalyzes the reaction. Recent work showed that caspase-1 must be activated by a complex known as the inflammasome. The inflammasome comprises NALP, which is an intracellular receptor involved in innate immunity, and an ASC adapter that ensures caspase-1 recruitment to the receptor. The most extensively described inflammasome to date is formed by the NALP3 receptor within monocytes. Mutations involving the NALP3 gene cause hereditary periodic fever syndromes in humans. Increased inflammasome activity responsible for uncontrolled IL-1beta production occurs in these syndromes. Inhibition of the IL-1beta pathway by IL-1 receptor antagonist (anakinra) is a highly effective treatment for inherited periodic fever syndromes. A major role for inflammasome activity in the development of gout attacks was established recently. Urate monosodium crystals are specifically detected via the NALP3 inflammasome, which results in marked IL-1beta overproduction and initiation of an inflammatory response. This finding opens up new possibilities for the management of gouty attacks.

DOI: 10.1016/j.jbspin.2007.04.004

PMID: 17714972 [Indexed for MEDLINE]

3869. Am J Hematol. 2008 Feb;83(2):165-6.

Severe Henoch-Schönlein purpura in a thalassemic patient under deferiprone treatment.

Unal S(1), Gücer S, Kale G, Besbas N, Ozen S, Gümrük F.

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Herein we present a 7-year-old beta-thalassemia major patient who developed severe Henoch-Schönlein purpura (HSP) with renal, pulmonary involvement and invagination while under iron chelation with deferiprone. DNA analysis for familial Mediterranean fever revealed M696V mutation. Various cellular and humoral immunological impairments have been described in thalassemia major patients and the severe course of HSP in our case may be related to these underlying immunological defects.

DOI: 10.1002/ajh.21052

PMID: 17712793 [Indexed for MEDLINE]

3870. Ann Hum Genet. 2008 Jan;72(Pt 1):41-7. Epub 2007 Aug 16.

Familial Mediterranean Fever in Lebanon: founder effects for different MEFV mutations.

Jalkh N(1), Génin E, Chouery E, Delague V, Medlej-Hashim M, Idrac CA, Mégarbané A, Serre JL.

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Haplotype analysis of 376 Familial Mediterranean Fever (FMF) patients and 100 controls from Lebanon was performed using 4 microsatellite loci to study founder effects for the five most frequent mutations within the MEFV gene (M694V, M694I, V726A, M680I and E148Q). Each of these mutations was associated with a particular haplotype that was less frequent among controls, confirming that they have probably arisen from unique mutation events and that the carrier chromosomes derived from a common ancestor. The estimated ages of the most recent common ancestor for each of the 5 mutations, using the ESTIAGE program, were 7000, 8500, 15000, 23000 and 30000 years for M694V, M694I, V726A, M680I and E148Q,

respectively. Varying the mutation rate at one of the markers led to younger age estimates, but the mutation E148Q remained the oldest one. Comparison of haplotype distributions among the different Lebanese religious groups confirmed that Muslim sub-populations (Shiites and Sunnites) as well as Christian ones, including Armenians who were formerly settled in the South-Eastern part of Asia Minor (Cilicia), are all derived from an ancient common ancestral population in which most of the MEFV mutations were already present with their respective associated haplotypes.

DOI: 10.1111/j.1469-1809.2007.00386.x

PMID: 17711558 [Indexed for MEDLINE]

3871. Genet Couns. 2007;18(2):259-62.

Co-occurrence of familial Mediterranean fever (FMF) heterozygote mutation and nail-patella syndrome (NPS) in 3 members of a family with LMX1B mutation analysis.

Balci S, Engiz O.

PMID: 17710881 [Indexed for MEDLINE]

3872. Arch Dermatol. 2007 Aug;143(8):1080-1.

Late-onset familial Mediterranean fever: an atypical presentation of dermatologic interest.

Satta R, Obici L, Merlini G, Cottoni F.

DOI: 10.1001/archderm.143.8.1080

PMID: 17709678 [Indexed for MEDLINE]

3873. Leuk Res. 2008 Mar;32(3):495-9. Epub 2007 Aug 13.

Copper deficiency with increased hematogones mimicking refractory anemia with

excess blasts.

Koca E(1), Buyukasik Y, Cetiner D, Yilmaz R, Sayinalp N, Yasavul U, Uner A.

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We describe a 19-year-old male patient with a previous diagnosis of familial Mediterranean fever (FMF), nephrotic syndrome and secondary amyloidosis, who presented with anemia and leukopenia. The bone marrow assessments showed dysplastic precursors including vacuolated myeloid and erythroid precursors and increased proportion of immature cells up to 19%. The patient received erythropoietin and G-CSF for myelodysplastic syndrome (MDS). No response was observed. During his evaluations copper deficiency was detected. One month after oral copper replacement, the peripheral blood counts and bone marrow findings became completely normalized. An evaluation to identify the cause of copper deficiency, revealed intestinal amyloidosis. Based on our experience we recommend serum copper determination in the diagnostic workup of MDS in patients with comorbidities.

DOI: 10.1016/j.leukres.2007.06.023

PMID: 17706281 [Indexed for MEDLINE]

3874. Rheumatol Int. 2008 Jan;28(3):289-91. Epub 2007 Aug 17.

Which statin should be used together with colchicine? Clinical experience in three patients with nephrotic syndrome due to AA type amyloidosis.

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Colchicine and statins are well known drugs that cause myopathy and neuropathy. Co-administration of certain drugs with statins may increase myotoxic effect, causing myopathy and varying degrees of rhabdomyolysis. Therefore, it is very

crucial to know which statin should be used during a combination therapy including colchicine and other drugs. We present three cases with AA amyloidosis secondary to familial Mediterranean fever, who developed neuromyopathy while receiving the combination of colchicine and statin. We also briefly discussed the different metabolic pathways of statins and colchicine when used together.

DOI: 10.1007/s00296-007-0435-1

PMID: 17703308 [Indexed for MEDLINE]

3875. Curr Allergy Asthma Rep. 2007 Sep;7(5):323-30.

Hereditary immunologic disorders caused by pyrin and cryopyrin.

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A new family of hereditary immunologic disorders known as the autoinflammatory diseases involves dysregulation of the innate immune system. Elucidation of the genetic basis of these disorders has resulted in improved understanding of the disease pathophysiology of systemic and tissue inflammation, and has also revealed novel nonpathologic innate immune mechanisms. These advances have also resulted in direct improvement in diagnosis and therapy for autoinflammatory disorders such as the cryopyrinopathies and familial Mediterranean fever and have implications for more common inflammatory diseases.

PMID: 17697637 [Indexed for MEDLINE]

3876. J Rheumatol. 2007 Oct;34(10):2070-5. Epub 2007 Aug 1.

The rate of pyrin mutations in critically ill patients with systemic inflammatory response syndrome and sepsis: a pilot study.

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**OBJECTIVE:** The role of individual genetic differences in susceptibility to systemic inflammatory response syndrome (SIRS) and sepsis is generally unrecognized or underestimated. We investigated the rate of pyrin mutations in critically ill patients with SIRS and sepsis, and compared whether carriers for pyrin mutations are associated with respect to the frequency of and certain features of sepsis and SIRS.

**METHODS:** We tested M694V, M680I, V726A, R761H, and M694I mutations in critically ill patients.

**RESULTS:** Twenty-four of 80 (30%) critically ill patients were found to carry some pyrin mutations; none had a history compatible with familial Mediterranean fever. We also found a high frequency of carriers in patients having pneumonia (30.3%), urinary tract infection (29.4%), and acute pancreatitis (30.8%). When we compared our results with the pyrin mutation carrier rate of a healthy Turkish population (10%), the rate of pyrin mutations in all patients ( $p < 0.001$ ), and patients with urinary tract infection ( $p < 0.001$ ), acute pancreatitis ( $p < 0.001$ ), and pneumonia ( $p < 0.001$ ) were found to be significantly high. The white blood cell count, erythrocyte sedimentation rate, lactic dehydrogenase, and rate of fever and pulse were significantly higher, whereas systolic and diastolic blood pressure and albumin levels were significantly lower in patients with pyrin mutation compared to those without the mutation.

**CONCLUSION:** Our results showed that critically ill patients with SIRS and sepsis have increased prevalence of pyrin mutations, and patients with SIRS and sepsis carrying the pyrin mutation seem to be highly susceptible for a severe disease course.

PMID: 17696266 [Indexed for MEDLINE]

3877. Med Clin (Barc). 2007 Jul 14;129(7):267-77.

[Hereditary systemic autoinflammatory diseases. Hereditary periodic fever syndromes].

[Article in Spanish]

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Systemic autoinflammatory diseases are an heterogeneous group of systemic disorders clinically characterized by recurrent or persistent inflammatory episodes, which occur in the absence of infectious, neoplastic or autoimmune etiology. During the past years, genetic defects affecting different proteins involved in the regulation of inflammatory processes have been identified in these diseases. These advances offer new genetic tools to clinicians, in order to achieve an accurate and definitive diagnostic, and to establish a tailored treatment. Present review is an updated and comprehensive overview on hereditary systemic autoinflammatory diseases, and it has been organized in 2 separate and independent parts. The first of them will introduce the group of hereditary periodic fever syndromes, which includes familial Mediterranean fever, hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), and tumour necrosis factor receptor-associated periodic syndrome (TRAPS).

PMID: 17683710 [Indexed for MEDLINE]

3878. Best Pract Res Clin Rheumatol. 2007 Aug;21(4):733-53.

Can a Multi-Dimensional Health Assessment Questionnaire (MDHAQ) and Routine Assessment of Patient Index Data (RAPID) scores be informative in patients with all rheumatic diseases?

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A multidimensional health assessment questionnaire (MDHAQ) is useful in standard care of patients with all rheumatic diseases in a busy clinical setting. The MDHAQ was adapted from the classical health assessment questionnaire (HAQ) for feasibility in standard clinical care, with reduction of the number of activities from 20 to 10, visual analog scales (VAS) as 21 circles rather than 10 cm lines, availability of all core data set patient self-report measures and scoring templates on the front side, and a review of systems symptom checklist and review of recent medical history on the reverse side of a single page. Scoring templates are also available for routine assessment of patient index data (RAPID) scores, based on a composite of the three patient reported outcome (PRO) measures from the core data set included on the HAQ and MDHAQ, physical function pain, and patient estimate of global status. Flow sheets illustrating use of the MDHAQ in standard clinical care of patients with various rheumatic diseases, including psoriatic arthritis, systemic lupus erythematosus, ankylosing spondylitis, gout, scleroderma, vasculitis, fibromyalgia, inflammatory bowel disease arthritis, Behcet's syndrome, and familial Mediterranean fever, are presented to illustrate use of this simple questionnaire to add to clinical decisions and document patient courses and outcomes in standard clinical care of patients with all rheumatic diseases.

DOI: 10.1016/j.berh.2007.02.006

PMID: 17678833 [Indexed for MEDLINE]

3879. Eur J Pediatr. 2008 Jul;167(7):827-8. Epub 2007 Aug 4.

Compound heterozygosity for three common MEFV mutations in a highly consanguineous family with familial Mediterranean fever.

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Consanguinity is not the only factor influencing the occurrence of autosomal recessive disorders such as familial Mediterranean fever (FMF). The extended, multiple consanguineous Turkish pedigree presented here demonstrates that the



population frequency of certain mutations (so-called "ancient" mutations) can be at least equally important. In high-risk populations different combinations of mutations can occur within the same family, increasing not only the intrafamilial clinical variability, but also causing considerable recurrence risks even in marriages with unrelated spouses.

DOI: 10.1007/s00431-007-0572-2

PMID: 17676340 [Indexed for MEDLINE]

3880. Intern Med. 2007;46(15):1247-9. Epub 2007 Aug 2.

Successful treatment with infliximab and low-dose methotrexate in a Japanese patient with familial Mediterranean fever.

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We report a Japanese patient with familial Mediterranean fever (FMF) who was successfully treated with the anti-tumor necrosis factor (TNF)-alpha monoclonal antibody, infliximab, and low-dose methotrexate. This patient was diagnosed as having FMF based on periodic fever with polyarthralgia typical of this disease and heterozygous mutations in the MEFV gene. Conventional treatment, such as colchicine and reserpine, failed to sufficiently control the FMF attacks. After starting infliximab (3 mg/kg) and low-dose methotrexate (6 mg/week), the frequency of the FMF attacks dramatically decreased and the clinical effect has remained unchanged for longer than 1 year. Combination therapy with infliximab and low-dose methotrexate may be a potent therapeutic option for FMF patients, particularly when conventional treatment is ineffective or cannot be employed because of adverse events.

PMID: 17675778 [Indexed for MEDLINE]

3881. Atherosclerosis. 2007 Dec;195(2):e161-7. Epub 2007 Aug 1.

## Impaired coronary microvascular function in familial Mediterranean fever.

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**BACKGROUND:** Patients with inflammatory rheumatic diseases have an increased risk of developing atherosclerosis. However, the question of whether patients with familial Mediterranean fever (FMF) are at risk of atherosclerosis and related diseases remains controversial.

**OBJECTIVE:** We aimed to use transthoracic Doppler echocardiography to investigate coronary flow reserve (CFR) and left ventricular (LV) diastolic function in patients with FMF.

**METHODS:** CFR and LV diastolic function were studied in 33 patients with FMF (16 men, 17 women; mean age, 36.7+/-12.0 years) and 35 healthy volunteers (20 men, 15 women; mean age, 36.8+/-5.2 years). Coronary diastolic peak flow velocities (DPFV) were measured at baseline and after dipyridamole infusion. LV diastolic function was assessed by standard and tissue Doppler imaging.

**RESULTS:** CFR was significantly lower in the FMF group than in the control group (2.27+/-0.38 versus 3.02+/-0.50,  $P<0.0001$ ). Significant between-group differences were found regarding LV diastolic function mitral E/A ratio, mitral E-wave deceleration time, and lateral A(m). Serum high sensitivity C-reactive protein (hsCRP) levels were significantly higher in the patients with FMF, and hsCRP values independently correlated with CFR.

**CONCLUSIONS:** Coronary microvascular function and LV diastolic function are impaired in patients with FMF. The severity of these impairments is correlated with hsCRP. Impaired CFR may be an early manifestation of cardiac involvement in patients with FMF.

DOI: 10.1016/j.atherosclerosis.2007.06.014

PMID: 17673217 [Indexed for MEDLINE]

Falling into TRAPS--receptor misfolding in the TNF receptor 1-associated periodic fever syndrome.

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TNF receptor-associated periodic syndrome (TRAPS) is a dominantly inherited disease caused by missense mutations in the TNF receptor 1 (TNFR1) gene. Patients suffer from periodic bouts of severe abdominal pain, localised inflammation, migratory rashes, and fever. More than 40 individual mutations have been identified, all of which occur in the extracellular domain of TNFR1. In the present review we discuss new findings describing aberrant trafficking and function of TNFR1 harbouring TRAPS mutations, challenging the hypothesis that TRAPS pathology is driven by defective receptor shedding, and we suggest that TNFR1 might acquire novel functions in the endoplasmic reticulum, distinct from its role as a cell surface receptor. We also describe the clinical manifestations of TRAPS, current treatment regimens, and the widening array of patient mutations.

DOI: 10.1186/ar2197

PMCID: PMC2206363

PMID: 17666110 [Indexed for MEDLINE]

3883. Arthritis Rheum. 2007 Aug;56(8):2774-83.

Late-onset tumor necrosis factor receptor-associated periodic syndrome in multiple sclerosis patients carrying the TNFRSF1A R92Q mutation.

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**OBJECTIVE:** Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is an autosomal-dominantly inherited autoinflammatory disorder caused by mutations in the TNFRSF1A gene. It is characterized by episodes of autoinflammation usually associated with fever, abdominal pain, myalgia, exanthema, arthralgia/arthritis, and ocular involvement. We undertook this study to investigate the prevalence of TRAPS in patients with multiple sclerosis (MS) who reported, in addition to their neurologic symptoms, at least 2 other symptoms compatible with TRAPS.

**METHODS:** Twenty-five unrelated MS patients were prospectively screened for TNFRSF1A mutations. In addition, blood samples from 365 unrelated MS patients and 407 unrelated Caucasian controls were analyzed to determine the R92Q carrier frequency.

**RESULTS:** Six of 25 adult MS patients (24%) with symptoms suggestive of TRAPS were found to carry the identical arginine-to-glutamine substitution at amino acid position 92 (R92Q or p.Arg121Gln) encoded by exon 4 of the TNFRSF1A gene. All R92Q heterozygotes had similar symptoms, including arthralgias/arthritis, myalgias, urticarial rash, and severe fatigue, which began before the onset of MS. In 5 of the 6 patients, we could identify family members who had TRAPS symptoms and had inherited the identical mutation. The R92Q exchange was also detected in 17 of 365 unselected MS patients (4.66%) and in 12 of 407 controls (2.95%) ( $P = 0.112$ ). Three patients were heterozygous carriers of MEFV variants, in 1 patient in combination with the R92Q mutation.

**CONCLUSION:** Autoinflammatory syndromes and especially late-onset TRAPS should be considered in MS patients who report symptoms such as arthralgias/arthritis, myalgias, urticarial rash, and severe fatigue.

DOI: 10.1002/art.22795

PMID: 17665448 [Indexed for MEDLINE]

3884. Arthritis Rheum. 2007 Aug;56(8):2765-73.

Mutant tumor necrosis factor receptor associated with tumor necrosis factor receptor-associated periodic syndrome is altered antigenically and is retained within patients' leukocytes.

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**OBJECTIVE:** To investigate the effect of mutations in tumor necrosis factor receptor superfamily member 1A (TNFRSF1A) in TNFR-associated periodic syndrome (TRAPS) on the binding of anti-TNFRSF1A monoclonal antibodies (mAb), and to investigate the subcellular distribution of mutant versus wild-type (WT) TNFRSF1A in patients with TRAPS.

**METHODS:** HEK 293 cells transfected with WT and/or mutant TNFRSF1A were used to investigate the interaction of anti-TNFRSF1A mAb with the WT and mutant proteins. Monoclonal antibodies that differentially bound to C33Y TNFRSF1A were used to investigate the distribution of WT and mutant TNFRSF1A in TRAPS patients with the C33Y mutation.

**RESULTS:** We identified a mAb whose binding to TNFRSF1A was completely abolished by the C33Y or C52F TRAPS-associated mutations, whereas other mutations (T50M, C88Y, R92Q) had lesser effects on the binding of this mAb. A different mAb was found to bind efficiently to all of the mutant forms of TNFRSF1A examined as well as to the WT receptor. Exploitation of the differential binding properties of these mAb indicated that mutant (as distinct from WT) TNFRSF1A showed abnormal intracellular retention in the neutrophils of TRAPS patients with the C33Y mutation, with little if any expression of mutant TNFRSF1A on the cell surface or as soluble receptor in plasma.

**CONCLUSION:** TRAPS-associated mutant TNFRSF1A has an antigenically altered structure and shows abnormal retention in the leukocytes of patients with TRAPS, which is consistent with previous findings from in vitro and transgenic model systems. This is consistent with a misfolded protein response contributing to the pathophysiology of TRAPS.

DOI: 10.1002/art.22740

PMID: 17665435 [Indexed for MEDLINE]

3885. Arthritis Rheum. 2007 Aug;56(8):2784-8.

An unexpectedly high frequency of MEFV mutations in patients with anti-citrullinated protein antibody-negative palindromic rheumatism.

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Comment in

Arthritis Rheum. 2008 Jun;58(6):1885; author reply 1885-6.

**OBJECTIVE:** To investigate whether the MEFV gene, which is involved in the regulation of the inflammatory response and has been associated with familial Mediterranean fever (FMF) and intermittent hydrarthrosis, is implicated in the pathogenesis of palindromic rheumatism (PR) and to examine its clinical presentation and its evolution in a Spanish cohort of PR patients.

**METHODS:** Family histories, demographic clinical data, and laboratory characteristics of 75 patients diagnosed as having PR were collected from medical records and personal interviews. The healthy control group included 325 blood bank donors. The FMF control group was made up of 84 Spanish FMF patients. Genomic DNA was isolated, and MEFV gene mutation analysis was performed by polymerase chain reaction amplification and sequence analysis.

**RESULTS:** Sixty-five unrelated PR patients were finally included in the study. MEFV gene mutation analysis identified 8 of these 65 patients (12.3%) as carriers of at least 1 mutated MEFV allele. Patients with MEFV mutations had higher mean age and age at disease onset, but lower mean serum levels of anti-citrullinated protein antibodies (ACPAs). No other significant differences were observed between patients with and those without mutations. The frequency of MEFV mutations in ACPA-negative PR patients was 22.2%, compared with 5.3% in ACPA-positive PR patients ( $P = 0.058$ ).

**CONCLUSION:** This study shows a previously unreported high prevalence of mutations of the MEFV gene in patients with ACPA-negative PR. This supports the hypothesis that it might be a susceptibility gene. Our findings also support the hypothesis that the MEFV gene might participate in the pathogenesis of other undifferentiated relapsing inflammatory rheumatic disorders.

DOI: 10.1002/art.22755

PMID: 17665427 [Indexed for MEDLINE]

3886. Clin Genet. 2007 Aug;72(2):162-3.

Transmission of familial Mediterranean fever mutations following bone marrow transplantation.

Touitou I, Dumont B, Pourtein M, Perelman S, Sirvent A, Soler C.

DOI: 10.1111/j.1399-0004.2007.00840.x

PMID: 17661824 [Indexed for MEDLINE]

3887. J Eur Acad Dermatol Venereol. 2007 Aug;21(7):1001-2.

Coexistence of lichen aureus with familial Mediterranean fever.

Erbil H, Sezer E, Koseoglu D, Filiz N, Kurumlu Z, Bülent Taştan H.

DOI: 10.1111/j.1468-3083.2006.02075.x

PMID: 17659028 [Indexed for MEDLINE]

3888. Saudi J Kidney Dis Transpl. 2003 Jul-Sep;14(3):378-85.

Familial mediterranean Fever and renal disease.

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Familial Mediterranean Fever (FMF) is a genetic disorder frequently diagnosed among the Arabs. It is also prevalent among Jews, Armenians and Turks. The clinical picture consists of febrile and painful attacks such as joint or chest pain that differ in quality across patients and even within the same patient. The gene responsible for FMF, MEFV, has been cloned and mutations were identified within its coding sequence. It encodes a protein that is expected to be a down regulator of inflammation. The major renal involvement in FMF is the occurrence of amyloidosis that primarily affects the kidneys causing proteinuria and ending

in death from renal failure. It can be treated by dialysis and renal transplantation, but can be prevented by a daily regimen of colchicine. Other renal manifestations of FMF are discussed.

PMID: 17657110

3889. Clin Rheumatol. 2008 Feb;27(2):189-94. Epub 2007 Jul 24.

The detailed assessment of left and right ventricular functions by tissue Doppler imaging in patients with familial Mediterranean fever.

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In the contrary to other rheumatologic disorders, there have been limited numbers of studies investigating the cardiac involvement in patients with familial Mediterranean fever (FMF), although the disease may carry a potential for cardiovascular disorders because of sustained inflammation during its course. In the present study, we used high usefulness tissue Doppler echocardiography for detailed analysis of cardiac changes in FMF patients. The study population included 30 patients with FMF (11 men, 19 women; mean age, 35 +/- 7 years, mean disease duration, 15.4 +/- 7.6 years) and 30 healthy subjects as controls (12 men, 18 women; mean age, 33 +/- 7 years). The diagnosis of FMF was established according to the Tell-Hashomer criteria. Left and right ventricular functions were measured using echocardiography comprising standard two-dimensional, M-mode, and conventional Doppler as well as tissue Doppler imaging. The conventional echocardiographic parameters were similar apart from left ventricular relaxation time was longer (107 +/- 25 vs 85 +/- 10 ms,  $p < 0.001$ , respectively) in patients with FMF. According to the tissue Doppler measurements, while systolic velocities of both ventricles were not different, diastolic filling velocities of left ventricle including  $E'(m)$  (12.6 +/- 3.4 vs 14.7 +/- 3.3 cm/s,  $p = 0.04$ ),  $A'(m)$  (10.1 +/- 2.6 vs 8.6 +/- 2.0 cm/s,  $p = 0.015$ ), and  $E'(m)/A'(m)$  (1.24 +/- 0.4 vs 1.71 +/- 0.5 cm/s,  $p = 0.012$ ) values were statistically different between the groups. Left ventricular myocardial performance indices and



right ventricular diastolic functions were found similar between two groups. In addition, there were no significant correlations between the disease duration, clinical features, and echocardiographic parameters. In conclusion, we have demonstrated that although systolic functions were comparable in the patients and controls, left ventricular diastolic function indices were impaired in FMF patients by using tissue Doppler analysis.

DOI: 10.1007/s10067-007-0676-0

PMID: 17646898 [Indexed for MEDLINE]

3890. Anesth Analg. 2007 Aug;105(2):351-7.

The anesthetic management of children with neonatal-onset multi-system inflammatory disease.

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**BACKGROUND:** Neonatal-onset multi-system inflammatory disease (NOMID), a rare autosomal dominantly inherited disease, belongs to a growing spectrum of autoinflammatory diseases, is characterized by urticarial rash, arthropathy, and chronic aseptic meningitis, and is associated with mutations in the cold-induced autoinflammatory gene, CIAS1, the gene that encodes the protein, cryopyrin. As little is known about the anesthetic considerations of the disease, we sought to identify the main features and respective anesthetic and perioperative implications of NOMID.

**METHODS:** We examined perianesthetic records of children with NOMID who were anesthetized for invasive diagnostic and therapeutic interventions between 2003 and 2006. In addition, we conducted an extensive literature review of the genetic, clinical, and biochemical abnormalities of the disease.

**RESULTS:** Seventeen children with NOMID (median age 8 yr, range 9 mo to 11 yr) were anesthetized for diagnostic and therapeutic procedures. All patients had neurological involvement, including increased intracranial pressure, chronic aseptic meningitis, and developmental delay; 7 had bony overgrowth, 15 ocular, and 14 otological manifestations of NOMID. Despite the complexity of the disease,

the perioperative course was uncomplicated, and no serious adverse events were observed.

**CONCLUSIONS:** This study is the first to investigate the anesthetic implications of NOMID, an autoinflammatory disease associated with arthropathy, recurrent fevers, urticarial rash, and chronic aseptic meningitis. While for the pediatric anesthesiologist, the presence of fever and aseptic meningitis might make the conduct of anesthetics for elective procedures less desirable, our findings suggest that without evidence of active infection, even in the presence of fever and chronic aseptic meningitis, general and regional anesthesia may be conducted in patients with NOMID without untoward complications.

DOI: 10.1213/01.ane.0000270764.99119.1b

PMCID: PMC3380421

PMID: 17646489 [Indexed for MEDLINE]

3891. Hepatogastroenterology. 2007 Jun;54(76):1061-5.

Secondary amyloidosis due to FMF.

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Familial Mediterranean fever (FMF) is an ethnically restricted disease with an autosomal recessive inheritance characterized by recurrent attacks of fever, painful manifestations in the abdomen, chest and joints. The disease affects mainly non-Ashkenazi Jews, Armenians, Turks Arabs and other people of Mediterranean origin. The disease may present at any age, more than 80% of patients being symptomatic by the age of 20. Although the inflammatory attacks that characterize the disease may sometimes be debilitating, secondary (AA) amyloidosis remains the most serious manifestation of FMF causing considerable morbidity due mostly to nephropathic amyloidosis. The largest series of secondary amyloidosis in FMF have been reported from Turkey. The pathophysiological steps in progressing a patient from FMF to amyloidosis are not definitely known. Daily treatment with colchicine can prevent both the attacks and amyloid deposition but no effective alternative treatment exists for colchicine resistant cases.

Meanwhile more population based epidemiological and genetic data should be gathered by worldwide collaborative studies to elucidate the link between FMF and amyloidosis and to develop alternative therapies.

PMID: 17629039 [Indexed for MEDLINE]

3892. MMW Fortschr Med. 2006 Oct 19;148(42):10-2, 14.

[Fever of unknown origin--no infection--responds to antibiotics: what is likely--and what else should be considered].

[Article in German]

Stiefelhagen P.

PMID: 17621791 [Indexed for MEDLINE]

3893. J Immunol. 2007 Jul 15;179(2):1274-81.

Pyrin levels in human monocytes and monocyte-derived macrophages regulate IL-1beta processing and release.

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Macrophages and their precursors, monocytes, are key cells involved in the innate immune response. Although both monocytes and macrophages produce caspase-1, the key enzyme responsible for pro-IL-1beta processing; macrophages are limited in their ability to activate the enzyme and release functional IL-1beta. In this context, because mutations in the pyrin gene (MEFV) cause the inflammatory disorder familial Mediterranean fever, pyrin is believed to regulate IL-1beta processing. To determine whether variations in pyrin expression explain the

difference between monocytes and macrophages in IL-1 $\beta$  processing and release, pyrin was studied in human monocytes and monocyte-derived macrophages. Although monocytes express pyrin mRNA and protein, which is readily inducible by endotoxin, monocyte-derived macrophages express significantly less pyrin mRNA and protein. Pyrin levels directly correlated with IL-1 $\beta$  processing in monocytes and macrophages; therefore, we asked whether pyrin might promote IL-1 $\beta$  processing and release. HEK293 cells were transfected with pyrin, caspase-1, apoptotic speck protein with a caspase recruitment domain, and IL-1 $\beta$ . Pyrin induced IL-1 $\beta$  processing and release in a dose-dependent manner. Conversely, pyrin small interference RNA suppressed pro-IL-1 $\beta$  processing in both THP-1 cells and fresh human monocytes. In summary, both pyrin expression and IL-1 $\beta$  processing and release are diminished upon the maturation of monocytes to macrophages. When pyrin is ectopically expressed or silenced, IL-1 $\beta$  processing and release parallels the level of pyrin. In conclusion, in the context of endotoxin-induced activation of mononuclear phagocytes, pyrin augments IL-1 $\beta$  processing and release.

PMID: 17617620 [Indexed for MEDLINE]

3894. J Rheumatol. 2007 Jul;34(7):1540-4. Epub 2007 Jun 15.

Association of drug transporter gene ABCB1 (MDR1) 3435C to T polymorphism with colchicine response in familial Mediterranean fever.

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**OBJECTIVE:** Colchicine is a mainstay of treatment in familial Mediterranean fever (FMF); however, 5%-10% of patients do not respond to colchicine. Adenosine triphosphate-binding cassette subfamily B member 1 (ABCB1 or MDR1) is a drug transporter that extrudes colchicine out of cells. ABCB1 gene 3435C to T polymorphism has been demonstrated to alter MDR1 expression in mononuclear cells. Thus, the amount of MDR1 in mononuclear cells may alter response to colchicine.

We investigated the association between MDR1 3435C to T polymorphism and colchicine response in patients with FMF.

METHODS: Patients (n = 120) were examined for colchicine responses. ABCB1 gene 3435C to T genotypes were determined to analyze associations with colchicine resistance.

RESULTS: Ninety-eight patients were evaluated as responders and 22 as nonresponders. The distributions of ABCB1 CC, CT, and TT genotypes were significantly different between responsive and nonresponsive groups (chi-square = 6.86, p = 0.032). Colchicine resistance was significantly higher in patients harboring the C allele than in patients with TT genotype (odds ratio 9.71, 95% CI 1.58-58.76). Similarly, the mean colchicine dose to prevent remission was significantly lower in the TT group compared with subjects with the C allele (p = 0.014).

CONCLUSION: Our study revealed an association between 3435C to T polymorphism and colchicine response in patients with FMF. Patients with the TT genotype for the ABCB1 3435C to T variant responded better to colchicine in terms of treatment efficacy and colchicine dose requirements.

PMID: 17610314 [Indexed for MEDLINE]

3895. N Engl J Med. 2007 Jun 28;356(26):2671-3.

Mevalonate kinase deficiency and autoinflammatory disorders.

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Comment in

N Engl J Med. 2007 Nov 1;357(18):1871-2.

Comment on

N Engl J Med. 2007 Jun 28;356(26):2700-3.

DOI: 10.1056/NEJMp078083

PMID: 17596600 [Indexed for MEDLINE]

3896. Klin Monbl Augenheilkd. 2007 Jun;224(6):473-6.

[Other rheumatic diseases with uveitis besides juvenile idiopathic arthritis].

[Article in German]

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In childhood and adolescence, uveitis is part of the clinical spectrum of many inflammatory-rheumatic diseases. Besides juvenile idiopathic arthritis juvenile, ankylosing spondylitis, infection-associated arthritides, infantile sarcoidosis, systemic vasculitides, inflammatory bowel diseases, hereditary autoinflammatory syndromes and the TINU syndrome have to be excluded. These inflammatory diseases can be differentiated clinically in connection with immunogenetic and molecular genetic investigations. Early diagnosis of uveitis as well as the underlying diseases is mandatory for an early treatment and therefore for a good prognosis.

DOI: 10.1055/s-2007-963091

PMID: 17594615 [Indexed for MEDLINE]

3897. Rheumatol Int. 2007 Dec;28(2):167-9. Epub 2007 Jun 27.

A novel mutation of the familial Mediterranean fever gene in a Greek family related to a non-classical, variably expressed FMF phenotype.

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DOI: 10.1007/s00296-007-0389-3

PMID: 17594097 [Indexed for MEDLINE]

3898. J Gastrointestin Liver Dis. 2007 Jun;16(2):141-5.

Clinical and molecular diagnosis of Familial Mediterranean Fever in Egyptian children.

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**BACKGROUND:** Familial Mediterranean Fever (FMF) is an autosomal inherited disorder affecting certain races including Arabs. Diagnosis depends mainly on clinical basis, but mild forms may remain undiagnosed.

**OBJECTIVES:** This study aims at an accurate diagnosis of FMF in Egyptian children by detection of genetic mutations in addition to clinical assessment.

**SUBJECTS AND METHODS:** Subjects included 66 Egyptian cases (37 males and 29 females) with a mean age of onset of 6.9 years. They had been referred from health centers and hospitals of the Delta region, Egypt. Analysis of the clinical manifestations was performed using Tel-Hashomer criteria in addition to 10 items clinical score system. For all these cases, DNA analysis was made for three common mutations M680I, M694V, and V726A using amplification refractory mutation system (ARMS-PCR) technique.

**RESULTS:** Most of the cases had attacks ranging from 3-5 days duration with the mean of 3.6 days. Their rate of recurrence was variable but 47 % of them had suffered attacks 10-30 times/year. Abdominal pain was the most common symptom (87.9%) followed by fever (82%), arthritis or arthralgia (56.1%), chest pain (45%) and myalgia (6%). Laparotomy had been done during attacks for exploration or appen-dectomy in 27.7% of cases. Positive mutations were detected among 42 cases (63.6%), of them 14 (21.2%) were compound heterozygotes, 7 (10.6%) were had homozygotes while 21 (31.8%) were simple heterozygotes. Allele M694V was the most frequent one (18.8%) followed by V726A (17.4%) and M680I (12.1%). Taking positive mutation as a guide for diagnosis, a cutoff clinical score level was determined with =15 for unlikely, =20 for definite and 15-20 for probable diagnosis.

CONCLUSION: Diagnosis of FMF among Egyptian children cases although based mainly on clinical suspicion requires to be confirmed through detection of the corresponding mutation which can be easily made using the simple ARMS-PCR technique.

PMID: 17592559 [Indexed for MEDLINE]

3899. Eur J Pediatr. 2008 Jun;167(6):695-6. Epub 2007 Jun 23.

The efficacy of anakinra in an adolescent with colchicine-resistant familial Mediterranean fever.

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Colchicine is the treatment of choice in familial Mediterranean fever (FMF) for the prevention of both attacks and secondary amyloidosis. The overall nonresponder rate is about 5-10%. Anakinra is known to have good effectiveness in a severe autoinflammatory syndrome [chronic infantile neurological cutaneous and articular (CINCA) syndrome] and other recurrent hereditary periodic fevers. Pyrin--the protein involved in FMF--has a role in activating the proinflammatory cytokine interleukin (IL)-1beta. We report the effectiveness of the addition of an IL-1-receptor inhibitor (anakinra) to colchicine in controlling the febrile attacks and acute phase response in an adolescent with FMF resistant to colchicine.

DOI: 10.1007/s00431-007-0547-3

PMCID: PMC2292480

PMID: 17588171 [Indexed for MEDLINE]

3900. Semin Arthritis Rheum. 2007 Dec;37(3):137-48. Epub 2007 Jun 21.

Schnitzler syndrome: beyond the case reports: review and follow-up of 94 patients



with an emphasis on prognosis and treatment.

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Comment in

Semin Arthritis Rheum. 2008 Oct;38(2):163; author reply 164.

**OBJECTIVE:** Schnitzler syndrome is a rare disorder characterized by a chronic urticarial rash and monoclonal gammopathy, accompanied by intermittent fever, arthralgia or arthritis, bone pain, and lymphadenopathy. Our objectives are to systematically review disease characteristics of Schnitzler syndrome and collect follow-up information to gain insight into treatment efficacy and long-term prognosis.

**METHODS:** PubMed and MEDLINE databases (1966-2006) were searched, using the key words "Schnitzler syndrome," and the combination of "urticaria" with "monoclonal gammopathy," "immunoglobulin M (IgM)," or "paraproteinemia," as well as secondary references. Data on a total of 94 patients who met the criteria for Schnitzler syndrome were reviewed. Questionnaires sent to all authors retrieved additional follow-up data on 43 patients, resulting in a mean follow-up of 9.5 years after onset of symptoms, and a follow-up of 20 years or more in 10 patients.

**RESULTS:** Symptoms, signs, and laboratory findings as found in the 94 patients are reviewed in detail. There have been promising developments in therapeutic options, especially antiinterleukin-1 treatment, which induced complete remission in all 8 patients treated so far. To date, no spontaneous complete remissions have been reported. Patients with Schnitzler syndrome showed no increased mortality during the present follow-up. However, they had a 10-year risk of 15% of developing a lymphoproliferative disorder, most notably Waldenström's macroglobulinemia. Three cases of type amyloid A (AA) amyloidosis associated with Schnitzler syndrome were reported.

**CONCLUSIONS:** Schnitzler syndrome is a disabling disorder which affects multiple systems and which can be considered as an autoinflammatory syndrome. There are new, effective treatment options, but close monitoring remains warranted because of the increased risk of lymphoproliferative disease.

DOI: 10.1016/j.semarthrit.2007.04.001  
PMID: 17586002 [Indexed for MEDLINE]

3901. J Pediatr Orthop. 2007 Jul-Aug;27(5):587-91.

Successful treatment of chronic recurrent multifocal osteomyelitis with indomethacin: a preliminary report of five cases.

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Chronic recurrent multifocal osteomyelitis (CRMO) is a disease of children and young adults. Clinically, the disease is characterized by the insidious onset of local pain and swelling in affected bones. Its course is one of intermittent periods of exacerbation and remission with successive bones affected. The pathogenesis of CRMO remains unknown, although an autoinflammatory disorder may be the cause, with inflammation of bone. This lesion is radiologically characterized as multiple lucencies surrounded by defined zones of patchy but dense sclerosis, cortical thickening from periosteal new bone formation, and increased bone size with different bones involved. Multiple therapeutic regimens had shown only a partial or temporary response. Because indomethacin has been successfully applied in inhibition of ossification and inflammatory processes, we initiated therapy with indomethacin in patients with CRMO. We report on the cases of 5 patients who responded dramatically to treatment with indomethacin. All underwent progressive clinical improvement (mean, 2.8 months). Radiological lesions disappeared after a mean period of 10.5 months. In 1 case where treatment was started late, small osteolytic zones persisted but with no clinical consequences. There were no additional recurrences or new bones affected during follow-up period (mean, 4 years). Our observation indicates that indomethacin may be an effective treatment for CRMO.

DOI: 10.1097/BPO.0b013e318070cbd3  
PMID: 17585272 [Indexed for MEDLINE]

3902. Amyloid. 2007 Jun;14(2):133-40.

Diagnostic performance of amyloid A protein quantification in fat tissue of patients with clinical AA amyloidosis.

Hazenberg BP(1), Bijzet J, Limburg PC, Skinner M, Hawkins PN, Butrimiene I, Livneh A, Lesnyak O, Nasonov EL, Filipowicz-Sosnowska A, Gül A, Merlini G, Wiland P, Ozdogan H, Gorevic PD, Maiz HB, Benson MD, Direskeneli H, Kaarela K, Garceau D, Hauck W, Van Rijswijk MH.

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Erratum in

Amyloid. 2007 Dec;14(4):325.

**OBJECTIVE:** Amyloid A protein quantification in fat tissue is a new immunochemical method for detecting AA amyloidosis, a rare but serious disease. The objective was to assess diagnostic performance in clinical AA amyloidosis.

**METHODS:** Abdominal subcutaneous fat tissue of patients with AA amyloidosis was studied at the start of an international clinical trial with eprodisate (NC-503; 1,3-propanedisulfonate; Kiacta), an antiamyloid compound. All patients had renal findings, i.e. proteinuria ( $>$  or  $=$  1 g/day) or reduced creatinine clearance (20 - 60 ml/min). Controls were patients with other types of amyloidosis and arthritic patients without amyloidosis. Amyloid A protein was quantified by ELISA using monoclonal antihuman serum amyloid A antibodies. Congo red stained slides were scored by light microscopy in a semiquantitative way (0 to 4+).

**RESULTS:** Ample fat tissue ( $>$ 50 mg) was available for analysis in 154 of 183 patients with AA amyloidosis and in 354 controls. The sensitivity of amyloid A protein quantification for detection of AA amyloidosis ( $>$ 11.6 ng/mg fat tissue) was 84% (95% CI: 77 - 89%) and specificity 99% (95% CI: 98 - 100%). Amyloid A protein quantification and semiquantitative Congo red scoring were concordant. Men had lower amyloid A protein values than women ( $p < 0.0001$ ) and patients with familial Mediterranean fever had lower values than patients with arthritis ( $p < 0.001$ ) or other inflammatory diseases ( $p < 0.01$ ).

**CONCLUSIONS:** Amyloid A protein quantification in fat tissue is a sensitive and specific method for detection of clinical AA amyloidosis. Advantages are

independence from staining quality and observer experience, direct confirmation of amyloid AA type, and potential for quantitative monitoring of tissue amyloid over time.

DOI: 10.1080/13506120701260224

PMID: 17577686 [Indexed for MEDLINE]

3903. Eur J Hum Genet. 2007 Sep;15(9):911-6. Epub 2007 Jun 13.

Population genetics of familial Mediterranean fever: a review.

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In this review, some principal population genetic features of familial Mediterranean fever (FMF) are considered. These relate to the time and the place of founder mutations' origins, the role of ancient migrations and contacts between populations in the spatial spreading of the disorder, the influence of environmental factors and cultural traditions on the rate of FMF incidence, and possible selective advantage in carriers of FMF causing gene (MEFV) mutations.

DOI: 10.1038/sj.ejhg.5201869

PMID: 17568393 [Indexed for MEDLINE]

3904. Mol Biol Rep. 2008 Sep;35(3):447-51. Epub 2007 Jun 14.

MEFV gene mutations spectrum among Lebanese patients referred for Familial Mediterranean Fever work-up: experience of a major tertiary care center.

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Familial Mediterranean Fever (FMF) is an autosomal recessive inflammatory disorder predominantly affecting people living in or originating from areas around the Mediterranean Sea, mainly Jews, Armenians, Turks, and Arabs. It is characterized by recurrent attacks of inflammation of serosal membranes and fever resulting in acute abdominal, chest, or joint pain. Over 50 Mediterranean Fever (MEFV) mutations and polymorphisms have been identified in FMF patients. The objective of this study was to analyze the distribution and frequencies of 12 MEFV mutations in 266 referred Lebanese patients using a reverse-hybridization assay. Of the 266 patients, 129 (48.5%) were positive for at least one mutation and 137 (51.5%) had no mutations detected. Of the 129 patients with mutations, 35 were homozygous, 41 were compound heterozygous and 53 were heterozygous. The five most common mutations M694V, E148Q, V726A, M694I and M680I (G/C) accounted for 26.1, 22.2, 21.3, 9.6 and 7.7%, respectively. The A744S, F479L, R761H and I692del were encountered in 2.9% of patients; P369S and M680I (G/A) were found in 1.2% of patients while K695R was absent. The spectrum of the MEFV mutations among our sampled Lebanese FMF patients shows the high heterogeneity at the allelic level when compared to Arab and non-Arab populations. The most important feature was the relatively high frequency of the E148Q in our study group that allows us to question it as a mutation rather than a polymorphism. Further studies should be conducted to evaluate the role of the E148Q allele.

DOI: 10.1007/s11033-007-9105-3

PMID: 17566872 [Indexed for MEDLINE]

3905. Mod Rheumatol. 2007;17(3):265-6. Epub 2007 Jun 20.

Tumor necrosis factor receptor-associated periodic syndrome with a C30R mutation in a Japanese family.

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DOI: 10.1007/s10165-007-0580-0

PMID: 17564788 [Indexed for MEDLINE]

3906. N Engl J Med. 2007 Jun 7;356(23):2361-71.

Natural history and outcome in systemic AA amyloidosis.

Lachmann HJ(1), Goodman HJ, Gilbertson JA, Gallimore JR, Sabin CA, Gillmore JD, Hawkins PN.

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Comment in

Nefrologia. 2008;28 Suppl 2:8-9.

N Engl J Med. 2007 Sep 13;357(11):1153; author reply 1153-4.

**BACKGROUND:** Deposition of amyloid fibrils derived from circulating acute-phase reactant serum amyloid A protein (SAA) causes systemic AA amyloidosis, a serious complication of many chronic inflammatory disorders. Little is known about the natural history of AA amyloidosis or its response to treatment.

**METHODS:** We evaluated clinical features, organ function, and survival among 374 patients with AA amyloidosis who were followed for a median of 86 months. The SAA concentration was measured serially, and the amyloid burden was estimated with the use of whole-body serum amyloid P component scintigraphy. Therapy for inflammatory diseases was administered to suppress the production of SAA.

**RESULTS:** Median survival after diagnosis was 133 months; renal dysfunction was the predominant disease manifestation. Mortality, amyloid burden, and renal prognosis all significantly correlated with the SAA concentration during

follow-up. The risk of death was 17.7 times as high among patients with SAA concentrations in the highest eighth, or octile, ( $\geq 155$  mg per liter) as among those with concentrations in the lowest octile ( $< 4$  mg per liter); and the risk of death was four times as high in the next-to-lowest octile (4 to 9 mg per liter).

The median SAA concentration during follow-up was 6 mg per liter in patients in whom renal function improved and 28 mg per liter in those in whom it deteriorated ( $P < 0.001$ ). Amyloid deposits regressed in 60% of patients who had a median SAA concentration of less than 10 mg per liter, and survival among these patients was superior to survival among those in whom amyloid deposits did not regress

(P=0.04).

**CONCLUSIONS:** The effects of renal dysfunction dominate the course of AA amyloidosis, which is associated with a relatively favorable outcome in patients with SAA concentrations that remain in the low-normal range (<4 mg per liter).

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DOI: 10.1056/NEJMoa070265

PMID: 17554117 [Indexed for MEDLINE]

3907. N Engl J Med. 2007 Jun 7;356(23):2349-60.

Eprodisate for the treatment of renal disease in AA amyloidosis.

Dember LM(1), Hawkins PN, Hazenberg BP, Gorevic PD, Merlini G, Butrimiene I, Livneh A, Lesnyak O, Puéchal X, Lachmann HJ, Obici L, Balshaw R, Garceau D, Hauck W, Skinner M; Eprodisate for AA Amyloidosis Trial Group.

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Comment in

N Engl J Med. 2007 Sep 13;357(11):1153; author reply 1153-4.

N Engl J Med. 2007 Jun 7;356(23):2413-5.

Nat Clin Pract Nephrol. 2007 Nov;3(11):592-3.

**BACKGROUND:** Amyloid A (AA) amyloidosis is a complication of chronic inflammatory conditions that develops when proteolytic fragments of serum amyloid A protein (SAA) are deposited in tissues as amyloid fibrils. Amyloid deposition in the kidney causes progressive deterioration in renal function. Eprodisate is a member of a new class of compounds designed to interfere with interactions between amyloidogenic proteins and glycosaminoglycans and thereby inhibit polymerization of amyloid fibrils and deposition of the fibrils in tissues.

**METHODS:** We performed a multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of eprodisate in patients with AA amyloidosis and kidney involvement. We randomly assigned 183 patients from 27 centers to receive eprodisate or placebo for 24 months. The primary composite end point was an assessment of renal function or death. Disease was classified as

worsened if any one of the following occurred: doubling of the serum creatinine level, reduction in creatinine clearance by 50% or more, progression to end-stage renal disease, or death.

RESULTS: At 24 months, disease was worsened in 24 of 89 patients who received eprodisate (27%) and 38 of 94 patients given placebo (40%,  $P=0.06$ ); the hazard ratio for worsening disease with eprodisate treatment was 0.58 (95% confidence interval, 0.37 to 0.93;  $P=0.02$ ). The mean rates of decline in creatinine clearance were 10.9 and 15.6 ml per minute per 1.73 m<sup>2</sup> of body-surface area per year in the eprodisate and the placebo groups, respectively ( $P=0.02$ ). The drug had no significant effect on progression to end-stage renal disease (hazard ratio, 0.54;  $P=0.20$ ) or risk of death (hazard ratio, 0.95;  $P=0.94$ ). The incidence of adverse events was similar in the two groups.

CONCLUSIONS: Eprodisate slows the decline of renal function in AA amyloidosis. (ClinicalTrials.gov number, NCT00035334.)

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DOI: 10.1056/NEJMoa065644

PMID: 17554116 [Indexed for MEDLINE]

3908. J Clin Rheumatol. 2007 Jun;13(3):124-7.

Behcet disease in adult Druzes in north Israel: the influence of ethnic origin on disease expression and severity.

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BACKGROUND: Behcet's disease (BD) is known to vary in severity and manifestations in different populations.

OBJECTIVE: In an attempt to sort out genetic and environmental influences on disease expression, we carried out a study to assess the clinical features of BD in the adult Druze and Arab populations in north Israel, comparing 2 disparate ethnic groups of similar genetic background inhabiting the same geographic region.



**METHODS:** We compared 23 Druze and 30 Arab patients with BD. All patients fulfilled the classification criteria of the International Study Group for BD.

**RESULTS:** Manifestations were similar in 2 groups. The most frequent BD manifestations among the Druzes were recurrent oral aphthae (100%) and genital aphthae (61%) versus 100% and 53% in Arab patients, followed by inflammatory ocular involvement, 65% versus 53%, respectively. Arthritis was noted in 39% of Druze, with 27% in Arabs. Anterior uveitis occurred in 9 Druze patients (48%) and panuveitis in 4, with no case of blindness when compared with 30% with anterior uveitis, 4 with panuveitis, and 4 cases of blindness ( $P < 0.04$ ) among the Arabs. One Druze BD patient had deep vein thrombosis versus 8 Arab patients ( $P < 0.017$ ). No pulmonary embolism, aortic aneurysm, nor valvular involvement was documented in the Druze versus 1 case of each in Arabs. No case of neuro-Behcet was reported in Druzes versus 6 cases of neuro-Behcet among Arabs ( $P < 0.023$ ). The severity score was 4.0 (SD, 1.2) in Druze and 5.8 (SD, 1.9) in Arabs ( $P = 0.0004$ ). The prevalence of HLA B51 did not differ significantly between the groups.

**CONCLUSION:** Druze BD patients in Israel have a milder disease than do Arabs, similar to observations in familial Mediterranean fever. Druze BD patients had significantly less severe ocular disease and neurologic manifestations. Our results suggest an ethnic influence on expression of BD not related to HLA B 51.

DOI: 10.1097/RHU.0b013e3180645878

PMID: 17551376 [Indexed for MEDLINE]

3909. *Pediatr Rheumatol Online J.* 2007 Jun 5;5:12.

Association between celiac sprue and cryopyrin associated autoinflammatory disorders: a case report.

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Cryopyrin-associated diseases may be characterized by rashes, fever, and sensorineural deafness, while celiac disease may present with symptoms of malabsorption and fatigue. Arthritis is seen in both conditions. We report a young child with histologically diagnosed celiac disease and a cryopyrinopathy.

DOI: 10.1186/1546-0096-5-12

PMCID: PMC1892774

PMID: 17550587

3910. Ann Intern Med. 2007 Jun 5;146(11):825-6.

Treatment of familial Mediterranean fever with anakinra.

Belkhir R, Moulonguet-Doleris L, Hachulla E, Prinseau J, Baglin A, Hanslik T.

PMID: 17548423 [Indexed for MEDLINE]

3911. Eur J Pediatr. 2008 Apr;167(4):391-3. Epub 2007 May 23.

The familial Mediterranean fever (MEFV) gene may be a modifier factor of inflammatory bowel disease in infancy.

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Pediatric inflammatory bowel disease (IBD) usually manifests in childhood or adolescence, but a small number of cases present in infancy. Genetic factors are more important than environmental ones in the onset of pediatric IBD. We report here the concurrent manifestation of IBD and familial Mediterranean fever (FMF) in three infants (less than 6 months of age) in whom infantile ulcerative colitis (UC) was associated with the MEFV mutation. One patient required colectomy before the diagnosis of FMF, and in the other two patients, the UC could not be controlled until colchicine was added to the drug regimen. We suggest that the onset of UC in infants should prompt a search for MEFV mutations as this association may influence the management of the disease.

DOI: 10.1007/s00431-007-0508-x

PMID: 17520284 [Indexed for MEDLINE]

3912. Blood. 2007 Oct 1;110(7):2371-80. Epub 2007 May 21.

Mutations in the cofilin partner Aip1/Wdr1 cause autoinflammatory disease and macrothrombocytopenia.

Kile BT(1), Panopoulos AD, Stirzaker RA, Hacking DF, Tahtamouni LH, Willson TA, Mielke LA, Henley KJ, Zhang JG, Wicks IP, Stevenson WS, Nurden P, Watowich SS, Justice MJ.

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A pivotal mediator of actin dynamics is the protein cofilin, which promotes filament severing and depolymerization, facilitating the breakdown of existing filaments, and the enhancement of filament growth from newly created barbed ends. It does so in concert with actin interacting protein 1 (Aip1), which serves to accelerate cofilin's activity. While progress has been made in understanding its biochemical functions, the physiologic processes the cofilin/Aip1 complex regulates, particularly in higher organisms, are yet to be determined. We have generated an allelic series for WD40 repeat protein 1 (Wdr1), the mammalian homolog of Aip1, and report that reductions in Wdr1 function produce a dramatic phenotype gradient. While severe loss of function at the Wdr1 locus causes embryonic lethality, macrothrombocytopenia and autoinflammatory disease develop in mice carrying hypomorphic alleles. Macrothrombocytopenia is the result of megakaryocyte maturation defects, which lead to a failure of normal platelet shedding. Autoinflammatory disease, which is bone marrow-derived yet nonlymphoid in origin, is characterized by a massive infiltration of neutrophils into inflammatory lesions. Cytoskeletal responses are impaired in Wdr1 mutant neutrophils. These studies establish an essential requirement for Wdr1 in megakaryocytes and neutrophils, indicating that cofilin-mediated actin dynamics are critically important to the development and function of both cell types.

DOI: 10.1182/blood-2006-10-055087

PMCID: PMC1988957

PMID: 17515402 [Indexed for MEDLINE]

3913. Ann Rheum Dis. 2007 Jun;66(6):843-4.

Cryopyrin-associated autoinflammatory syndrome: a new mutation.

Zeft A, Bohnsack JF.

DOI: 10.1136/ard.2006.064899

PMCID: PMC1954656

PMID: 17513575 [Indexed for MEDLINE]

3914. Semin Arthritis Rheum. 2007 Dec;37(3):182-8. Epub 2007 May 23.

A single testing of serum amyloid A levels as a tool for diagnosis and treatment dilemmas in familial Mediterranean fever.

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**OBJECTIVES:** In a significant proportion of patients with familial Mediterranean fever (FMF), serum amyloid A (SAA) remains elevated during attack-free periods, thereby increasing the risk of developing amyloidosis. The aim of the study was to determine various correlates of elevated SAA and evaluate the role of SAA measurement in the diagnosis and management of FMF.

**METHODS:** We reviewed the medical files of all 204 patients from our FMF center in whom SAA measurements were performed. SAA levels and the resulting diagnostic and therapeutic decisions were analyzed in relation to the reasons of SAA testing and to several clinical and genetic parameters.

**RESULTS:** SAA measurements were made for diagnostic purposes in 29% of the patients. In the remainder, SAA measurements were used for adjustment of colchicine dose. Elevated SAA levels are found in a third of FMF patients during an attack-free period. The highest rate of elevated SAA levels was found in patients with proteinuria (60% of this patient group), followed by noncompliant

(40%) and genetically positive asymptomatic patients (38%). Elevated SAA levels during remission were associated with family history of FMF, M694V homozygosity, and elevated C-reactive protein (CRP) ( $P < 0.05$  for each). Patients homozygous for the M694V mutation had the highest level of SAA. SAA measurement led to a change in colchicine dose in 30% of the patients, predominantly in noncompliant patients and patients with proteinuria or with atypical manifestations.

CONCLUSIONS: Measurement of SAA level may help in the diagnosis of FMF and in adjustment of the colchicine dose.

DOI: 10.1016/j.semarthrit.2007.03.005

PMID: 17512038 [Indexed for MEDLINE]

3915. *Pediatr Neurol*. 2007 May;36(5):338-41.

Nonclassic neurologic features in cryopyrin-associated periodic syndromes.

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Neurologic manifestations in early childhood occur in the cryopyrin-associated periodic syndromes, especially in the chronic infantile neurological, cutaneous, and articular syndrome (CINCA) and the Muckle-Wells syndrome.

Cryopyrin-associated periodic syndromes are commonly linked to mutations in the cold-induced autoinflammatory syndrome gene CIAS1 (current symbol, NLRP3) on chromosome 1. We describe three children with atypical cryopyrin-associated periodic syndromes, neurologic symptoms, and a Q705K mutation.

Cryopyrin-associated periodic syndrome screening should be considered for children with neurologic and other periodic symptoms with elevated inflammatory markers. This syndrome is treatable with anakinra.

DOI: 10.1016/j.pediatrneurol.2006.12.008

PMID: 17509468 [Indexed for MEDLINE]

3916. *Ren Fail*. 2007;29(3):315-9.

The effect of dialytic modalities on clinical outcomes in ESRD patients with familial Mediterranean fever.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is an autosomal recessive disease seen primarily in Sephardic Jews, Turks, and Armenians. The disease manifests as recurrent attacks of fever and serositis. The most important complication of FMF is the development of renal failure due to AA type amyloidosis. There has not been extensive experience with renal replacement therapy in FMF amyloidosis. Nevertheless, there may be a concern about the possibility of higher rates of morbidity and mortality in amyloidotic patients maintained on chronic hemodialysis. Moreover, there is not enough experience regarding patients on chronic peritoneal dialysis. As a result, the best treatment modality of end-stage renal disease (ESRD) in these circumstances still remains unclear. This study aimed to compare the effect of hemodialysis and peritoneal dialysis modalities on clinical outcomes in ESRD patients associated with FMF amyloidosis.

**METHODS:** Forty FMF patients with ESRD due to amyloidosis were retrospectively analyzed. All 40 patients were on renal replacement therapy, 20 on hemodialysis (HD), 20 on peritoneal dialysis (PD). Peritoneal solute transport rates, weekly mean creatinine clearance, and daily mean ultrafiltration (UF) of the patients on chronic peritoneal dialysis were evaluated. Weekly dialysis durations, dialysis membrane properties, Kt/V values, interdialytic weight gains, and frequency of hypotension during dialysis were evaluated on hemodialysis patients. All of the patients were examined according to their demographic characteristics, laboratory results, duration time on dialysis, erythropoietin requirements, frequencies of infectious complications requiring hospitalization, and the two renal replacement modalities mentioned above were compared in terms of these parameters.

**RESULTS:** Serum albumin levels of the patients with FMF amyloidosis who were maintained on peritoneal dialysis treatment were lower (2.87 vs 3.45) and the frequency of infections of the same group was higher (4.2 vs 0.5) than the patients with ESRD secondary to other diseases in the CAPD group.

**CONCLUSIONS:** This retrospective analysis showed that peritoneal dialysis may have some disadvantages in amyloidotic patients. Due to the high frequency of

hypoalbuminemia and infectious complications seen in this group, peritoneal dialysis is widely accepted as an alternative choice of treatment when hemodialysis is not appropriate.

DOI: 10.1080/08860220601166560

PMID: 17497446 [Indexed for MEDLINE]

3917. Clin Orthop Relat Res. 2007 Sep;462:11-9.

Chronic recurrent multifocal osteomyelitis: a concise review and genetic update.

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Chronic recurrent multifocal osteomyelitis is an autoinflammatory disorder characterized by bone pain and fever, a course of exacerbations and remissions, and a frequent association with other inflammatory conditions. Because its etiology is largely unknown, the diagnosis is still based on clinical criteria; treatment is empiric and not always successful. The diagnosis is supported by the presence of osteolytic lesions with surrounding sclerosis apparent on radiographs, and silent asymptomatic lesions frequently appear on nuclear scans. The histologic findings in bone biopsies are nonspecific, showing inflammatory changes with granulocytic infiltration. Several observations suggest the contribution of genetic factors to the etiology of chronic recurrent multifocal osteomyelitis. Indeed, mutations in LPIN2 cause a syndromic form of chronic recurrent multifocal osteomyelitis known as Majeed syndrome, while mutations in pstpip2 cause a murine form of the disorder. The roles played by LPIN2 and the human homolog of pstpip2, PSTPIP2, in the etiology of chronic recurrent multifocal osteomyelitis are uncertain but are currently being investigated. We emphasize the need to validate diagnostic clinical criteria and develop new pathogenesis-based targeted therapy.

DOI: 10.1097/BLO.0b013e3180986d73

PMID: 17496555 [Indexed for MEDLINE]

3918. Saudi J Kidney Dis Transpl. 2007 Jun;18(2):151-8.

Childhood Henoch Schonlein purpura in Middle East countries.

Akl K.

HSP is the most common systemic vasculitis in children that is characterized by small vessel leukocytoclastic vasculitis. However, it is a self limiting disease, with few documented cases in Middle Eastern countries. Classic symptoms of the disease have been established in the literature, but new clinical features have recently been reported from Middle Eastern countries which include penile swelling, temporomandibular joint involvement, skin rash over the flexor surfaces of the extremities and pleural hemorrhagic effusion. Familial Mediterranean fever (FMF) may present as HSP. The prevalence of the FMF gene in Middle Eastern countries raises interesting questions regarding the use of colchicine in HSP patients.

PMID: 17496388 [Indexed for MEDLINE]

3919. Clin Genet. 2007 May;71(5):458-67.

MEFV alterations and population genetics analysis in a large cohort of Greek patients with familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is a disease characterized by recurrent, self-limiting bouts of fever and serositis and caused by altered pyrin due to mutated MEFV gene. FMF is common in the Mediterranean Basin populations, although with varying genetic patterns. The spectrum and clinical significance of MEFV alterations in Greece has yet not been elucidated. The aim of this study was to



analyze the spectrum of MEFV alterations in FMF patients and healthy individuals in Greece. A cohort of 152 Greek FMF patients along with 140 Greek healthy controls was enrolled. Non-isotopic RNase cleavage assay (NIRCA) and sequencing allowed mutational and haplotypic analysis of the entire coding sequence of MEFV. The ARLEQUIN 2.0, DNASP 4.0 and PHYLIP software were used for population genetics analysis. Among patients, 127 (83.6%) carried at least one known mutation. The most common mutations identified were M694V (38.1%), M680I (19.7%), V726A (12.2%), E148Q (10.9%) and E230K (6.1%). The total carrier rate among healthy individuals was 0.7%. The presence of R202Q homozygosity in 12 of the remaining 25 MEFV negative FMF patients might be considered as disease related in Greeks. Population genetics analysis revealed that Greeks rely closer to the eastern rather than western populations of the Mediterranean Basin.

DOI: 10.1111/j.1399-0004.2007.00789.x

PMID: 17489852 [Indexed for MEDLINE]

3920. *Pediatr Nephrol.* 2007 Sep;22(9):1391-4. Epub 2007 May 8.

A variant Muckle-Wells syndrome with a novel mutation in CIAS1 gene responding to anakinra.

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Muckle-Wells syndrome (MWS) is a subset of autoinflammatory diseases. It is characterized by recurrent inflammatory crises associated with fever, abdominal pain, persistent urticaria, arthralgia, sensorineural deafness, and possible development of multiorgan amyloid A protein (AA)-type amyloidosis. Mutations in the CIAS1 gene have been reported in MWS. Interleukin 1B (IL-1B) probably plays a major role in the pathophysiology of the disease, and IL-1B blockade may be therapeutic for this syndrome. We report here a Turkish child with MWS treated with anakinra. A novel mutation (I480F) was identified in exon 3 of the CIAS1 gene in this patient. The resolution of inflammatory symptoms, normalization of serological values, and improvement in hearing was noted with anakinra treatment.

DOI: 10.1007/s00467-007-0500-8  
PMID: 17486372 [Indexed for MEDLINE]

3921. Nihon Rinsho Meneki Gakkai Kaishi. 2007 Apr;30(2):123-32.

[Clinical features of Blau syndrome and early-onset sarcoidosis and associating CARD15/NOD2 gene mutations].

[Article in Japanese]

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Sarcoidosis is a systemic inflammatory disease clinically characterized by swelling of bilateral hilar lymph nodes and histologically defined by non-caseating epithelioid cell granulomas. Among child cases, a special subtype, called the early-onset sarcoidosis, is known to appear in children younger than 4 years of age and to be characterized by a distinct triad of skin, joint and eye disorders without pulmonary involvement. On the other hand, autosomal dominantly-transmitted disease with a characteristic features similar to those of early-onset sarcoidosis has been reported as Blau syndrome. By a linkage analysis, the responsible gene for Blau syndrome has been mapped close to the IBD (Inflammatory Bowel Disease) 1 locus. After CARD15 (NOD2), originally identified as the susceptibility gene for Crohn's disease, was also proved to be responsible for Blau syndrome, the same gene mutations have been found in sporadic early-onset sarcoidosis cases. Nod2 recognizes a signal from bacterial cell wall component in the cytoplasm of monocytic cells to activate NF-kappaB, and thus can work as an intracellular sensor of bacteria. While the loss-of-function mutations in its LRR domain are associated with Crohn's disease, Blau syndrome and early-onset sarcoidosis are autoinflammatory diseases that are caused by the gain-of-function mutations in its NOD domain.

PMID: 17473515 [Indexed for MEDLINE]

3922. Nihon Rinsho Meneki Gakkai Kaishi. 2007 Apr;30(2):114-22.

[Biological and clinical aspects of Muckle-Wells syndrome].

[Article in Japanese]

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Muckle-Wells syndrome (MWS), as well as familial cold autoinflammatory syndrome (FCAS) and chronic infantile neurological cutaneous and articular syndrome (CINCA), arises from a missense mutation in the CIAS1 gene. Current progress of biology revealed that NALP3, a protein coded by the CIAS1 and expressed in monocytes, recognizes some bacterial products or harmful metabolites invaded in the cytoplasm, and forms inflammasome with other molecules. As a result, caspase-1 is activated leading to cleavage of pro-IL-1beta and extracellular release of IL-1beta. NALP3 of patients with MWS can be spontaneously activated without obvious stimulation, which causes recurrent attacks of inflammatory symptoms characterized by fever, urticarial rash, conjunctivitis and arthritis, and some patients develop amyloidosis. In addition, sensorineural hearing disturbance progresses gradually. Recently, significant efficacy of anakinra, a recombinant IL-1 receptor antagonist, has been demonstrated in treatment of MWS. So far, only a few cases have been reported from Japan, however an accurate diagnosis has to be established for the latent cases who have not received optimum treatment before occurrence of irreversible deafness or renal failure.

PMID: 17473514 [Indexed for MEDLINE]

3923. Nihon Rinsho Meneki Gakkai Kaishi. 2007 Apr;30(2):108-13.

[Clinical features of CINCA syndrome: effects and problems of IL-1Ra].

[Article in Japanese]

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CINCA syndrome is an autoinflammatory syndrome characterized by neonatal onset of urticarial rash, central nervous system lesions and arthropathy. Laboratory findings show leucocytosis, anemia, elevation of CRP levels and acceleration of ESR. The syndrome is associated with CIAS1 gene and its encoding protein cryopyrin. The CIAS1 gene is expressed in monocytes, polymorphonuclear cells and chondrocytes. Mutations of cryopyrin lead to the persistent production of IL-1beta and activation of NF-kappaB, followed by excessive inflammatory reactions. In spite of aggressive therapies, the inflammation persists and the lesions are progressive. Recently, there have been reports of clinical improvement using human recombinant IL-1 receptor antagonist anakinra in the patients with CINCA syndrome and its related diseases, Muckle-Wells syndrome and familial cold-autoinflammatory syndrome, suggesting that IL-1beta plays an important role in the pathogenesis of the inflammation associated with the CIAS1 gene mutations. No serious adverse reaction of anakinra has not been reported. Following the diagnosis of CINCA syndrome, anakinra therapy should be started as the first line of therapy before irreversible disabilities develop. Treatment with anakinra has just begun, therefore, it is necessary to carry out further investigations concerning the adverse effects of anakinra and long-term prognosis for CINCA syndrome treated with anakinra.

PMID: 17473513 [Indexed for MEDLINE]

3924. Nihon Rinsho Meneki Gakkai Kaishi. 2007 Apr;30(2):101-7.

[Diagnosis and management of periodic fever with aphthous pharyngitis and adenitis (PFAPA)].

[Article in Japanese]

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PFAPA is non-hereditary syndrome characterized by periodic episodes of high fever, aphthous stomatitis, pharyngitis and cervical adenitis. It manifests usually in early childhood, especially before 5 years of age, and last for several years. Its etiology is unknown, but some recent reports suggest a dysregulation of the immune response with continuous pro-inflammatory cytokine activation and a reduced anti-inflammatory response both during and between febrile attacks. The diagnosis is clinical and it is important to exclude other entities of similar presentation with periodic fever and orofacial manifestations. The findings of laboratory are unspecified and show only nonspecific acute inflammatory response. Several treatments have been performed but with various results. Most effective therapy for a fast resolution of the symptoms is one or two doses of oral prednisone, but its efficacy is not permanent. Effectiveness of cimetidine and tonsillectomy in PFAPA is not clear as yet. PFAPA is a benign syndrome and the prognosis is better than other autoinflammatory syndromes, because PFAPA patients grow normally and symptoms diminish within a few years.

PMID: 17473512 [Indexed for MEDLINE]

3925. Nihon Rinsho Meneki Gakkai Kaishi. 2007 Apr;30(2):90-100.

[TNF receptor-associated periodic syndrome (TRAPS) in Japan: clinical characterization, pathogenesis, diagnostic criteria, and treatment].

[Article in Japanese]

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TNF receptor-associated periodic syndrome (TRAPS) is an autosomal dominant inherited disease characterized by prolonged episodes of periodic fever and localized inflammation. The hypothetical pathogenesis of TRAPS is defective TNF receptor 1 (TNFRSF1A) shedding from cell membranes in response to a stimulus

including TNFalpha. This mechanism has recently been shown to account for a minor population of TRAPS patients and other mechanisms are reported to explain the disease, such as resistance to apoptosis, TNFRSF1A internalization, or TNFRSF1A misfolding and aggregation, leading to NF-kappaB activation and apoptosis. Until now 15 TRAPS patients from 5 pedigree including 5 different mutations (C30R, C30Y, T61I, C70S, C70G) had been reported in Japan. There were many sporadic cases of TRAPS without TNFRSF1A mutation in our epidemiological study. In this issue, we described the clinical characterization, pathogenesis, diagnostic criteria, and treatment of TRAPS according to our case and literature.

PMID: 17473511 [Indexed for MEDLINE]

3926. Nihon Rinsho Meneki Gakkai Kaishi. 2007 Apr;30(2):86-9.

[MVK gene abnormality and new approach to treatment of hyper IgD syndrome and periodic fever syndrome].

[Article in Japanese]

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Hyper IgD and periodic fever syndrome (HIDS; OMIM 260920) is one of the hereditary autoinflammatory syndromes characterized by recurrent episodes of fever and inflammation.. HIDS is an autosomal recessive disorder characterized by recurrent fever attacks in early childhood. HIDS caused by mevalonate kinase (MK) mutations, also that is the gene of mevalonic aciduria (OMIM 251170). During febrile episodes, urinary mevalonate concentrations were found to be significantly elevated in patients. Diagnosis of HIDS was retrieving gene or measurement of the enzyme activity in peripheral blood lymphocyte in general. This of HIDS is an activity decline of MK, and a complete deficiency of MK becomes a mevalonic aciduria with a nervous symptom. The relation between the fever and inflammation of mevalonate or isoprenoid products are uncertain. The therapy attempt with statins, which is inhibited the next enzyme after HMG-CoA reductase, or inhibit the proinflammatory cytokines.

PMID: 17473510 [Indexed for MEDLINE]

3927. Nihon Rinsho Meneki Gakkai Kaishi. 2007 Apr;30(2):78-85.

[Familial Mediterranean fever: MEFV gene mutations and treatment].

[Article in Japanese]

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Familial Mediterranean fever (FMF) is an autosomal recessive disease which predominantly affects certain ethnic groups mainly Sephardic Jews, Turks, Arabs and Armenians. FMF has been rarely reported in Japan. Characteristic symptoms include self-limited recurrent attacks of fever with serositis such as peritonitis, pleuritis, and arthritis. The most serious complications of FMF are secondary AA amyloidosis and subsequent chronic renal failure. FMF is caused by mutations in MEFV gene which encodes a protein called pyrin. Pyrin regulates processing of IL-1beta, NF-kappaB activation and apoptosis. Dysregulated function of pyrin results in excessive production of proinflammatory cytokine thereby evoking inflammatory attacks. The mainstay of treatment is colchicine which is effective for both relieving symptoms and preventing secondary amyloidosis.

PMID: 17473509 [Indexed for MEDLINE]

3928. Nihon Rinsho Meneki Gakkai Kaishi. 2007 Apr;30(2):68-77.

[The molecular mechanism of autoinflammatory disease--lessons from the function of NOD protein families].

[Article in Japanese]

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The latest decade, our understanding of pattern-recognizing receptors involved in innate immune system has been accumulated. One class of the pattern recognizing receptors, the toll-like receptors (TLRs) are well known to detect extracellular pathogens on the cell surface membrane. On the other hand, recently discovered the nucleotide-binding oligomerization domain proteins (NODs) are involved in recognizing intracellular pathogens. Since Nod2, one of the NODs, mutations were found to associate with susceptibility of Crohn's disease, the NODs have been highlighted. For example, cryopyrin mutations have been reported to associate with Familial cold urticaria (FCU)/Familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), Neonatal onset multisystem inflammatory disease (NOMID)/Chronic infantile neurologic cutaneous and articular syndrome (CINCA). Here, we summarize the discovery of the NODs and related molecules, and also discuss the function of the NODs and molecular mechanisms of the autoinflammatory diseases.

PMID: 17473508 [Indexed for MEDLINE]

3929. Nihon Rinsho Meneki Gakkai Kaishi. 2007 Apr;30(2):63-7.

[Clinical observation of autoinflammatory diseases].

[Article in Japanese]

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A disease, which repeats inflammations but is not based on infections or autoimmunity, was recently defined as autoinflammatory diseases. The



autoinflammatory diseases are a new and expanding classification of inflammatory diseases characterized by recurrent episodes of systemic inflammation in the absence of pathogens, autoantibodies or antigen specific T cells. This disease is developed by the abnormality of molecules which regulate inflammation, innate immunity and apoptosis, and patients have been suffered with treatment by the difficulty of making a diagnosis. However, a diagnosis is comparatively easy by their presenting the characteristic clinical observation. In addition, genetic analysis can put the diagnosis on a firm basis. Giving that therapies for individual disorder of autoinflammatory diseases are different, we always put these disorders in mind when we saw patients who have unknown persistent inflammation.

PMID: 17473507 [Indexed for MEDLINE]

3930. Nihon Rinsho Meneki Gakkai Kaishi. 2007 Apr;30(2):61-2.

[Autoinflammatory syndrome].

[Article in Japanese]

[No authors listed]

PMID: 17473506 [Indexed for MEDLINE]

3931. J Leukoc Biol. 2007 Aug;82(2):259-64. Epub 2007 Apr 30.

The inflammasome in pathogen recognition and inflammation.

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(1)Infectious Diseases, Yale University School of Medicine, New Haven, Connecticut 06520, USA.

The nucleotide-binding oligomerization domain-like receptor (NLR) family of

proteins is involved in the regulation of innate immune responses and cell death pathways. Some NLR family members promote the activation of proinflammatory caspases within multiprotein complexes, called inflammasomes. Recent studies analyzing mice deficient in various components of the inflammasome have provided insight into the role of these molecules in host defense against pathogens and in autoinflammatory disorders. Here, we review these studies and propose that membrane disruption leads to activation of the inflammasome.

DOI: 10.1189/jlb.1206755

PMID: 17470531 [Indexed for MEDLINE]

3932. Ned Tijdschr Geneesk. 2007 Apr 7;151(14):836-7; author reply 837.

[A Dutch family with the hereditary periodic fever or tumour necrosis factor receptor-associated periodic syndrome (TRAPS)].

[Article in Dutch]

Bodar EJ, Drenth JP, Simon A, van der Meer JW.

Comment on

Ned Tijdschr Geneesk. 2006 Dec 9;150(49):2711-4.

PMID: 17469326 [Indexed for MEDLINE]

3933. Arthritis Rheum. 2007 May;56(5):1706-12.

Country as the primary risk factor for renal amyloidosis in familial Mediterranean fever.

Touitou I(1), Sarkisian T, Medlej-Hashim M, Tunca M, Livneh A, Cattan D, Yalçinkaya F, Ozen S, Majeed H, Ozdogan H, Kastner D, Booth D, Ben-Chetrit E, Pugnère D, Michelon C, Séguret F, Gershoni-Baruch R; International Study Group for Phenotype-Genotype Correlation in Familial Mediterranean Fever.

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Comment in

Arthritis Rheum. 2007 Nov;56(11):3879-80; author reply 3880.

**OBJECTIVE:** Familial Mediterranean fever (FMF), the prototype of autoinflammatory disorders, is caused by recessive mutations in the MEFV gene. Some FMF patients develop renal amyloidosis, a potentially fatal condition. This complication has mainly been associated with the M694V mutation, although the different study designs, small numbers of patients, and/or evaluation of few or no covariables calls this association into question. The aim of this study was to examine the controversial issue of amyloidosis susceptibility in FMF by determining the relative contributions of MEFV and numerous epidemiologic factors to the risk of renal amyloidosis.

**METHODS:** Online questionnaires were completed at the MetaFMF database by patients at 35 centers in 14 countries. Using a standardized mode of data collection, we retrieved crude initial data from over half of the genetically confirmed FMF patients referred worldwide until May 2003 (2,482 cases, including 260 patients who developed renal amyloidosis).

**RESULTS:** Amyloid nephropathy was present in 11.4% of the cases. In the total study population, country of recruitment was the leading risk factor for this manifestation (odds ratio 3.2 [95% confidence interval 1.8-5.9]), followed by M694V homozygosity, proband status, and disease duration. Differing results were found when countries were stratified.

**CONCLUSION:** Country of recruitment, rather than MEFV genotype, is the key risk factor for renal amyloidosis in FMF. This risk, which parallels infant mortality rates, indicates a possible environmental origin of amyloidosis susceptibility. The patient's country should be considered in addition to MEFV genotype as an indication for prophylactic colchicine, a treatment suggested for asymptomatic individuals who are incidentally discovered to be M694V homozygous.

DOI: 10.1002/art.22507

PMID: 17469185 [Indexed for MEDLINE]

3934. Scand J Rheumatol. 2007 Jan-Feb;36(1):48-52.

Common FMF alleles may predispose to development of Behcet's disease with

increased risk for venous thrombosis.

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**BACKGROUND:** Behcet's disease (BD) is an inflammatory disorder of unknown cause, associated with vasculitis. Arterial or venous thrombosis occurs in about 25% of BD patients. Familial Mediterranean fever (FMF) is another inflammatory disorder, which stems from mutations in the FMF gene (MEFV) and shares a number of features with BD.

**OBJECTIVE:** MEFV analysis in patients with BD suggests that mutated MEFV may act as a susceptibility gene in BD. We studied the rate and the clinical correlates of MEFV mutations in Israeli BD patients.

**METHODS:** Included were 54 BD patients who satisfied the International Study Group criteria for BD. All BD patients were genotyped using polymerase chain reaction (PCR) and restriction enzyme analysis for the three most common MEFV mutations (M694V, V726A, and E148Q). The association between BD manifestations and MEFV alleles was analysed.

**RESULTS:** Twenty-one BD patients were found to carry a single MEFV mutation and three additional patients were compound heterozygotes, a frequency significantly higher than that expected for ethnically matched healthy individuals. There were no statistically significant differences between carriers and non-carriers with respect to gender, frequency of HLA B5 antigen, cutaneous lesions, joint disease, and severity score. However, carriers did experience thrombosis more often [54% vs. 17%,  $p < 0.005$ , odds ratio (OR) = 6.9, 95% confidence interval (CI) 1.75-26.9] and uveitis less often (20% vs. 40%,  $p < 0.05$ , OR = 0.2, 95% CI 0.04-0.92).

**CONCLUSIONS:** MEFV appears to be a susceptibility and modifier gene in BD.

DOI: 10.1080/03009740600759639

PMID: 17454935 [Indexed for MEDLINE]

3935. J Leukoc Biol. 2007 Aug;82(2):220-5. Epub 2007 Apr 18.

Caspase-1 inflammasomes in infection and inflammation.

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Nucleotide-binding and oligomerization domain-like receptors (NLRs) constitute a family of germline-encoded pattern-recognition receptors, which allow the host to respond rapidly to a wide variety of pathogenic microorganisms. Here, we discuss recent advances in the study of a subset of NLRs, which control the activation of caspase-1 through the assembly of large protein complexes, inflammasomes. The NALP1b inflammasome recognizes anthrax lethal toxin, and flagellin from *Salmonella* and *Legionella* induces assembly of the Ipaf inflammasome. Cryopyrin/NALP3 mediates caspase-1 activation in response to a wide variety of bacterial ligands, imidazoquinolines, dsRNA, and the endogenous danger signal uric acid. The importance of these cytosolic receptors in immune regulation is underscored by the identification of mutations in cryopyrin/NALP3, which are genetically linked to human autoinflammatory disorders.

DOI: 10.1189/jlb.1206756

PMID: 17442855 [Indexed for MEDLINE]

3936. Eur J Pediatr. 2008 Mar;167(3):279-85. Epub 2007 Apr 14.

Is Familial Mediterranean Fever a thrombotic disease or not?

Demirel A(1), Celkan T, Kasapcopur O, Bilgen H, Ozkan A, Apak H, Arisoy N, Yildiz I.

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The aim of our study was to show how the progression and severity of Familial Mediterranean Fever (FMF) is affected by procoagulant activity and alterations in the markers of thrombosis and fibrinolysis. The study cohort comprised 64 FMF patients who were classified as attack-free patients (Group 1; n = 34 patients, aged 3-19 years) and attack patients (Group 2; n = 30 patients, aged 3-21 years).

All patients were on colchicine treatment with the exception the newly diagnosed patients in Group 2. A total of 14 healthy subjects between 5-12 years of age were enrolled as controls (Group 3). Laboratory tests, including leukocyte and thrombocyte counts, erythrocyte sedimentation rate, CRP, fibrinogen, PT, aPTT, Factor VIII, vW factor, D-dimer, P-selectin, tPA and PAI-1, were carried out on all patients. Inflammation continued both during the attack and attack-free period in FMF. The prolongation of PT was observed during attacks (PT = 13.6 s in Group 2, and PT = 12.6 s in Group 3;  $p = 0.002$ ). tPA levels increased in FMF patients (tPA levels of group 1, 2 and 3 were 12.6, 13.2 and 9.7 ng/ml, respectively;  $p = 0.01$ ). P-selectin was lower in both patient groups than in the control group. During attack periods PAI-1 levels increased (PAI-1 level of Group 1: 89.6 ng/ml and PAI-1 level of Group 2: 335.7 ng/ml,  $p = 0.000$ ). Inflammation with increased acute phase reactants continued during both attack and attack-free periods in FMF patients. Prolongation of PT and differences in tPA and P-selectin levels suggest that hypercoagulability may have a role in the etiopathogenesis of FMF. It may be possible to use PAI-1 as a marker for the attacks of FMF.

DOI: 10.1007/s00431-007-0475-2

PMID: 17436016 [Indexed for MEDLINE]

3937. Cell Death Differ. 2007 Aug;14(8):1457-66. Epub 2007 Apr 13.

The SPRY domain of Pyrin, mutated in familial Mediterranean fever patients, interacts with inflammasome components and inhibits proIL-1 $\beta$  processing.

Papin S(1), Cuenin S, Agostini L, Martinon F, Werner S, Beer HD, Grütter C, Grütter M, Tschopp J.

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The autoinflammatory disorders Muckle-Wells syndrome, familial cold urticaria and chronic infantile neurological cutaneous and articular syndrome are associated with mutations in the NALP3 (Cryopyrin) gene, which is the central platform of the proinflammatory caspase-1 activating complex, named the inflammasome. In patients with another autoinflammatory disorder, familial Mediterranean fever (FMF), mutations in the SPRY domain of the Pyrin protein are frequently found.

Recent evidence suggests that Pyrin associates with ASC, an inflammasome component, via its Pyrin domain, thereby halting the inflammatory response. This interaction, however, does not explain the effects of mutations of the SPRY domain found in FMF patients. Here we show that the Pyrin SPRY domain not only interacts with NALP3, but also with caspase-1 and its substrate pro-interleukin(IL)-1beta. Whereas a Pyrin knockdown results in increased caspase-1 activation and IL-1beta secretion, overexpression of the SPRY domain alone blocks these processes. Thus Pyrin binds to several inflammasome components thereby modulating their activity.

DOI: 10.1038/sj.cdd.4402142

PMID: 17431422 [Indexed for MEDLINE]

3938. Clin Rheumatol. 2007 Dec;26(12):2059-2062. doi: 10.1007/s10067-007-0617-y. Epub 2007 Apr 6.

Accurate diagnosis of acute abdomen in FMF and acute appendicitis patients: how can we use procalcitonin?

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Comment in

This study was conducted to define the value of procalcitonin (PCT) levels in the differential diagnosis of abdominal familial Mediterranean fever (FMF) attacks from acute appendicitis. From October 2006 to January 2007, 28 FMF (12 males, 16 females) patients with acute abdominal attacks and 34 patients (18 males) with acute abdomen who underwent operation with the clinical diagnosis of acute appendicitis were consecutively enrolled in this study. FMF patients with concurrent infectious diseases were excluded. PCT values were measured by an immunofluorescent method using the B.R.A.H.M.S. PCT kit (B.R.A.H.M.S. Diagnostica, Berlin, Germany). Erythrocyte sedimentation rate (ESR), C-reactive proteins (CRP) and leucocyte levels were also noted. Mean disease duration in FMF patients was 9.6 +/- 8.1 years (range 2-33 years) and all were on colchicine therapy with a mean colchicine dosage of 1.2 +/- 0.4 mg/day. Among the operated patients, 5 were excluded: 3 patients had normal findings and 2 had intestinal perforation (PCT levels were 2.69 and 4.93 ng/ml, respectively) at operative and pathologic evaluation. There were no significant differences between the two groups with respect to gender and age (p was not significant (NS) for all). Acute phase reactants and PCT levels were increased in patients with FMF compared to patients with acute appendicitis (0.529[0.12 +/- 0.96] vs 0.095 [0.01-0.80] p < 0.001, respectively). PCT levels higher than 0.5 ng/ml were found in 11% (3/28) of FMF patients compared to 62% (18/29) of acute appendicitis patients (p < 0.001). Our results suggest that PCT could be a useful test in the differentiation of abdominal FMF attacks from acute appendicitis, though it should not supplant more conventional investigations.

DOI: 10.1007/s10067-007-0617-y

PMID: 17415505 [Indexed for MEDLINE]

3939. Pediatr Infect Dis J. 2007 Apr;26(4):353-4.

The hereditary autoinflammatory syndromes.

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DOI: 10.1097/01.inf.0000258777.86510.da

PMID: 17414402 [Indexed for MEDLINE]

3940. J Dermatol. 2007 May;34(5):344-8.

Juvenile psoriatic arthritis carrying familial Mediterranean fever gene mutations in a 14-year-old Turkish girl.

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Juvenile psoriatic arthritis (JPsA) is characterized by asymmetric arthritis of big and small joints, enthesitis, dactylitis, psoriatic skin lesions and nail pitting. Investigators agree that JPsA is a relatively common chronic arthropathy of childhood that differs clinically, serologically, and genetically from both juvenile idiopathic arthritis and juvenile ankylosing spondylitis. Familial Mediterranean fever (FMF) is a multisystemic autosomal recessive disease occasionally accompanied by sacroiliitis. This is characterized by recurrent self-limited attacks of fever and accompanying abdominal, chest and arthritic pain. We present a 14-year-old Turkish girl with JPsA and carrying FMF gene mutations. In this patient, JPsA was diagnosed according to her physical, laboratory and skin biopsy findings and a treatment with methotrexate and sulfasalazine was started. As an inadequate clinical and laboratory response was obtained after the first month of therapy, the patient was investigated for FMF, and was diagnosed by molecular analyses of related gene (E148Q heterozygous/V726A homozygous mutation) besides clinical findings. After 2 weeks of the colchicine treatment, symptoms of the patient regressed and acute phase reactants decreased. To our knowledge, this is the first case presenting with psoriatic arthritis and FMF gene mutations together and responds to colchicine, methotrexate and sulfasalazine dramatically in clinical and laboratory findings. This case has been presented to remind that cases with psoriatic arthritis may also carry mutations in the MEFV gene.

DOI: 10.1111/j.1346-8138.2007.00285.x

PMID: 17408446 [Indexed for MEDLINE]

3941. J Leukoc Biol. 2007 Jul;82(1):177-83. Epub 2007 Apr 2.

MDP-induced interleukin-1beta processing requires Nod2 and CIAS1/NALP3.

Pan Q(1), Mathison J, Fearn C, Kravchenko VV, Da Silva Correia J, Hoffman HM, Kobayashi KS, Bertin J, Grant EP, Coyle AJ, Sutterwala FS, Ogura Y, Flavell RA, Ulevitch RJ.

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Nucleotide-binding oligomerization domain (Nod)2 is a sensor of muramyl dipeptides (MDP) derived from bacterial peptidoglycan. Nod2 also plays a role in some autoinflammatory diseases. Cold-induced autoinflammatory syndrome 1 (CIAS1)/NACHT domain, leucine-rich repeat, and pyrin domain-containing protein 3 (NALP3) has been suggested to be sufficient for MDP-dependent release of mature IL-1beta, but the role of Nod2 in this process is unclear. Using mice bearing selective gene deletions, we provide in vitro and in vivo data showing that MDP-induced IL-1beta release requires Nod2 and CIAS1/NALP3 as well as receptor-interacting protein-2 (Rip2), apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (ASC), and caspase-1. In contrast, MDP-dependent IL-6 production only requires Nod2 and Rip2. Together, our data provide a new understanding of this important pathway of IL-1beta production and allow for further studies of the role of these proteins within the broader context of inflammatory disease.

DOI: 10.1189/jlb.1006627

PMID: 17403772 [Indexed for MEDLINE]

3942. Proc Natl Acad Sci U S A. 2007 Apr 10;104(15):6200-5. Epub 2007 Mar 30.

Structural basis for PRYSPRY-mediated tripartite motif (TRIM) protein function.

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The human tripartite motif (TRIM) family comprises 70 members, including HIV restriction factor TRIM5alpha and disease-associated proteins TRIM20 (pyrin) and TRIM21. TRIM proteins have conserved domain architecture but diverse cellular roles. Here, we describe how the C-terminal PRYSPRY domain mediates diverse TRIM functions. The crystal structure of TRIM21 PRYSPRY in complex with its target IgG Fc reveals a canonical binding interface comprised of two discrete pockets formed by antibody-like variable loops. Alanine scanning of this interface has identified the hot-spot residues that control TRIM21 binding to Fc; the same hot-spots control HIV/murine leukemia virus restriction by TRIM5alpha and mediate severe familial Mediterranean fever in TRIM20/pyrin. Characterization of the IgG binding site for TRIM21 PRYSPRY reveals TRIM21 as a superantigen analogous to bacterial protein A and suggests that an antibody bipolar bridging mechanism may contribute to the pathogenic accumulation of anti-TRIM21 autoantibody immune complex in autoimmune disease.

DOI: 10.1073/pnas.0609174104

PMCID: PMC1851072

PMID: 17400754 [Indexed for MEDLINE]

3943. Arthritis Rheum. 2007 Apr;56(4):1273-1285. doi: 10.1002/art.22491.

The clinical continuum of cryopyrinopathies: novel CIAS1 mutations in North American patients and a new cryopyrin model.

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(#)Contributed equally

**OBJECTIVE:** The cryopyrinopathies are a group of rare autoinflammatory disorders that are caused by mutations in CIAS1, encoding the cryopyrin protein. However, cryopyrin mutations are found only in 50% of patients with clinically diagnosed cryopyrinopathies. This study was undertaken to investigate the structural effect of disease-causing mutations on cryopyrin, in order to gain better understanding of the impact of disease-associated mutations on protein function.

**METHODS:** We tested for CIAS1 mutations in 22 patients with neonatal-onset multisystem inflammatory disease/chronic infantile neurologic, cutaneous, articular syndrome, 12 with Muckle-Wells syndrome (MWS), 18 with familial cold-induced autoinflammatory syndrome (FCAS), and 3 probands with MWS/FCAS. In a subset of mutation-negative patients, we screened for mutations in proteins that are either homologous to cryopyrin or involved in the caspase 1/interleukin-1 $\beta$  signaling pathway. CIAS1 and other candidate genes were sequenced, models of cryopyrin domains were constructed using structurally homologous proteins as templates, and disease-causing mutations were mapped.

**RESULTS:** Forty patients were mutation positive, and 7 novel mutations, V262A, C259W, L264F, V351L, F443L, F523C, and Y563N, were found in 9 patients. No mutations in any candidate genes were identified. Most mutations mapped to an inner surface of the hexameric ring in the cryopyrin model, consistent with the hypothesis that the mutations disrupt a closed form of cryopyrin, thus potentiating inflammasome assembly. Disease-causing mutations correlated with disease severity only for a subset of known mutations.

**CONCLUSION:** Our modeling provides insight into potential molecular mechanisms by which cryopyrin mutations can inappropriately activate an inflammatory response. A significant number of patients who are clinically diagnosed as having cryopyrinopathies do not have identifiable disease-associated mutations.

DOI: 10.1002/art.22491

PMCID: PMC4321998

PMID: 17393462 [Indexed for MEDLINE]

3944. Rheumatol Int. 2007 Sep;27(11):1083-5. Epub 2007 Mar 27.

Protracted familial mediterranean fever arthritis presenting as septic arthritis.

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In Familial Mediterranean Fever (FMF), arthritis is the initial symptom in 25% of patients. Although FMF arthritis is acute and self-limited, in 5% of cases protracted arthritis usually affecting large joints such as knee may occur. In this report, two cases are presented who were initially diagnosed as septic arthritis, first of which had four and the second had two synovectomy operations with the diagnosis of septic arthritis. Later on they were diagnosed as FMF with detailed history. We aimed to emphasize the importance of diagnosis of FMF, which is based mainly on history and clinical features in order to prevent unnecessary operations and suffering of the patient.

DOI: 10.1007/s00296-007-0329-2

PMID: 17387477 [Indexed for MEDLINE]

3945. J Mol Diagn. 2007 Apr;9(2):228-36.

Comprehensive arrayed primer extension array for the detection of 59 sequence variants in 15 conditions prevalent among the (Ashkenazi) Jewish population.

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Erratum in

J Mol Diagn. 2008 Jan;10(1):109.

In the Ashkenazi Jewish population, serious and lethal genetic conditions occur with relatively high frequency. A single test that encompasses the majority of population-specific mutations is not currently available. For comprehensive carrier screening and molecular diagnostic purposes, we developed a population-specific and inclusive microarray. The arrayed primer extension genotyping microarray carries 59 sequence variant detection sites, of which 53 are detectable bi-directionally. These sites represent the most common variants in Tay-Sachs disease, Bloom syndrome, Canavan disease, Niemann-Pick A, familial

dysautonomia, torsion dystonia, mucopolidosis type IV, Fanconi anemia, Gaucher disease, factor XI deficiency, glycogen storage disease type 1a, maple syrup urine disease, nonsyndromic sensorineural hearing loss, familial Mediterranean fever, and glycogen storage disease type III. Several mutations in the selected disorders that are not prevalent per se in the Ashkenazi Jewish populations, as well pseudodeficiency alleles, are also included in the array. The initial technical evaluation of this microarray demonstrates that it is comprehensive, robust, sensitive, specific, and easily modifiable. This cost-effective array is based on a diversely applied platform technology and is suitable for both carrier screening and disease detection in Ashkenazi and Sephardic Jewish populations.

DOI: 10.2353/jmoldx.2007.060100

PMCID: PMC1867437

PMID: 17384215 [Indexed for MEDLINE]

3946. N Engl J Med. 2007 Mar 22;356(12):1216-25.

NALP1 in vitiligo-associated multiple autoimmune disease.

Jin Y(1), Mailloux CM, Gowan K, Riccardi SL, LaBerge G, Bennett DC, Fain PR, Spritz RA.

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Comment in

N Engl J Med. 2007 Mar 22;356(12):1263-6.

**BACKGROUND:** Autoimmune and autoinflammatory diseases involve interactions between genetic risk factors and environmental triggers. We searched for a gene on chromosome 17p13 that contributes to a group of epidemiologically associated autoimmune and autoinflammatory diseases. The group includes various combinations of generalized vitiligo, autoimmune thyroid disease, latent autoimmune diabetes in adults, rheumatoid arthritis, psoriasis, pernicious anemia, systemic lupus erythematosus, and Addison's disease.

**METHODS:** We tested 177 single-nucleotide polymorphisms (SNPs) spanning the 17p13 linkage peak for association with disease and identified a strong candidate gene.

We then sequenced DNA in and around the gene to identify additional SNPs. We carried out a second round of tests of association using some of these additional SNPs, thus elucidating the association with disease in the gene and its extended promoter region in fine detail.

**RESULTS:** Association analyses resulted in our identifying as a candidate gene NALP1, which encodes NACHT leucine-rich-repeat protein 1, a regulator of the innate immune system. Fine-scale association mapping with the use of DNA from affected families and additional SNPs in and around NALP1 showed an association of specific variants with vitiligo alone, with an extended autoimmune and autoinflammatory disease phenotype, or with both. Conditional logistic-regression analysis of NALP1 SNPs indicated that at least two variants contribute independently to the risk of disease.

**CONCLUSIONS:** DNA sequence variants in the NALP1 region are associated with the risk of several epidemiologically associated autoimmune and autoinflammatory diseases, implicating the innate immune system in the pathogenesis of these disorders.

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DOI: 10.1056/NEJMoa061592

PMID: 17377159 [Indexed for MEDLINE]

3947. Arch Dermatol. 2007 Mar;143(3):386-91.

Widespread granulomatous dermatitis of infancy: an early sign of Blau syndrome.

Schaffer JV(1), Chandra P, Keegan BR, Heller P, Shin HT.

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**BACKGROUND:** Pediatric sarcoidosis has traditionally been divided into 2 distinct groups: (1) school-aged children and adolescents with frequent involvement of the lungs and mediastinal lymph nodes (similar to adult sarcoidosis) and (2) infants and preschoolers with the triad of arthritis, uveitis, and a cutaneous eruption of discrete small papules, referred to as early-onset sarcoidosis. Blau syndrome, a rare autosomal dominant genodermatosis caused by mutations in the NOD2

(nucleotide-binding oligomerization domain 2) gene, has been considered as the familial form of early-onset sarcoidosis.

**OBSERVATIONS:** A 9-month-old boy developed an asymptomatic eruption of 1- to 2-mm, red-brown to pinkish tan, flat-topped papules on the face, trunk, and extremities. There was no evidence of ocular involvement or arthritis. The skin lesions were characterized histologically by noncaseating granulomas in a periadnexal distribution within the dermis. A family history of uveitis supported a diagnosis of Blau syndrome, and analysis of the NOD2 gene revealed a heterozygous gain-of-function missense mutation (Arg334Trp) that has previously been detected in Blau syndrome kindreds.

**CONCLUSION:** We draw attention to granulomatous dermatitis as an early manifestation of Blau syndrome and highlight emerging molecular evidence that this heritable autoinflammatory disorder and early-onset sarcoidosis represent a single disease entity.

DOI: 10.1001/archderm.143.3.386

PMID: 17372104 [Indexed for MEDLINE]

3948. Ren Fail. 2007;29(1):73-7.

Urinary glycosaminoglycan levels as a marker of renal amyloidosis in patients with familial Mediterranean fever.

Nadir H(1), Unver S, Ozel AM, Yazgan Y, Gultepe M, Evrenkaya TR, Demirturk L, Gurbuz AK.

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**INTRODUCTION AND AIM:** Familial Mediterranean Fever (FMF) is an autosomal recessive disease with a defect in the pyrine gene and is manifested with short attacks of inflammatory serositis, fever, and erysipelas-like skin lesions.

Secondary amyloidosis is the most serious complication of the disease, in which extracellular deposits of amyloid (an amorphous and eosinophilic protein) are seen in tissues. Glycosaminoglycans are mucopolysaccharide molecules that take place in amyloid deposits with fibrillar links to amyloid. They form glycoproteins by linking to proteins, and their free forms are excreted in the



urine in the form of polysaccharides. The aims of this study were to evaluate if the urinary levels of glycosaminoglycans have a predictive value in the diagnosis of amyloidosis secondary to FMF and if these levels are affected by treatment with colchicine.

**MATERIALS AND METHODS:** The study included 55 volunteer patients (age range: 18-36 years) with FMF (15 with amyloidosis) of the same socio-economic circumstances without other concomitant inflammatory, malignant, or chronic diseases, along with 20 healthy subjects as control. Urinary glycosaminoglycan levels were determined twice, once when the patients were on medication and once after they have stopped treatment for two weeks.

**RESULTS:** Initial mean urinary GAG levels were significantly lower in amyloidosis patients. Mean urinary GAG levels determined two weeks after the cessation of colchicine was also significantly lower than controls in both amyloidosis and non-amyloidosis FMF patients. Likewise, in patients with a disease duration longer than ten years, urinary GAG levels were also lower than those with a disease duration of less than three years.

**CONCLUSION:** Urinary GAG level can have a predictive value for amyloidosis in patients with FMF, and it can also be used as a non-invasive marker for screening the effects of colchicine on fibrillogenesis as well as for the follow-up of the patients.

DOI: 10.1080/08860220601039064

PMID: 17365913 [Indexed for MEDLINE]

3949. Arthritis Res Ther. 2007;9(2):R28.

A pilot study of IL-1 inhibition by anakinra in acute gout.

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Monosodium urate crystals stimulate monocytes and macrophages to release IL-1beta through the NALP3 component of the inflammasome. The effectiveness of IL-1 inhibition in hereditary autoinflammatory syndromes with mutations in the NALP3

protein suggested that IL-1 inhibition might also be effective in relieving the inflammatory manifestations of acute gout. The effectiveness of IL-1 inhibition was first evaluated in a mouse model of monosodium urate crystal-induced inflammation. IL-1 inhibition prevented peritoneal neutrophil accumulation but TNF blockade had no effect. Based on these findings, we performed a pilot, open-labeled study (trial registration number ISRCTN10862635) in 10 patients with gout who could not tolerate or had failed standard antiinflammatory therapies. All patients received 100 mg anakinra daily for 3 days. All 10 patients with acute gout responded rapidly to anakinra. No adverse effects were observed. IL-1 blockade appears to be an effective therapy for acute gouty arthritis. The clinical findings need to be confirmed in a controlled study.

DOI: 10.1186/ar2143

PMCID: PMC1906806

PMID: 17352828 [Indexed for MEDLINE]

3950. Int J Clin Pract. 2008 May;62(5):754-61. Epub 2007 Mar 1.

Effect of *Helicobacter pylori* infection and eradication therapy on interleukin-6 levels in patients with Familial Mediterranean Fever.

Ozel AM(1), Demirturk L, Aydogdu A, Gultepe M, Yazgan Y, Imirzalioglu N, Gurbuz AK, Narin Y.

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It is being questioned if *Helicobacter pylori* infection, which causes a chronic inflammatory response, can increase the frequency and severity of attacks in patients with Familial Mediterranean Fever (FMF) and if the impact of inflammatory response can be diminished by eradication of the infection. To evaluate if there is difference in interleukin (IL)-6 levels of *H. pylori*-positive and -negative patients both before and during FMF attacks; if there is a change in IL-6 levels following successful eradication treatment; and if MEFV gene mutations have an effect on IL-6 levels. IL-6 levels were evaluated in 47 FMF patients before and during FMF attacks. Genetic testing to determine M694V, M694I, E148Q, V726V, M680I mutations was also performed in all patients.

IL-6 levels were also determined after successful eradication of the infection in H. pylori-positive patients. IL-6 levels were compared in H. pylori-positive and -negative patients, and before and after eradication treatment in patients who cleared the infection. Number of patients in tested mutation groups was not enough to compare IL-6 levels in these groups. Thirty-four patients (73.9%) were H. pylori-positive. Before FMF attack there was no statistically significant difference in IL-6 levels of H. pylori-positive and -negative groups. IL-6 levels were significantly higher in both groups during the attacks than before the attacks ( $p < 0.05$ ). There was a statistically significant decline in IL-6 levels both before and during FMF attacks, following eradication therapy in patients who cleared the infection ( $p < 0.05$ ). In patients with homozygous M694V mutation, IL-6 levels before and during the FMF attacks were not significantly different in H. pylori-positive and -negative groups, despite a much lower level found in H. pylori-negative group ( $p > 0.05$ ). Comparisons were not performed in other mutation groups because of small number of patients in each group. C-reactive protein (CRP) and fibrinogen levels were not significantly different between the groups ( $p > 0.05$ ). We believe that the observation of IL-6 levels are lower both before and during FMF attacks both in H. pylori-negative patients and in patients who cleared the infection after eradication therapy is very important in the determination of the role of eradication of H. pylori on decreasing the frequency and severity of FMF attacks. As for today, the correlation between H. pylori infection and FMF seems unlikely; however, studies evaluating the interaction of cytokines in both diseases and their relations and roles will be needed to reach better conclusions.

DOI: 10.1111/j.1742-1241.2006.01098.x

PMID: 17343670 [Indexed for MEDLINE]

3951. Gut. 2007 Mar;56(3):342.

When does severe diarrhoea disclose a hereditary disease?

Boujaoude J(1), Honein K, Hobeika E, Ghorra C, Ghorra P, Hobeika E.

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DOI: 10.1136/gut.2006.093468

PMCID: PMC1856794

PMID: 17339243 [Indexed for MEDLINE]

3952. Am J Kidney Dis. 2007 Mar;49(3):477-81.

Successful treatment of renal amyloidosis due to familial cold autoinflammatory syndrome using an interleukin 1 receptor antagonist.

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Familial cold autoinflammatory syndrome (FCAS) is an autosomal dominant disorder characterized by episodic fever, arthralgias, conjunctivitis, and rash triggered by cold exposure. FCAS is rarely associated with progressive renal insufficiency caused by renal amyloidosis. The genetic defect in patients with this disorder is caused by a mutation in the gene encoding the protein cryopyrin, leading to uninhibited activation of systemic inflammation through specific cellular signaling with increased production of a number of key cytokines, including interleukin 1. We describe the successful treatment of a patient with renal amyloidosis caused by FCAS by using a novel interleukin 1-receptor antagonist. Use of specific anticytokine therapy may be a new paradigm in the treatment of patients with renal amyloidosis caused by systemic inflammatory diseases.

DOI: 10.1053/j.ajkd.2006.10.026

PMID: 17336710 [Indexed for MEDLINE]

3953. East Mediterr Health J. 2006 Nov;12(6):818-23.

Familial Mediterranean fever in children: a single centre experience in Jordan.

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Familial Mediterranean fever is quite prevalent among Arabs. We reviewed the files of 56 patients diagnosed with familial Mediterranean fever and followed up at King Hussein Medical Centre in Jordan over 4 years for their clinical profile, course, genotype, treatment and complications. There were 30 males and 26 females with a mean age at onset of 5.2 years. Abdominal pain (79%) was the commonest manifestation, followed by arthritis (13%) and chest pain (4%). Family history was positive in 50% of patients. Regarding treatment, 97% of patients responded well to colchicine, and amyloidosis was not documented in any patients after 5 years follow-up. The commonest genotype was M694 (64%), followed by heterozygous M694V-V726A (23%) and E148Q (8%).

PMID: 17333828 [Indexed for MEDLINE]

3954. Eur J Pediatr. 2008 Feb;167(2):245-7. Epub 2007 Mar 2.

A CIAS1 mutation in a Japanese girl with familial cold autoinflammatory syndrome.

Kanegane H(1), Itazawa T, Saito M, Nishikomori R, Makino T, Shimizu T, Adachi Y, Nakahata T, Miyawaki T.

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DOI: 10.1007/s00431-007-0451-x

PMID: 17333269 [Indexed for MEDLINE]

3955. Pediatr Rev. 2007 Mar;28(3):111-7.

Index of suspicion.

Luck RP(1), Soltani MA, Villalona JF, Lehman RK, Brown MR, Kooros K, Kwon JM.

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(1)Temple University Children's Medical Center, Philadelphia, PA, USA.

Erratum in

Pediatr Rev. 2007 Jun;28(6):234.

PMID: 17332170 [Indexed for MEDLINE]

3956. Arthritis Rheum. 2007 Mar;56(3):960-4.

A splice site mutation confirms the role of LPIN2 in Majeed syndrome.

Al-Mosawi ZS(1), Al-Saad KK, Ijadi-Maghsoodi R, El-Shanti HI, Ferguson PJ.

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Majeed syndrome is an autoinflammatory disorder consisting of chronic recurrent multifocal osteomyelitis, congenital dyserythropoietic anemia, and neutrophilic dermatosis. To date, 2 unrelated families with Majeed syndrome have been reported. Mutations in LPIN2 have been found in both families. Here we report a third consanguineous family with Majeed syndrome with a novel mutation. The patient, a 3-year-old Arabic girl, had hepatosplenomegaly and anemia as a neonate. At age 15 months, she developed recurrent episodes of fever and multifocal osteomyelitis. In addition, bone marrow aspiration demonstrated significant dyserythropoiesis, suggesting Majeed syndrome. Coding sequences and splice sites of LPIN2 were sequenced in the patient and her mother. A homozygous single-basepair change was detected in the donor splice site of exon 17 (c.2327+1G>C) in the patient; her mother was heterozygous at this site. These data confirm the role of LPIN2 mutations in the etiology of Majeed syndrome.

DOI: 10.1002/art.22431

PMID: 17330256 [Indexed for MEDLINE]

3957. Intern Med. 2007;46(5):221-5. Epub 2007 Mar 1.

Clinical study of 7 cases of familial Mediterranean fever with MEFV gene mutation.

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**OBJECTIVE:** Familial Mediterranean fever (FMF) had been considered a rare disease in Japan, but since the identification of the causative gene (MEFV) for pyrin/marenostrin in 1997, the occurrence of FMF has been successively reported. We reviewed the clinical features of 7 patients diagnosed with FMF by gene analysis.

**METHODS:** During April 2003 and March 2005, we investigated the clinical symptoms, treatment and MEFV types of 7 FMF patients who consulted the General Outpatient Clinic of Chiba University Hospital.

**RESULTS:** Six patients were in their 20-30s, and one was 54 years of age. There were 4 males and 3 females including a mother and child, and an adult male and his female cousin. Three were solitary incidences. In addition to intermittent fever, 4 patients had chest pain, 1 had abdominal pain, and 1 had chest or abdominal pain. The frequency of attacks was once per 3 months to 1 year in the early stage of the disease, but it slowly increased with disease progression.

Leukocytosis and C-reactive protein (CRP) elevation were noted during attacks in all patients. On investigation of MEFV, heterozygosity for the compound pyrin L110P-E148Q/M694I, E148Q/M694I, L110P/E148Q and heterozygosity for pyrin variant M694I alone were detected. Daily administration of colchicine at 0.5 mg prevented attacks in 6 patients, however 1 patient required 1.0 mg for adequate prevention.

**CONCLUSIONS:** Although the incidence is rare, internists should be aware of the characteristic symptoms of FMF: periodic fever and serositis symptoms, and its presence in Japan despite the disease name.

PMID: 17329916 [Indexed for MEDLINE]

3958. Hum Immunol. 2007 Feb;68(2):122-7. Epub 2006 Dec 27.

IL-10 genotype analysis in patients with Behçet's disease.

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Behçet's disease (BD) is a multisystem inflammatory disease characterized by recurrent orogenital ulceration, ocular inflammation, and skin lesions. The etiology of the disease is currently unknown but evidence suggests that there is a strong genetic component mediating the chronicity of the disorder. We have examined the association between polymorphisms at position -1082, and -819 in the promoter region of the gene encoding IL-10 in patients with Behçet's disease from two distinct patient populations. The IL-10 -1082AA genotype was weakly associated with BD when all patients were analyzed as a group ( $p = 0.04$ , OR 1.4, 95% CI 1.1-1.9), but not in the UK or Middle Eastern (ME) cohorts of patients alone compared to local controls. An association with IL-10 -819T was evident in all BD patients, ( $p = 0.02$ , OR 1.5, 95% CI 1.1-2.0), and this was because of an association in the UK but not ME patients ( $p = 0.0004$ , OR 2.1, 95% CI 1.4-3.3). The -1082A/-819T haplotype, which is linked to low production of this cytokine, was not significantly associated with Behçet's disease. This link between BD, a chronic, relapsing, autoinflammatory condition, and a genotype associated with low IL-10 production provides evidence that abnormalities in the genetic control of cytokine levels may be relevant in influencing the immune response in Behçet's disease in some patient groups.

DOI: 10.1016/j.humimm.2006.11.010

PMID: 17321902 [Indexed for MEDLINE]

3959. J Allergy Clin Immunol. 2007 Apr;119(4):991-6. Epub 2007 Feb 22.

Monocytes from familial cold autoinflammatory syndrome patients are activated by mild hypothermia.

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**BACKGROUND:** Familial cold autoinflammatory syndrome (FCAS) is characterized by rash, fever, and arthralgia in response to cold exposure. CIAS1, the gene that codes for cryopyrin, is mutated in FCAS. Treatment with anakinra (IL-1 receptor antagonist) prevents symptoms, indicating a crucial role for IL-1 in this disease.

**OBJECTIVE:** To study cytokine responses to cold exposure in monocytes from subjects with FCAS.

**METHODS:** Adherence-enriched monocytes were incubated at 32 degrees C or 37 degrees C. Transcription and release of IL-1beta, IL-6, and TNF-alpha were monitored by quantitative PCR and ELISA.

**RESULTS:** The FCAS monocytes but not control cells responded to 4 h incubation at 32 degrees C with significant secretion of IL-1beta. At 16 h, IL-1beta, IL-6, and TNF-alpha were all significantly elevated in FCAS monocytes at 32 degrees C. Increased cytokine transcription was observed in all monocytes at 4 hours, but at 16 hours it was only seen in FCAS monocytes incubated at 32 degrees C. Incubation at 32 degrees C for as little as 1 hour sufficed to induce measurable IL-1beta release. Caspase-1 inhibitors prevented the cold-induced IL-1beta release, whereas a purinergic antagonist did not. Anakinra had no effect on the early IL-1beta release but significantly reduced the late-phase transcription and release of all cytokines.

**CONCLUSION:** FCAS monocytes respond to mild hypothermia with IL-1beta release, which in turn induces autocrine transcription and secretion of IL-6 and TNF-alpha as well as stimulation of further IL-1beta production.

**CLINICAL IMPLICATIONS:** These results confirm the central role of IL-1beta in FCAS and support the use of IL-1 targeted therapy in these patients.

DOI: 10.1016/j.jaci.2006.12.649

PMCID: PMC4322003

PMID: 17320940 [Indexed for MEDLINE]

3960. Rev Neurol (Paris). 2007 Jan;163(1):93-5.

[Myalgia in familial Mediterranean fever].

[Article in French]

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**INTRODUCTION:** Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent attacks of fever and painful episodes of sterile peritonitis, pleuritis and arthritis. Among rare symptoms of the disease, muscular manifestations, first described in 1945, sometimes as one of the main clinical manifestations or as its sole feature should be recognized. We present a patient with FMF in whom severe myalgia were predominant.

**CASE REPORT:** An 18 year-old Tunisian boy treated with corticosteroids for an "inflammatory myopathy" in another institution was admitted for abdominal pain. FMF was suspected because of a history of paroxysmal abdominal pain with fever from the age of 5 leading two times to laparotomy and one attack of left knee arthritis at the age of 14. FMF diagnosis was confirmed genetically, corticosteroids were tapered and a treatment with colchicine was started. Two years and a half later, he was admitted for severe and incapacitating myalgia of the upper and lower limbs without fever nor abdominal pain that responded well to rest and colchicine. Myalgia was then definitively attached to FMF.

**CONCLUSION:** Three clinical patterns of myalgia are now well identified in FMF: the spontaneous pattern as observed in our patient, the exercise-induced pattern and the protracted febrile myalgia syndrome. The three patterns differ in the severity of pain, grade of fever and duration of the episode.

PMID: 17304178 [Indexed for MEDLINE]

3961. *Pediatr Dermatol.* 2007 Jan-Feb;24(1):85-9.

Response to IL-1-receptor antagonist in a child with familial cold  
autoinflammatory syndrome.

O'Connell SM(1), O'Regan GM, Bolger T, Hoffman HM, Cant A, Irvine AD, Watson RM.

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Familial cold auto-inflammatory syndrome, Muckle-Wells syndrome and chronic infantile neurologic, cutaneous, articular syndrome are related disorders associated with mutations in the CIAS1 gene. They appear to represent a continuum of one disease characterized by IL-1-mediated inflammation. Until recently, these conditions have been difficult to treat; however, with the advent of IL-1-receptor antagonist therapy, many reports of successful treatment of patients with these autoinflammatory diseases have emerged in the past 2 years. We describe an 8-year-old girl, diagnosed with Familial cold auto-inflammatory syndrome, confirmed by presence of a novel CIAS1 mutation, who was refractory to symptomatic treatment. As frequent attacks of urticaria and associated arthralgia had a debilitating effect on the child's lifestyle, a trial of IL-1-receptor antagonist (anakinra) was instituted. Dramatic sustained clinical improvement was evident within days and serum amyloid and C-reactive protein levels normalized within a month. Although several authors have reported successful use of this agent in children with chronic infantile neurologic, cutaneous, articular syndrome, we believe ours is the first report of successful treatment with anakinra in a young child with familial cold auto-inflammatory syndrome.

DOI: 10.1111/j.1525-1470.2007.00343.x

PMID: 17300660 [Indexed for MEDLINE]

3962. Patol Fiziol Eksp Ter. 2006 Oct-Dec;(4):11-2.

[Spontaneous and inducible respiratory burst of monocytes and neutrophils in periodic autoinflammatory fever].

[Article in Russian]

Avetisyan SA, Davtian TK, Akopian GS, Manukian AM, Pogolian DA.

We investigated spontaneous, chemotaxis-, phagocytosis- and protein kinase C-dependent respiratory burst of neutrophils and monocytes in the whole blood of patients with familial Mediterranean fever (FMF). We also analysed transient

activation of neutrophils and monocytes on the level of a single cell using flow cytometry. It is shown that compared to healthy donors, the respiratory burst of monocytes and neutrophils in the patients is characterized by an increase in both spontaneous and inducible production of free radicals. In FMF patients probability of transient activation of chemotaxis- and phagocytosis-dependent respiratory burst is higher. This has an important influence rather on production of free radical by activated cells than on their number.

PMID: 17300081 [Indexed for MEDLINE]

3963. Trends Cell Biol. 2007 Mar;17(3):145-56. Epub 2007 Feb 12.

Pombe Cdc15 homology (PCH) proteins: coordinators of membrane-cytoskeletal interactions.

Chitu V(1), Stanley ER.

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Cellular adhesion, motility, endocytosis, exocytosis and cytokinesis involve the coordinated reorganization of the cytoskeleton and of the plasma membrane. The 'Pombe Cdc15 homology' (PCH) family of adaptor proteins has recently been shown to coordinate the membrane and cytoskeletal dynamics involved in these processes by curving membranes, recruiting dynamin and controlling the architecture of the actin cytoskeleton. Mutations in PCH family members or proteins that interact with them are associated with autoinflammatory, neurological or neoplastic diseases. Here, we review the nature, actions and disease associations of the vertebrate PCH family members, highlighting their fundamental roles in the regulation of processes involving membrane-cytoskeletal interactions.

DOI: 10.1016/j.tcb.2007.01.003

PMID: 17296299 [Indexed for MEDLINE]

3964. Int Arch Allergy Immunol. 2007;143(3):190-3. Epub 2007 Feb 6.

A novel missense mutation in CIAS1 encoding the pyrin-like protein, cryopyrin, causes familial cold autoinflammatory syndrome in a family of Ethiopian origin.

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**BACKGROUND:** Cold-induced urticaria is a form of physical urticaria which is characterized by rapid onset of pruritus, erythema, and swelling after exposure to a cold stimulus. Familial cold autoinflammatory syndrome (FCAS) is a rare autosomal-dominant condition characterized by unremitting attacks of cold-induced urticaria, often accompanied by other systemic manifestations. The disorder was previously shown to be caused by mutations in CIAS1, encoding a pyrin-like protein also involved in the pathogenesis of Muckle-Wells syndrome (MWS), and chronic infantile neurological cutaneous and articular syndrome (CINCA).

**METHODS:** In the present study, using direct sequencing, we assessed a two-generation family of Jewish Ethiopian origin, including 3 members affected with FCAS.

**RESULTS:** We identified a novel CIAS1 mutation, F525C. The mutation was shown to affect a highly conserved residue of the protein and to segregate with the disease throughout the extended family.

**CONCLUSIONS:** Our results add to the expanding spectrum of mutations in CIAS1 and provide evidence for striking phenotypic heterogeneity in inherited autoinflammatory syndromes. This is the first report of inherited cold urticaria in a family of Ethiopian origin.

DOI: 10.1159/000099311

PMID: 17284928 [Indexed for MEDLINE]

3965. J Clin Rheumatol. 2007 Feb;13(1):38-40.

Familial Mediterranean fever successfully treated with etanercept.

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Colchicine is the only drug known to effectively prevent familial Mediterranean fever (FMF) attacks, as well as FMF-associated amyloidosis. Unfortunately, colchicine is neither always effective nor always well tolerated, leaving some patients and their physicians with inadequate weaponry to fight this hazardous disease. We present a patient with recurrent episodes of abdominal, scrotal, and joint attacks, who was diagnosed with FMF and advised to take colchicine. Diarrhea prevented optimal treatment with this drug and led to a trial of etanercept, with resolution of FMF manifestations. This case adds to a growing body of evidence suggesting that tumor necrosis factor (TNF) blockade may result in resolution and prevention of further FMF attacks.

DOI: 10.1097/01.rhu.0000255772.25658.7c

PMID: 17278949 [Indexed for MEDLINE]

3966. Rev Med Chil. 2006 Dec;134(12):1558-61. Epub 2007 Jan 24.

[Tumor necrosis factor receptor associated periodic syndrome (TRAPS). Report of two cases].

[Article in Spanish]

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Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) is an autoinflammatory disorder associated to a mutation of the Tumor Necrosis Factor Receptor 1 (TNFR1) whose clinical presentation consists on recurrent episodes of prolonged fever, abdominal pain, myalgias, migratory cutaneous erythema, conjunctivitis or periorbital edema. The diagnosis is confirmed by genetic

analysis of the TNFR1 gene. Its main complication is amyloidosis and the treatment is based on the use of corticosteroids or anti-TNF antibodies. We report a 17 year-old male and 23 year-old female with the syndrome. Both cases had heterozygous mutations of the TNFR1 gene, C30R in the first case and T50M in the second case.

DOI: /S0034-98872006001200010

PMID: 17277873 [Indexed for MEDLINE]

3967. N Z Med J. 2007 Jan 26;120(1248):U2402.

Colchicine overdose: the devil is in the detail.

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Comment in

N Z Med J. 2007;120(1249):U2429.

N Z Med J. 2007;120(1252):U2503.

Colchicine, a highly poisonous alkaloid, is a commonly used treatment for gout, Bechet's disease, and familial Mediterranean fever. Despite the knowledge of its side effects, the near universally fatal consequence of a significant overdose is commonly under-appreciated. In this report, we present a case series of 9 patients over the past 15 years (from within the Auckland region of New Zealand) that have presented with a colchicine overdose. Surprisingly, a significant number were accidental overdoses and all cases, apart from one, resulted in death. We question the current knowledge base about the toxicity of this drug amongst prescribers, patients, and their families and its use in the treatment of acute gout. Given its extremely narrow therapeutic index, should the manner in which medical practitioners prescribe this drug be reassessed?

PMID: 17277818 [Indexed for MEDLINE]

3968. Eye (Lond). 2007 Jun;21(6):849-50. Epub 2007 Feb 2.

Muckle-Wells syndrome: another cause of acute anterior uveitis.

Shakeel A, Gouws P.

DOI: 10.1038/sj.eye.6702704

PMID: 17277755 [Indexed for MEDLINE]

3969. Semin Arthritis Rheum. 2007 Jun;36(6):397-401. Epub 2007 Feb 5.

MEFV mutations in Tunisian patients suffering from familial Mediterranean fever.

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**OBJECTIVES:** To identify the frequency and distribution of familial Mediterranean fever (FMF) gene (MEFV) mutations in Tunisian patients.

**PATIENTS AND METHODS:** This study was performed in the Genetic Department of Tunis University Hospital. A clinical diagnosis of FMF was made according to published criteria. Mutation screening of the MEFV gene was performed in the Human Genetic Laboratory of the "Faculté de Medecine de Tunis" for 8 mutations including the 5 most common known mutations M694V, V726A, M694I, M680I, and E148Q. The tests performed were polymerase chain reaction (PCR) restriction-digestion for M694V, V726A, M680I, R761H, E148Q; amplification refractory mutation system for A744S, M694I; and PCR-electrophoresis assay for I692del.

**RESULTS:** Of the 139 unrelated patients investigated, 61 (44%) had 1 or 2 mutations. In 78 (56%) probands no mutation was identified: 28 patients were homozygous; 16 were compound-heterozygous; 2 had complex alleles; and 17 had only 1 identifiable mutation. Of the mutations, M680I, M694V, M694I, V726A, A744S, R761H, I692DEL, and E148Q accounted for 32, 27, 13, 5, 3, 1, 1, and 18%, respectively.

**CONCLUSION:** The profile of the MEFV gene mutations in the Tunisian population is



concordant with other Arab populations but with some differences. M680I is the most common mutation, while V726A, the commonest mutation among Arabs, is rare in our population.

DOI: 10.1016/j.semarthrit.2006.12.004

PMID: 17276496 [Indexed for MEDLINE]

3970. Cytokine. 2007 Jan;37(1):92-5. Epub 2007 Jan 31.

Macrophage inflammatory protein-1alpha: a link between innate immunity and familial Mediterranean fever?

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The aim of this study is to investigate the relationship between chemokines and the inflammation in Familial Mediterranean Fever (FMF). Forty-nine patients with FMF (41 in remission and 8 in acute attack period) and 20 healthy controls were included in the study. Serum levels of macrophage inflammatory protein-1alpha (MIP-1alpha) were assessed in the patients and the controls, along with other parameters of disease activity, i.e., fibrinogen, C-reactive protein and erythrocyte sedimentation rate. Serum MIP-1alpha levels of the patients with FMF in acute attack period were significantly higher than the patients in remission and healthy controls ( $p=0.02$  and  $p=0.038$ , respectively). MIP-1alpha levels were weakly correlated with CRP ( $r=0.32$ ,  $p=0.032$ ) levels. MIP-1alpha may have a role in the pathogenesis of FMF attacks. MIP-1alpha and other chemokines may constitute a link between the innate immune system and FMF.

DOI: 10.1016/j.cyto.2006.12.005

PMID: 17270460 [Indexed for MEDLINE]

3971. Curr Opin Rheumatol. 2007 Jan;19(1):85-9.

Bibliography. Current world literature. Systemic disorders with rheumatic manifestations.

[No authors listed]

PMID: 17265583 [Indexed for MEDLINE]

3972. Arthritis Rheum. 2007 Feb;56(2):658-61.

First report of macrophage activation syndrome in hyperimmunoglobulinemia D with periodic fever syndrome.

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We describe for the first time a case of macrophage activation syndrome in a child with hyperimmunoglobulinemia D with periodic fever syndrome who required intensive care support. Up-regulated monokine production, high serum levels of triglycerides and ferritin, clotting abnormalities with hypofibrinogenemia, and rapidly evolving pancytopenia should alert the clinician to the possible diagnosis of macrophage activation syndrome, even in autoinflammatory diseases characterized basically by the periodic recurrence of unprovoked inflammatory attacks. Bone marrow aspiration showing well-differentiated macrophages phagocytosing hematopoietic elements remains the main tool for a final diagnosis, and cyclosporine is the best strategy for treatment.

DOI: 10.1002/art.22409

PMID: 17265501 [Indexed for MEDLINE]

3973. Rheumatol Int. 2007 Aug;27(10):969-73. Epub 2007 Jan 31.

Synovial angiostatic non-ELR CXC chemokines in inflammatory arthritides: does

## CXCL4 designate chronicity of synovitis?

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In our previous studies, we found higher synovial fluid (SF) levels of angiogenic ELR(+) CXC chemokines such as CXCL1, CXCL5, CXCL6 and CXCL8, which play an important role in neutrophil migration and angiogenesis, and more abundant synovial CXCR2 chemokine receptor expression in patients with rheumatoid arthritis (RA) than those with Behçet's disease (BD), familial Mediterranean fever and osteoarthritis (OA). As a continuation of our previous studies, we investigated synovial levels of angiostatic non-ELR CXC chemokines (CXCL4, CXCL9 and CXCL10) in patients with RA, BD, spondyloarthritis (SpA), and OA. Seventy (17 RA, 15 BD, 19 SpA, and 19 OA) patients were enrolled in the study. The levels of CXCL4, CXCL9, and CXCL10 were measured by ELISA. The SF levels of CXCL4 in patients with RA were higher than those of the patients with BD, SpA, and OA ( $P = 0.007$ ,  $P = 0.022$ , and  $P = 0.017$ , respectively). No difference was found with respect to CXCL4 levels among the BD, SpA, and OA patients. The synovial CXCL9 levels of patients with RA and SpA were found to be higher than those of the patients with OA ( $P = 0.002$  and  $P = 0.005$ , respectively), while no statistically significant difference was detected among the other groups. With regard to SF CXCL10 levels, patients with RA had higher levels as compared to patients with OA ( $P = 0.002$ ), but no significant difference was found among the other groups. CXCL9 correlated with CXCL4 and CXCL10 ( $P < 0.05$  for both) in patients with RA. No correlation was found in other parameters. The angiostatic non-ELR CXC chemokines were expressed in synovial inflammation. We proposed that angiostatic non-ELR CXC chemokines may increase to balance angiogenic ELR (+) CXC chemokines in which increased levels were shown in patients with inflammatory arthritides and CXCL4 may contribute to designate the chronicity of synovitis in patients with RA. In addition, as CXCL-9 and CXCL-10 play crucial role in inflammation characterized by Th1 polarization, we suggested that they may contribute to the commencement and the perpetuation of synovitis seen in these groups of arthritides.

DOI: 10.1007/s00296-007-0317-6

PMID: 17265155 [Indexed for MEDLINE]

3974. Pediatrics. 2007 Feb;119(2):e523-7. Epub 2007 Jan 29.

Diagnostics and therapeutic insights in a severe case of mevalonate kinase deficiency.

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Mevalonate kinase deficiency is a rare inborn disorder of isoprenoid and sterol biosynthesis characterized by a recurrent autoinflammatory syndrome and, in most severe cases, psychomotor delay. Clinical manifestations can be very complex and, in some cases, mimic a chronic inflammatory disease. Diagnosis is also complex and often requires immunologic, genetic, and biochemical investigations. There is no standardized therapy, but biological agents could help to control inflammatory complaints in some cases. A severe case of mevalonate kinase deficiency that was associated with nephritis and successfully treated with anakinra (interleukin 1 receptor antagonist) is reported here, and new insights into diagnosis and therapy of this complex disorder are discussed.

DOI: 10.1542/peds.2006-2015

PMID: 17261617 [Indexed for MEDLINE]

3975. Adv Dermatol. 2006;22:67-90.

Autoinflammatory diseases: clinical and dermatologic features, genetics, pathogenesis and therapy.

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PMID: 17249296 [Indexed for MEDLINE]

3976. Clin Rheumatol. 2007 Sep;26(9):1467-73. Epub 2007 Jan 23.

Early ultrasonographic markers of atherosclerosis in patients with familial Mediterranean fever.

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Systemic inflammation plays an important role in the development of atherosclerosis (AS). The aim of this study was to evaluate the presence of early AS in patients with familial Mediterranean fever (FMF) that is characterized by recurrent inflammatory attacks of serositis. Sixty-one FMF patients (30 Male/31 Female; 31.5 [18-54] years) and 31 healthy controls (16 Male/15 Female; 31 [22-58] years) were studied. All FMF patients were on regular daily colchicine treatment and during attack-free periods. Both the FMF patients and controls with a history of diabetes mellitus (DM), hypertension, and hyperlipidemia were excluded. Body mass index (BMI) was calculated. Serum lipids, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were assessed. Two-hour oral glucose tolerance test was performed to rule out DM and glucose intolerance. To investigate early AS "endothelium-dependent flow-mediated dilatation (FMD%)," "nitroglycerin-induced endothelium-independent peripheral vasodilatation (NTG%)," and intima-media thickness (IMT) of common carotid arteries (CCA) were measured by ultrasonography. The median disease duration for FMF patients was 16 (1-45) years. Age, sex, BMI, smoking status, and serum lipids were comparable in patients and controls ( $p > 0.05$ ). However, ESR and standard CRP were significantly higher in the patients group ( $p < 0.05$ ). There were no differences in the measurements of right, left, and averaged IMT of CCA between patients and controls ([0.49 vs 0.5], [0.51 vs 0.52] and [0.5 vs 0.51];  $p > 0.05$ , respectively). None of the subjects had carotid artery plaques. FMD% and NTG% were also similar in patients and controls group ([18.2 vs 20.6] and [24.2 vs 22.5];  $p > 0.05$ , respectively). This study suggests that the markers of early AS

are not impaired in FMF patients on regular daily colchicine treatment.

DOI: 10.1007/s10067-006-0529-2

PMID: 17242867 [Indexed for MEDLINE]

3977. Pediatrics. 2007 Feb;119(2):e474-83. Epub 2007 Jan 22.

Colchicine use in children and adolescents with familial Mediterranean fever: literature review and consensus statement.

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The daily application of colchicine is the standard therapy for prophylaxis of attacks and amyloid deposition in familial Mediterranean fever. However, because of many issues (eg, dosage, time of introduction, etc), no standardized treatment recommendations have been established. In this work we review the available literature on colchicine use with respect to its indication, efficacy, mode of application, and safety in children and adolescents with familial Mediterranean fever. On the basis of this analysis, a consensus statement on the application of colchicine in children and adolescents with familial Mediterranean fever was developed by caregivers from Germany, Austria, and Turkey.

DOI: 10.1542/peds.2006-1434

PMID: 17242135 [Indexed for MEDLINE]

3978. Acta Clin Belg. 2006 Sep-Oct;61(5):264-9.

Autoinflammatory diseases.

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Autoinflammatory diseases can be specified as inborn errors of the innate immune system. The main component of autoinflammatory diseases is the group of hereditary periodic fevers which are characterised by intermittent bouts of clinical inflammation with focal organ involvement mainly: abdomen, musculoskeletal system and skin. The most frequent one is familial Mediterranean fever that affects patients of Mediterranean descent all over the world.

Recently, three other types have been characterised, clinically as well as genetically: Tumor Necrosis Factor receptor superfamily 1A Associated Periodic Fever Syndrome, hyperimmunoglobulinemia D and periodic fever syndrome/ mevalonate kinase deficiency, and the most recently recognised entity which includes Muckle Wells, familial cold autoinflammatory/familial cold urticaria, and the Chronic infantile neurological cutaneous and articular/Neonatal onset multisystemic inflammatory disease syndromes. A thorough diagnosis is warranted, as clinical and therapeutic management is specific for each of these diseases. In addition to hereditary periodic fever, autoinflammatory diseases also encompass Blau, Majeed, and PAPA syndromes. The underlying genetic defects of these inflammatory diseases appear to be specific for each type, involving several so far unknown proteins involved in innate immunity, and have already opened new avenues in our understanding of the inflammatory response.

DOI: 10.1179/acb.2006.045

PMID: 17240743 [Indexed for MEDLINE]

3979. Semin Arthritis Rheum. 2007 Apr;36(5):316-21. Epub 2007 Jan 22.

Peritoneal adhesions and intestinal obstructions in patients with familial Mediterranean fever--are they more frequent?

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**OBJECTIVE:** Familial Mediterranean fever (FMF) is characterized by recurrent episodes of peritonitis. A controversy exists as to whether intestinal obstruction due to peritoneal adhesions is more common among FMF patients compared with healthy controls. The aim of the study was to estimate the rate of spontaneous or postsurgical small-bowel obstruction (SBO) in FMF patients.

**METHODS:** We reviewed the charts of 560 FMF patients followed in our clinic for the occurrence of spontaneous SBO. We also assessed the occurrence of postappendectomy intestinal obstruction among 89 FMF patients compared with 417 individuals without FMF who underwent an appendectomy without other abdominal surgery in the same medical center.

**RESULTS:** Ten of 471 FMF patients (2.1%) developed spontaneous SBO, 8 of whom required laparotomy and adhesiolysis. Six of 89 FMF patients (6.7%) who underwent appendectomy developed SBO. None of the non-FMF patients developed SBO.

**CONCLUSIONS:** Our retrospective study showed that FMF patients are at a higher risk than healthy individuals for developing SBO either spontaneously or as a postsurgical complication. Physicians should be alert to this possible complication when FMF patients arrive at the emergency room.

DOI: 10.1016/j.semarthrit.2006.11.002

PMID: 17240429 [Indexed for MEDLINE]

3980. Clin Rheumatol. 2007 Oct;26(10):1729-32. Epub 2007 Jan 19.

Cerebral vasculitis in a child with Henoch-Schönlein purpura and familial Mediterranean fever.

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In this case report, a 10-year-old girl with Henoch-Schönlein purpura (HSP) with severe central nervous system involvement and also having familial Mediterranean fever (FMF) is presented.

DOI: 10.1007/s10067-006-0485-x

PMID: 17235658 [Indexed for MEDLINE]



3981. Rheumatol Int. 2007 Jul;27(9):807-11. Epub 2007 Jan 17.

Serum proinflammatory cytokines directing T helper 1 polarization in patients with familial Mediterranean fever.

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Th1 type polarization has been implicated in the pathogenesis of familial Mediterranean fever (FMF). Interleukin-12 (IL-12) and IL-10 are proinflammatory cytokines, which play crucial role in Th1 and Th2 type immune response, respectively. IL-18 has a dual effect on T cell response: it was recognized as an IFN-gamma-inducing factor in T cells; acting in synergy with IL-12, leading to the development of Th1 type immune responses. But, in the absence of IL-12, IL-18 can promote the production of Th2 cytokines and take part in allergic inflammation. The aim of this study is to measure serum levels of IL-10, IL-12, and IL-18 in patients with FMF, and to investigate the relationship of their expressions with FMF attacks. Serum IL-10, IL-12, and IL-18 levels from patients with FMF were investigated. Thirty-one FMF patients with attack-free, 24 FMF patients with attack and 20 healthy controls were enrolled in the study. The levels of IL-10, IL-12p70 and IL-18 were measured by ELISA. Serum IL-10 levels were not different in FMF patients with attack and attack-free, and healthy controls. Serum IL-12 levels in FMF patients both with attack and attack-free were significantly higher than healthy controls ( $P = 0.002$  and  $P = 0.047$ , respectively). There were no differences between FMF patients with attack and attack-free with regard to serum IL-12 levels. Serum IL-18 levels in FMF patients with attack and attack-free were significantly higher than healthy controls ( $P < 0.001$  for both groups). With respect to serum IL-18 levels, no difference was found between FMF patients with attack and attack-free. Our results suggest that IL-12 and IL-18 contribute to the establishment of Th1 polarization seen in FMF and play a part in its pathogenesis. Detection of increased levels of IL-12 and IL-18 in patients with inactive disease implies that they seem to assist Th1 activation and subclinical inflammation persisting during the attack-free period of the disease.

DOI: 10.1007/s00296-006-0301-6  
PMID: 17225924 [Indexed for MEDLINE]

3982. Clin Exp Immunol. 2007 Feb;147(2):227-35.

Chronic inflammation: importance of NOD2 and NALP3 in interleukin-1beta generation.

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Inflammation is part of the non-specific immune response that occurs in reaction to any type of bodily injury. In some disorders, the inflammatory process - which under normal conditions is self-limiting - becomes continuous and chronic inflammatory diseases might develop subsequently. Pattern recognition molecules (PRMs) represent a diverse collection of molecules responsible for sensing danger signals, and together with other immune components they are involved in the first line of defence. NALP3 and NOD2, which belong to a cytosolic subgroup of PRMs, dubbed Nod-like-receptors (NLRs), have been associated recently with inflammatory diseases, specifically Crohn's disease and Blau syndrome (NOD2) and familial cold autoinflammatory syndrome, Muckle-Wells syndrome and chronic infantile neurological cutaneous and articular syndrome (NALP3). The exact effects of the defective proteins are not fully understood, but activation of nuclear factor (NF)-kappaB, transcription, production and secretion of interleukin (IL)-1beta and activation of the inflammasome are some of the processes that might hold clues, and the present review will provide a thorough update in this area.

DOI: 10.1111/j.1365-2249.2006.03261.x  
PMCID: PMC1810472  
PMID: 17223962 [Indexed for MEDLINE]

3983. Joint Bone Spine. 2007 Jan;74(1):52-5. Epub 2006 Apr 17.

Plasma levels of soluble vascular endothelial growth factor receptor-1 (sVEGFR-1) in familial Mediterranean fever.

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AIMS: To assess the levels of soluble vascular endothelial growth factor receptor-1 (sVEGFR-1) in patients with familial Mediterranean fever (FMF).

METHODS: Plasma levels of sVEGFR-1 were investigated in 33 FMF patients in an attack-free period (mean age 30.8 years; males/females 10/23), in 15 patients with acute FMF attack (mean age 32.7 years; males/females 7/8), and 19 healthy controls (mean age 32 years; males/females 11/8). Levels of sVEGFR-1 were also compared among patients who were receiving colchicine and those who were not.

RESULTS: Plasma sVEGFR-1 levels were  $3.49 \pm 1.10$ ,  $3.53 \pm 1.02$ , and  $0.37 \pm 0.28$  ng/ml for FMF patients in the attack-free period, FMF patients with acute attack, and healthy controls, respectively. Plasma sVEGFR-1 levels were significantly higher in FMF patients with and without acute attack compared to the control group ( $p < 0.05$ ). sVEGFR-1 levels were not statistically significant between patients with acute attack and attack-free FMF patients ( $p > 0.05$ ). The plasma levels of sVEGFR-1 were also comparable in colchicine treated and untreated patients.

CONCLUSION: Our data suggest that sVEGFR-1 may have a role in the ongoing inflammatory cascade in FMF.

DOI: 10.1016/j.jbspin.2006.02.003

PMID: 17223601 [Indexed for MEDLINE]

3984. Clin Rheumatol. 2007 Oct;26(10):1783-5. Epub 2007 Jan 12.

Tumor necrosis factor blockade in the management of children with orphan diseases.

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Tumor necrosis factor (TNF) blockade has been used successfully to treat a number of rheumatic disorders that have a substantial burden of illness. In children, the TNF antagonists are used mainly for the treatment of juvenile idiopathic arthritis (JIA). There are, however, a variety of rare systemic inflammatory diseases, in which TNF blockade appears promising. Preliminary data in adults suggest that several forms of vasculitis appear to be responsive to TNF antagonists- Behçet's disease, polyarteritis nodosa, Wegener granulomatosis, among others. Some of them respond better to infliximab, a chimeric monoclonal anti-TNF antibody, than to etanercept, a recombinant p75 TNF receptor. We describe our limited experience with infliximab in the treatment of three children with rare vasculitic conditions.

DOI: 10.1007/s10067-006-0521-x

PMID: 17219021 [Indexed for MEDLINE]

3985. Ann Rheum Dis. 2007 Jun;66(6):832-4. Epub 2007 Jan 9.

Autoinflammatory gene mutations in Behçet's disease.

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**BACKGROUND:** Behçet's disease (BD) shares clinical features with well-recognised autoinflammatory disorders. In addition, mutations in genes for familial Mediterranean fever and tumour necrosis factor receptor-associated periodic syndrome have been reported to have increased in patients with BD.

**PATIENTS AND METHODS:** DNA samples from 97 patients with BD and 51 matched healthy controls were analysed for the mevalonate kinase (MVK), cold-induced autoinflammatory syndrome 1 (CIAS1) and proline/serine/threonine phosphatase-interacting protein 1 (PSTPIP1) genes, responsible for mevalonate

kinase deficiency (MKD), cryopyrin associated periodic syndromes (CAPS) and pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA) syndrome, respectively. Over 90% of known mutations were screened using restriction fragment length polymorphism analysis and/or sequencing.

RESULTS: Two patients had paired mutations in the MVK gene (genotypes V377I/V377I and V377I/S135L) and displayed typical features of BD and MKD. Another was heterozygotic for the V377I genotype. The V198M mutation in the CIAS1 gene was identified in one patient with typical BD but no symptoms of CAPS. No mutations were identified in the control group. PSTPIP1 analysis revealed a new exon 10 insertion variant (c.741+33\_741+34insGT) in 2 of 97 patients and in 1 of 51 controls ( $p>0.05$ ), indicating that it is a polymorphism rather than a true mutation.

DISCUSSION: This study could not demonstrate any significant increases in MVK, CIAS1 or PSTPIP1 mutations in patients with BD as compared with controls.

DOI: 10.1136/ard.2006.068841

PMCID: PMC1954666

PMID: 17213252 [Indexed for MEDLINE]

3986. Clin Exp Rheumatol. 2006 Nov-Dec;24(6):694-7.

Restricted specificity of anti-ribosomal P antibodies to SLE patients in Israel.

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OBJECTIVE: Anti-ribosomal P antibodies (aRib-P Ab) are highly specific for systemic lupus erythematosus (SLE), but their correlatation with disease activity and manifestations including renal, hepatic and central nervous system (CNS) involvement is still controversial. The aim of our study was to evaluate the prevalence of aRib-P Ab and their correlation with clinical manifestations and anti-dsDNA antibodies in SLE patients from Israel.

METHODS: Elevated titers of aRib-P Ab utilizing the ELISA method were analyzed in 141 sera samples from 44 SLE patients, 20 Familial Mediterranean Fever (FMF)

patients, 22 primary antiphospholipid syndrome (PAPS) patients, 12 patients with infections, and 43 healthy individuals. The SLEDAI score was utilized for assessing SLE disease activity.

**RESULTS:** Elevated titers of aRib-P Ab were present in 11% of SLE patients (n = 6). The mean SLEDAI was 7 (range: 3-10). No statistically significant association was observed between the presence of aRib-P Ab and disease manifestations present in the SLEDAI. The 6 SLE patients had renal disease (n = 1), leucopenia (n = 1), rash (n = 3), and CNS involvement manifested as psychosis (n = 1) or depression (n = 1). Elevated titers of anti-dsDNA antibodies were found in 50% of patients with elevated titers of aRib-P Ab. Patients with PAPS, FMF, infections or healthy controls did not harbor elevated titers of aRib-P Ab.

**CONCLUSION:** Elevated titers of aRib-P Ab were restricted to SLE patients. We confirm previously reported associations of aRib-P Ab reactivity with disease activity and elevated anti-dsDNA Ab titers. No significant correlation with a specific manifestation described on the SLEDAI score was established in this small cohort of patients.

PMID: 17207387 [Indexed for MEDLINE]

3987. Tohoku J Exp Med. 2007 Jan;211(1):9-14.

Selective serotonin reuptake inhibitors reduce the attack frequency in familial mediterranean Fever.

Onat AM(1), Oztürk MA, Ozçakar L, Ureten K, Kaymak SU, Kiraz S, Ertenli I, Calgüneri M.

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Familial Mediterranean Fever (FMF) is characterized by recurrent acute attacks of fever and serositis, and colchicine is the primary treatment. The pathogenesis of the disease has not been fully understood. Resistance to colchicine remains to be a problem in up to 30% of the patients and yet there seems to be no alternative treatment. In this study our objective was to investigate whether a selective serotonin re-uptake inhibitor (SSRI) could affect the attack frequency and acute

phase response in FMF patients who were unresponsive to colchicine. We retrospectively evaluated the hospital files of 11 colchicine-unresponsive FMF patients who had been treated with SSRIs. According to the records and re-evaluation of the patients, the total number of the FMF attacks was calculated before and after the SSRI, adjunct to colchicine. The laboratory values including erythrocyte sedimentation rate, C-reactive protein, fibrinogen and white blood cell counts were also noted before and after the SSRI treatment from their hospital files. The mean attack frequency before adding SSRI to colchicine was  $8.09 \pm 3.53$  per 6 months, and at the end of this period there was a great decline in the number of mean attack frequency ( $0.36 \pm 0.50$  attacks per 6 months) ( $p < 0.001$ ). Acute phase reactants were significantly decreased after SSRI treatment ( $p < 0.001$ ). All of the colchicine-unresponsive patients had depression and 3 of those patients also had fibromyalgia. SSRIs appear to be useful adjuncts in the management of FMF patients who continue to have attacks despite regular colchicine treatment.

PMID: 17204829 [Indexed for MEDLINE]

3988. Ter Arkh. 2006;78(11):78-80.

[Periodic disease in a patient with admittance diagnosis yersiniosis].

[Article in Russian]

Shestakova IV, Iushchuk ND, Popova TI.

PMID: 17195534 [Indexed for MEDLINE]

3989. Arthritis Rheum. 2007 Jan;56(1):345-50.

Association between reduced levels of MEFV messenger RNA in peripheral blood leukocytes and acute inflammation.

Ustek D(1), Ekmekci CG, Selçukbiricik F, Cakiris A, Oku B, Vural B, Yanar H, Taviloglu K, Ozbek U, Gül A.

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(1)Istanbul University, Institute for Experimental Medical Research, Istanbul, Turkey.

**OBJECTIVE:** Familial Mediterranean fever (FMF) is associated with more than 70 missense mutations in the MEFV gene. The purpose of this study was to investigate the relative expression of messenger RNA (mRNA) for the MEFV gene in peripheral blood leukocytes (PBLs) obtained from patients with FMF during attacks of acute abdominal inflammation as well as during asymptomatic periods.

**METHODS:** We studied 16 patients with FMF during an attack of acute peritonitis and 17 otherwise healthy individuals who were undergoing surgery because of acute appendicitis. Blood samples were collected from both groups of patients during both acute inflammatory and asymptomatic periods. Relative levels of MEFV mRNA in PBLs were detected with real-time reverse transcriptase-polymerase chain reaction using LightCycler, with 2 sets of primers for the MEFV gene (exons 7-10 and exons 2-3) and with primers for CIAS1 and PSTPIP1 genes. Expression levels were compared with beta(2)-microglobulin as an internal control.

**RESULTS:** MEFV expression was reduced in FMF patients during asymptomatic periods as compared with the non-FMF controls ( $P < 0.001$ ). We observed a further decrease in MEFV expression in FMF patients during periods of inflammation ( $P = 0.01$ ).

Reduced levels of MEFV mRNA were also noted during the preoperative period as compared with asymptomatic periods in control patients with acute appendicitis ( $P = 0.01$ ). CIAS1 expression in PBLs from patients with FMF was also found to be lower than that in the control patients. However, CIAS1 expression did not change with acute inflammation.

**CONCLUSION:** This study confirmed that reduced expression of the MEFV gene is associated with inflammation and that it may be one of the pathogenic mechanisms of the attacks of inflammation in FMF patients, along with disease-associated variations in pyrin.

DOI: 10.1002/art.22320

PMID: 17195238 [Indexed for MEDLINE]

3990. Ned Tijdschr Geneesk. 2006 Dec 9;150(49):2711-4.

[A Dutch family with the hereditary periodic fever or tumour necrosis factor receptor-associated periodic syndrome (TRAPS)].



[Article in Dutch]

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Erratum in

Ned Tijdschr Geneeskd. 2007 Feb 3;151(5):336.

Comment in

Ned Tijdschr Geneeskd. 2007 Apr 7;151(14):836-7; author reply 837.

A 9-month-old girl was referred to the paediatrician because of fever of unknown origin. Since the age of 4 years she had recurrent attacks of muscle, joint and abdominal pain, in addition to periodic fever. Her sister and her mother had similar symptoms. The tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) was suspected and confirmed by DNA analysis. Several members of the extended family were carriers of the same mutation. In patients with recurrent unexplained periods of fever in combination with myalgia, arthralgia and abdominal pain, and in whom these symptoms also occur in members of the family, TRAPS should be considered as the cause. Glucocorticosteroids and etanercept, a TNF-receptor antagonist, may be effective in the treatment of attacks. Early recognition of this syndrome is important because of the risk of developing amyloidosis.

PMID: 17194009 [Indexed for MEDLINE]

3991. Rheumatol Int. 2007 Jun;27(8):691-4. Epub 2006 Dec 23.

Is the CD14 C159T polymorphism effective in the development of secondary amyloidosis in Familial Mediterranean fever?

Keskin O(1), Yilmaz E, Kutlay S, Bakkaloglu A, Topaloglu R, Arici M, Kalayci O, Ozen S.

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The most important complication of FMF is the development of amyloidosis. It is more common in the eastern Mediterranean compared to the US. The individual response to endotoxin may have a significant effect on the development of amyloidosis in FMF patients. To investigate the association between CD14 promotor C-159T polymorphism and development of amyloidosis, one hundred and forty-six patients who had FMF and had not developed amyloidosis; 26 with FMF and secondary amyloidosis and 92 controls were genotyped at the CD14-C159T locus. There was no difference between the genotype distribution of FMF patients (CC 30.0%, CT 50.0%, TT 20.0%) and controls (CC 29.2%, CT 45.8%, TT 25%); or between FMF patients with amyloidosis (CC 30.8%, CT 53.8%, TT 15.4%) or without amyloidosis (CC 29.2%, CT 45.8%, TT 25%). Our study shows that the CD14-C159T polymorphism is not associated with FMF or development of amyloidosis in the population studied. The effect of the genetic variations in the endotoxin signaling pathway under different environmental conditions such as high and low endotoxin exposure remain to be determined.

DOI: 10.1007/s00296-006-0286-1

PMID: 17187267 [Indexed for MEDLINE]

3992. Arch Dermatol. 2006 Dec;142(12):1591-7.

Phenotype, genotype, and sustained response to anakinra in 22 patients with autoinflammatory disease associated with CIAS-1/NALP3 mutations.

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Author information:

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OBJECTIVE: To characterize the multisystem chronic inflammatory phenotype, dermatopathologic features, and response to therapy with interleukin 1 receptor antagonist (anakinra) in patients with mutations in the CIAS-1/NALP3 gene.

DESIGN: Retrospective review of medical records and evaluation of histologic

findings.

SETTING: The National Amyloidosis Centre, London, and a tertiary referral clinic for urticaria.

PATIENTS: Twenty-two individuals from 13 families with autoinflammatory disease associated with CIAS-1/NALP3 mutations.

MAIN OUTCOME MEASURES: Phenotype, genotype, skin histologic findings, and response to treatment with anakinra.

RESULTS: Five heterozygous missense mutations were identified in CIAS-1/NALP3. Skin histologic findings revealed marked vascular dilatation and neutrophilic infiltration involving small vessels and eccrine glands. Serologic evidence of intense inflammation was present in untreated patients, with median serum amyloid A protein and C-reactive protein levels of 141 and 38 mg/L, respectively. Fifteen patients received anakinra for up to 39 months, all of whom achieved serologic remission and complete resolution of fever, rash, conjunctivitis, and rheumatic symptoms, without any adverse effects. Six patients had AA (reactive systemic) amyloidosis, 2 of whom died of renal failure complications before interleukin 1-inhibiting therapy was available; 1 patient underwent renal transplantation and remains clinically well taking anakinra, and in the remaining 3 patients, anakinra therapy resulted in remission of their nephrotic syndrome.

CONCLUSIONS: Anakinra therapy was well tolerated and has sustained efficacy on dermatologic and rheumatic manifestations in these patients with CIAS-1/NALP3 mutations. This treatment also resulted in resolution of AA amyloidosis-associated nephrotic syndrome in all affected patients.

DOI: 10.1001/archderm.142.12.1591

PMID: 17178985 [Indexed for MEDLINE]

3993. Rheumatology (Oxford). 2007 Apr;46(4):709-14. Epub 2006 Dec 18.

A cryopyrin-associated periodic syndrome with joint destruction.

Lequerré T(1), Vittecoq O, Saugier-veber P, Goldenberg A, Patoz P, Frébourg T, Le Loët X.

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**OBJECTIVE:** Describe four generations (11 members) of a family with a cryopyrin-associated periodic syndrome (CAPS), including joint destruction, associated with a CIAS1-gene mutation and good responses to anakinra.

**METHODS:** In addition to detailed questioning and physical examination, six family members underwent haematological, immunological and biochemical testing. Exon 3 of the CIAS1 gene was sequenced in search of a mutation in the 1q44 region.

**RESULTS:** During childhood or adolescence, four family members developed different combinations of the following CAPS manifestations: deafness (3/4); arthritis (4/4) with joint destruction for two of them; nervous (cerebral demyelination, 2/4), cutaneous (livedo and/or urticaria, 3/4) and eye lesions (episcleritis and/or papilloedema, 4/4); IgA hypergammaglobulinaemia (4/4) and inflammatory syndrome (3/4). Sequencing of six family members' CIAS1-gene exon 3 identified a heterozygous mutation, c.1043C > T. Pertinently, this CAPS is distinct from chronic infantile neurological cutaneous and arthritis syndrome/neonatal onset multisystemic inflammatory disease syndrome and Muckle-Wells syndrome (MWS), which also result from exon 3 mutations in this gene. Moreover, this family did not have the usual neurological manifestations, typical morphological features and frequent amyloidosis of MWS.

**CONCLUSIONS:** We describe a previously unreported form of CAPS with atypical neurological signs, joint destruction and livedo. This observation extends the clinical spectrum associated with CIAS1 mutations. Anakinra, an interleukin-1-receptor antagonist, prescribed to two family members, was highly effective.

DOI: 10.1093/rheumatology/kel399

PMID: 17178739 [Indexed for MEDLINE]

3994. Community Genet. 2007;10(1):52-60.

Jordan: communities and community genetics.

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The population in Jordan mounted from half a million in 1952 to 5.3 millions in

2004 and is composed of a variety of ethnic groups, the majority being Arabs. Couples nowadays tend to have fewer children, with the total fertility rate falling from 7.4 in 1976 to 3.7 in 2004. Consanguineous marriages are traditionally favored, with the preferred marriage partner being the offspring of the father's brother. First-cousin marriages declined from 28.5% for marriages contracted between 1950 and 1979 to 19.5% for marriages contracted after 1980. In the overall population, carrier rates for beta-thalassemia, alpha-thalassemia and sickle cell anemia are in the range of 2-4%, 3.2-12% of males have glucose-6-phosphate dehydrogenase deficiency, and the prevalences for familial Mediterranean fever and cystic fibrosis were estimated at around 0.04% each. A mandatory premarital screening program for beta-thalassemia carriers commenced in June 2004. The high consanguinity rate and the large family size in Jordan have contributed to the description of a number of rare and new autosomal recessive conditions. Genetic services in Jordan are still scarce and do not cover all the country due to the major impediments of a paucity of resources and trained health professionals in the area of medical genetics. The demographic data suggest that the health system in Jordan is capable of introducing some basic community genetic services into the primary health care program through comprehensive and cost-effective programs.

DOI: 10.1159/000096282

PMID: 17167252 [Indexed for MEDLINE]

3995. J Histochem Cytochem. 2007 May;55(5):443-52. Epub 2006 Dec 12.

Inflammasome components NALP 1 and 3 show distinct but separate expression profiles in human tissues suggesting a site-specific role in the inflammatory response.

Kummer JA(1), Broekhuizen R, Everett H, Agostini L, Kuijk L, Martinon F, van Bruggen R, Tschopp J.

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(1)Department of Pathology, University Medical Center Utrecht, Utrecht, The Netherlands.

Several autoinflammatory disorders such as Muckle-Wells syndrome are characterized by mutations in the NALP3/cryopyrin gene. NALP3 and NALP1 proteins

can assemble to inflammasomes that activate caspase-1, resulting in the processing of pro-inflammatory cytokines IL-1 $\beta$  and IL-18. The present study was designed to determine which cells and tissues express NALP1 and NALP3. Monoclonal antibodies were developed and their use revealed distinct distribution profiles of NALP1 and NALP3. Granulocytes, monocytes (very weakly), dendritic cells, and B and T cells all express NALP1 and NALP3. Highest levels of NALP1 are found in T cells and Langerhans cells. Furthermore, NALP1 is present in glandular epithelial structures such as stomach, gut, lung, and, surprisingly, in neurons and testis. In contrast to NALP1, NALP3 shows a more restricted tissue distribution with expression mainly in non-keratinizing epithelia in the oropharynx, esophagus, and ectocervix. Moreover, NALP3 expression is found in the urothelial layer in the bladder. Likewise, a difference in subcellular distribution between NALP1 and NALP3 is observed because NALP1 is localized mainly in the nucleus, whereas NALP3 is predominantly cytoplasmic. We propose that the presence of NALP3 in epithelial cells lining the oral and genital tracts allows the rapid sensing of invading pathogens, thereby triggering an innate immune response.

DOI: 10.1369/jhc.6A7101.2006

PMID: 17164409 [Indexed for MEDLINE]

3996. Blood. 2007 Apr 1;109(7):2903-11.

Disease-associated mutations in CIAS1 induce cathepsin B-dependent rapid cell death of human THP-1 monocytic cells.

Fujisawa A(1), Kambe N, Saito M, Nishikomori R, Tanizaki H, Kanazawa N, Adachi S, Heike T, Sagara J, Suda T, Nakahata T, Miyachi Y.

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Mutations in the cold-induced autoinflammatory syndrome 1 (CIAS1) gene are associated with a spectrum of autoinflammatory diseases, including familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and chronic infantile neurologic, cutaneous, articular syndrome, also known as neonatal-onset multisystem inflammatory disease. CIAS1 encodes cryopyrin, a protein that

localizes to the cytosol and functions as pattern recognition receptor. Cryopyrin also participates in nuclear factor-kappaB regulation and caspase-1-mediated maturation of interleukin 10. In this study, we showed that disease-associated mutations in CIAS1 induced rapid cell death of THP-1 monocytic cells. The features of cell death, including 7-AAD staining, the presence of cellular edema, and early membrane damage resulting in lactate dehydrogenase (LDH) release, indicated that it was more likely to be necrosis than apoptosis, and was effectively blocked with the cathepsin B-specific inhibitor CA-074-Me. CA-074-Me also suppressed induced by disease-associated mutation lysosomal leakage and mitochondrial damage. In addition, R837, a recently identified activator of cryopyrin-associated inflammasomes, induced cell death in wild type CIAS1-transfected THP-1 cells. These results indicated that monocytes undergo rapid cell death in a cathepsin B-dependent manner upon activation of cryopyrin, which is also a specific phenomenon induced by disease-associated mutation of CIAS1.

DOI: 10.1182/blood-2006-07-033597

PMID: 17164343 [Indexed for MEDLINE]

3997. J Am Coll Cardiol. 2006 Dec 5;48(11):2351-3. Epub 2006 Nov 9.

Are familial Mediterranean fever (FMF) patients at increased risk for atherosclerosis? Impaired endothelial function and increased intima media thickness are found in FMF.

Akdogan A, Calguneri M, Yavuz B, Arslan EB, Kalyoncu U, Sahiner L, Karadag O, Ertenli I, Kiraz S, Aytemir K, Akata D, Tokgozoglu L, Oto A.

DOI: 10.1016/j.jacc.2006.09.013

PMID: 17161270 [Indexed for MEDLINE]

3998. Rheumatol Int. 2007 May;27(7):689-90. Epub 2006 Dec 6.

Familial mediterranean fever unusually coexisted in an ankylosing spondylitis patient. MEFV mutation has any role?

Duman I, Balaban B, Tugcu I, Dincer K.

3999. Saudi Med J. 2006 Dec;27(12):1822-6.

Relationship of Tel Hashomer criteria and Mediterranean fever gene mutations in a cohort of Turkish familial Mediterranean fever patients.

Samli H(1), Dogru O, Bukulmez A, Yuksel E, Ovali F, Solak M.

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**OBJECTIVE:** To evaluate the frequency of 5 mutations and their relationship with the Tel Hashomer criteria in 85 FMF patients.

**METHODS:** We looked for mutations in the Mediterranean fever (MEFV) gene in 84 consecutive patients who admitted to the Department of Medical Genetics of Afyon Kocatepe University, with a variable (from high to low) clinical suspicion of FMF. By using polymerase chain reaction and Hybridization-ELISA methods, 5 mutations (M694V, M694I, V726A, M680I and E148Q) have been studied between December 2002 and January 2005.

**RESULTS:** We detected homozygote mutations in 12 patients (25.3%) and heterozygote mutations in 23 patients (48.9%) out of 47 patients with high clinical suspicion of FMF using Tel Hashomer criteria. In 12 patients (25.3%), no mutation was detected despite the clinical diagnosis of FMF was likely according to the Tel Hashomer clinical criteria. On the other hand, we detected homozygote mutations in 2 patients (5.4%) and heterozygote mutations in 17 patients (45.9%) out of 37 patients with low clinical suspicion of FMF using Tel Hashomer criteria. In 18 out of 37 patients (48.6%) in this group no mutation was detected.

**CONCLUSION:** In patients with high or low clinical suspicion of diagnosis of FMF according to Tel Hashomer criteria, the frequency of homozygote patients was significantly higher than the frequency of patients with no mutation, but it was not higher than the frequency of heterozygote patients.



PMID: 17143356 [Indexed for MEDLINE]

4000. Blood. 2007 Mar 15;109(6):2416-8. Epub 2006 Nov 30.

Defective apoptosis of peripheral-blood lymphocytes in hyper-IgD and periodic fever syndrome.

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Hereditary periodic fever syndromes are characterized by incapacitating attacks of fever and generalized inflammation. While the mutated genes for the major syndromes in this group are known, the pathogenesis remains unclear. The aim of this study was to investigate apoptosis in patients with periodic fever as a possible pathogenic factor. We measured anisomycin-induced apoptosis with annexin-V flow cytometry and caspase-3/7 activity in peripheral-blood lymphocytes from symptom-free patients with hyper-IgD and periodic fever syndrome (HIDS; n = 10), TNF-receptor-associated periodic syndrome (TRAPS; n = 7), and familial Mediterranean fever (FMF; n = 2). HIDS lymphocytes showed a decreased percentage of apoptosis during remission by both methods compared with controls (17.8% vs 55.4%), whereas no difference was observed in TRAPS or FMF lymphocytes. This defective apoptosis of lymphocytes may be a central pathogenic mechanism in HIDS, since dysfunction of one of the inhibitory mechanisms to curtail the immunologic response could cause an unbridled generalized inflammation after a trivial stimulus.

DOI: 10.1182/blood-2005-10-039578

PMID: 17138829 [Indexed for MEDLINE]

4001. J Nephrol. 2006 Sep-Oct;19(5):677-81.

Successful pregnancies in dialysis patients including those suffering from cystinosis and familial Mediterranean fever.

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For women on maintenance dialysis, pregnancy is still uncommon. The outcome of such pregnancies has improved in recent case series. Here, we report in detail the treatment of five successful pregnancies in dialysis patients from our centre. The present case series also includes the first successful pregnancy of a dialysis patient with underlying familial Mediterranean fever, and of a dialysis patient with cystinosis. We treated all patients with an intensified hemodiafiltration protocol, increased erythropoietin dosages, a generous application of water-soluble vitamins and trace elements in addition to a multidisciplinary clinical management approach with a very low threshold for hospital admission. Specifically, we report treatment of arterial hypertension with respect to changes in dry weight and pharmacological therapy. Mean gestational age at delivery was 32.8+/-3.3 weeks and mean birth weight was 1,765+/-554 g. All mothers and newborns were discharged healthy and in good condition. These modified management guidelines have led to a favourable outcome in all our patients including two patients with familial Mediterranean fever and with cystinosis, and may help to guide therapy in other pregnant dialysis patients.

PMID: 17136701 [Indexed for MEDLINE]

4002. *Pediatr Radiol*. 2007 Feb;37(2):145-52. Epub 2006 Nov 28.

Arthropathy of neonatal onset multisystem inflammatory disease (NOMID/CINCA).

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BACKGROUND: Neonatal onset multisystem inflammatory disease (NOMID), an

autoinflammatory disease, is characterized by fever, chronic urticarial rash, CNS manifestations, and arthropathy. Approximately 50% of patients with NOMID have de novo missense mutations in CIAS1, which is associated with modulation of the IL-1 $\beta$  and apoptotic pathways. Approximately 60% of NOMID patients have prominent arthropathy, most commonly involving the knees, the cause of which remains poorly understood.

**OBJECTIVE:** To more fully describe the findings of NOMID arthropathy on MRI and radiography and to provide a better understanding of the origin of the bony lesions.

**MATERIALS AND METHODS:** We imaged 20 patients with NOMID to further investigate NOMID-associated bony lesions.

**RESULTS:** Bony abnormalities were seen in the knees of 11/20 patients. The knee findings included enlarged, deformed femora and patellae in all and tibiae in the majority, without evidence of synovitis. Some patients had other joint involvement. Most had short stature and valgus or varus knee deformities. No association was noted between bony abnormalities and CIAS1 mutations. The abnormalities appeared to be the result of a mass-producing process. The resulting heterogeneously calcified masses appeared to originate in the physis and deformed the adjacent metaphysis and epiphysis.

**CONCLUSION:** These findings suggest that the arthropathy of NOMID is the result of abnormal endochondral bone growth. Further investigation is needed to determine whether this deformity is triggered by inflammation early in development or by CIAS1 mutations causing abnormal chondrocyte apoptosis.

DOI: 10.1007/s00247-006-0358-0

PMID: 17136361 [Indexed for MEDLINE]

4003. Curr Opin Immunol. 2007 Feb;19(1):10-6. Epub 2006 Nov 28.

Innate recognition of intracellular bacteria.

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The molecular repertoire for innate recognition of bacterial pathogens has expanded rapidly in the past decade. These immunosensors include Toll-like receptors and the more recently defined NOD-like receptors (NLRs): NODs, NALPs, NAIP and IPAF. Toll-like receptors signal from the cell surface or endosome upon ligand binding, whereas NLRs are activated by characteristic bacterially derived molecules, such as peptidoglycan, RNA, toxins and flagellin, in the cytosol. Studies using animal and culture models of bacterial infection indicate a pro-inflammatory role for NLRs, mediated by signaling through nuclear transcription factor kappaB and activation of caspase-1 by the inflammasome. These data also support a synergistic role for extracellular and intracellular bacterial sensing in regulating inflammation. In humans, NLR mutations are often associated with autoinflammatory syndromes, suggesting a complex role for cytosolic surveillance in systemic innate immunity.

DOI: 10.1016/j.coi.2006.11.005

PMID: 17126540 [Indexed for MEDLINE]

4004. Harefuah. 2006 Oct;145(10):743-5, 782.

[Amyloidosis of familial Mediterranean fever (FMF)--insights to FMF phenotype II].

[Article in Hebrew]

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Amyloidosis is the most grievous manifestation of Familial Mediterranean Fever (FMF), occurring in a high proportion of untreated patients. Continuously elevated serum amyloid A (SAA) levels during remissions, rather than a pulsatile rise during FMF attacks, underlies the development of amyloidosis. FMF phenotype II is one extreme of AA amyloidosis, evolving despite a complete absence of FMF attacks. FMF phenotype II is diagnosed in patients with AA amyloidosis in the context of a family history of FMF. In these patients and in patients with AA amyloidosis without family history of FMF and with unknown precipitating disease, MEFV gene analysis is mandatory. Moreover, since FMF phenotype II is an actual

hazard, a cost-benefit analysis suggests that MEFV mutation determination in all first-degree family members of FMF patients is warranted, as it will significantly reduce future patient treatment costs.

PMID: 17111710 [Indexed for MEDLINE]

4005. Harefuah. 2006 Oct;145(10):706-8, 784.

[Nephrotic syndrome as a first manifestation of familial Mediterranean fever].

[Article in Hebrew]

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AA amyloidosis may be a complication of Familial Mediterranean Fever (FMF). This is a case history of a female patient who did not have the classic symptoms of FMF, which usually precede the renal manifestation. The patient was admitted with edema of both legs, and the nephrotic syndrome was discovered, leading to the diagnosis of AA amyloidosis on kidney biopsy. Genetic testing uncovered the homozygous M694V type mutation, the most common mutation of FMF, which renders the patients prone to amyloidosis. This case represents the phenotype II of FMF, which presents with amyloidosis without prior classic attacks of FMF. Since effective prevention of the development of amyloidosis is available, genetic testing should be considered in order to identify mutations which carry high risk for the development of amyloidosis. This is also relevant in asymptomatic individuals with family history of FMF.

PMID: 17111701 [Indexed for MEDLINE]

4006. Ann Rheum Dis. 2006 Dec;65(12):1674-6.

Hyperimmunoglobulinaemia D syndrome in India: report of two siblings with a novel mutation.

Lawrence A, Hol F, Aggarwal A, Drenth JP.

Erratum in

Ann Rheum Dis. 2015 Jan;74(1):319.

DOI: 10.1136/ard.2006.054494

PMCID: PMC1798448

PMID: 17105862 [Indexed for MEDLINE]

4007. Rheumatol Int. 2007 Apr;27(6):517-22. Epub 2006 Nov 14.

The value of the levels of acute phase reactants for the prediction of familial Mediterranean fever associated amyloidosis: a case control study.

Yalçinkaya F(1), Cakar N, Acar B, Tutar E, Güriz H, Elhan AH, Oztürk S, Kansu A, Ince E, Atalay S, Girgin N, Doğru U, Aysev D, Ekim M.

Author information:

(1)Department of Pediatric Nephrology, Ankara University Faculty of Medicine, 38. Cadde, Mehmet Cakir Apt. 5/20, Cukurambar, Ankara, Turkey.

In order to determine the role of levels of acute phase proteins (APPs) for the development of amyloidosis in familial Mediterranean fever (FMF) patients, the levels of serum amyloid A (SAA), C reactive protein (CRP), fibrinogen and erythrocyte sedimentation rate were measured in paired sera of 36 FMF patients during and in between acute attacks, 39 of their healthy parents (obligate heterozygotes), and 15 patients with FMF associated amyloidosis. To compare the levels of APPs, 39 patients with chronic infections or inflammatory diseases who may develop secondary amyloidosis, 20 patients with acute infections who are known to have elevated acute phase response but will never develop amyloidosis and 19 healthy controls were included. The median levels of all APPs are increased in the patients with FMF during attacks and a significant decrease was observed after the attack was over. The level of SAA was above reference range in all FMF patients during the attack free period and the level of at least one other APP was also above normal in 64% of the patients. Both CRP and SAA levels

were found to be higher in obligate heterozygotes compared to controls. The levels of SAA in patients with FMF during the attack-free period, obligate heterozygotes and patients with FMF-amyloidosis were found to be similar. The levels in each group were found to be higher than SAA levels found in healthy controls yet lower than the levels measured in the patients with acute infections and patients with chronic inflammation or chronic infections. In conclusion, our results show that SAA level reflects subclinical inflammation with high sensitivity but its value for the prediction of amyloid formation process seems to be low.

DOI: 10.1007/s00296-006-0265-6

PMID: 17103173 [Indexed for MEDLINE]

4008. J Inherit Metab Dis. 2006 Dec;29(6):763. Epub 2006 Nov 10.

Anakinra is safe and effective in controlling hyperimmunoglobulinaemia D syndrome-associated febrile crisis.

Cailliez M(1), Garaix F, Rousset-Rouvière C, Bruno D, Kone-Paut I, Sarles J, Chabrol B, Tsimaratos M.

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Hyper-IgD and periodic fever syndrome (HIDS) is a hereditary autoinflammatory syndrome, characterized by recurrent inflammatory attacks. Treatment of HIDS is difficult. Recently, the IL-1ra analogue anakinra was reported to be successful in aborting the IgD inflammatory attacks in a vaccination model. We report a clinical case of spectacular reduction of febrile attacks in a severe HIDS patient.

DOI: 10.1007/s10545-006-0408-7

PMID: 17103011 [Indexed for MEDLINE]

4009. Rheumatol Int. 2007 Apr;27(6):545-51. Epub 2006 Nov 11.

The contribution of genotypes at the MICA gene triplet repeat polymorphisms and

MEFV mutations to amyloidosis and course of the disease in the patients with familial Mediterranean fever.

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**OBJECTIVE:** To evaluate the effects of MEFV genotypes and the major histocompatibility complex class I chain-related gene A (MICA) triplet repeat polymorphism on the severity and clinical features of familial Mediterranean fever (FMF) and amyloidosis in a group of Turkish FMF patients.

**METHODS:** We evaluated 105 adult FMF patients (with or without amyloidosis, 33 and 72, respectively) along with 107 healthy controls who were neither related to the patients nor had a family history of FMF or Behcet's disease. After recording the demographic and clinical data, the predominant mutations in the MEFV gene locus (M694V, M680I, V726A, M694I, and E148Q) were investigated by direct sequencing. MICA transmembrane polymorphisms in exon 5 were studied by vertical gel electrophoresis and fragment analysis of the amplicons obtained from MICA locus with appropriate primers.

**RESULTS:** Earlier age at onset, increased frequency of attacks, arthritis attacks, erysipelas-like erythema, increased severity scores and amyloidosis were significantly more common in M694V homozygous patients compared to the patients not M694V homozygous ( $P = 0.005$ , OR 4.55;  $P = 0.001$ , OR 7.60;  $P = 0.003$ , OR 4.57;  $P = 0.002$ , OR 7.58;  $P = 0.004$ , OR 5.15 and  $P = 0.018$ , OR 3.33, respectively). We did not detect any modifying effects of MICA alleles as an independently risk factor on the amyloidosis development. However, when we examined the effects of MICA alleles on the course of the disease and development of amyloidosis in the M694V homozygous patients, A5 allele had a protective effect against the development of amyloidosis ( $P = 0.038$ , OR(adj) 0.26 with A5 and  $P = 0.009$ , OR(adj) 4.42 without A5).

**CONCLUSION:** Though the effects of the MEFV genotypes seem clear, there are definitely other modifying factors or genes on the development of amyloidosis and on the course of the disease. For example, some MICA alleles have a protective effect on the prognostic factors in FMF.

DOI: 10.1007/s00296-006-0255-8

PMID: 17102945 [Indexed for MEDLINE]



4010. Can J Cardiol. 2006 Nov;22(13):1127-31.

The carotid-femoral (aortic) pulse wave velocity as a marker of arterial stiffness in familial Mediterranean fever.

Yildiz M(1), Masatlioglu S, Seymen P, Aytac E, Sahin B, Seymen HO.

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AIM: The purpose of the present study was to test the hypothesis that chronic inflammation impairs vascular function and leads to an arterial pulse wave velocity (PWV) increase in patients with familial Mediterranean fever (FMF).

PATIENTS AND METHODS: Twenty-three patients (17 women) with FMF, and 23 age- and sex-matched controls were recruited. Aortic PWV was determined by using an automatic device (Complior Colson, Createch Industrie, France) that allowed on-line pulse wave recording and automatic calculation of the PWV.

RESULTS: The PWV was slightly higher in patients with FMF than in control subjects ( $P=0.05$ ). A significant correlation between PWV and age ( $P<0.001$ ,  $r=0.67$ ), body mass index ( $P<0.001$ ,  $r=0.52$ ) and leukocytes ( $P<0.001$ ,  $r=0.66$ ) was found in both groups combined and also in patients with FMF ( $P<0.001$ ,  $r=0.73$ ;  $P=0.01$ ,  $r=0.52$ ;  $P<0.001$ ,  $r=0.69$ , respectively).

CONCLUSION: The PWV was slightly higher in patients with FMF compared with control subjects. Colchicine, an anti-inflammatory drug treatment, may have reduced the expected increased level of PWV in FMF patients. PWV is influenced by age, body mass index and leukocytes.

PMCID: PMC2569049

PMID: 17102830 [Indexed for MEDLINE]

4011. J Cardiovasc Electrophysiol. 2006 Dec;17(12):E9; author reply E10. Epub 2006 Nov 10.

Comment on "Familial pseudo-Wolff-Parkinson-White syndrome".

Green M, Gollob M.

Comment on

J Cardiovasc Electrophysiol. 2006 Jul;17(7):724-32.

DOI: 10.1111/j.1540-8167.2006.00650.x

PMID: 17096658 [Indexed for MEDLINE]

4012. Dement Geriatr Cogn Disord. 2007;23(1):55-9. Epub 2006 Nov 6.

The M694V variant of the familial Mediterranean fever gene is associated with sporadic early-onset Alzheimer's disease in an Italian population sample.

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**BACKGROUND:** Inflammation is deemed to play a crucial role in the pathogenesis of Alzheimer's disease (AD). We sought to determine whether the proinflammatory M694V mutation of pyrin, the gene responsible for familial Mediterranean fever, could lead to an increased risk for AD.

**METHODS:** We compared the M694V variant genotypes in 378 sporadic AD patients and 384 healthy control subjects of Italian descent.

**RESULTS:** After adjustment for potential confounders, the M694V mutation was found to be associated with an increased risk for AD in subjects with an age at onset of 65 years or younger (multivariate-adjusted odds ratio, OR: 3.01, 95% confidence interval, CI: 1.24-6.72,  $p = 0.021$ ), but not in patients with an age at onset older than 65 years (multivariate-adjusted OR: 0.81, 95% CI: 0.34-1.99,  $p = 0.847$ ). Kaplan-Meier analysis indicated that AD patients bearing the M694V mutation presented with disease onset 7 years earlier than carriers of the wild-type genotype (log rank = 41.61,  $p < 0.001$ ).

**CONCLUSION:** Our data indicate that the M694V sequence variant in the pyrin gene might influence the age at onset of AD in the Italian population.

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DOI: 10.1159/000096743

PMID: 17090974 [Indexed for MEDLINE]

4013. Curr Opin Allergy Clin Immunol. 2006 Dec;6(6):428-33.

Recent advances in the molecular pathogenesis of hereditary recurrent fevers.

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**PURPOSE OF REVIEW:** To discuss recent developments in the molecular basis of several hereditary recurrent fever syndromes, specifically the cryopyrin-associated periodic syndromes, familial Mediterranean fever and the tumor necrosis factor receptor associated periodic syndrome.

**RECENT FINDINGS:** Mutations of CIAS1, the gene encoding cryopyrin/NALP3, lead to a spectrum of disease states termed the cryopyrinopathies. Recently, cryopyrin-deficient mice have been used to show that the protein is a key regulator of interleukin-1 $\beta$  production that functions by recognizing stimuli such as bacterial RNA and infectious agents. Tumor necrosis factor receptor-associated periodic syndrome was initially thought to be caused by deficient metalloprotease-induced tumor necrosis factor receptor shedding, however new findings suggest that mutations in this receptor may result in inappropriate protein folding, leading to a host of other functional abnormalities that may cause inflammatory disease. Finally, data are emerging that address the possible function of the C-terminal B30.2 domain of pyrin, the familial Mediterranean fever protein. This motif has recently been shown to interact with and inhibit caspase-1, and the modeled structure of this complex highlights how mutations may affect the binding interface.

**SUMMARY:** Recent reports have advanced our understanding of the structural and functional biology underlying the hereditary recurrent fevers, and are beginning to suggest possible mechanisms by which specific mutations cause disease.

DOI: 10.1097/ACI.0b013e3280109b57

PMID: 17088647 [Indexed for MEDLINE]

4014. Z Rheumatol. 2006 Nov;65(7):610, 612.

[From gene to therapy. Hereditary fever syndromes gout and inflammation].

[Article in German]

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DOI: 10.1007/s00393-006-0123-7

PMID: 17077976 [Indexed for MEDLINE]

4015. Allergol Int. 2006 Sep;55(3):337-41.

Tumor necrosis factor receptor-associated periodic syndrome mimicking systemic juvenile idiopathic arthritis.

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**BACKGROUND:** We report two cases of tumor necrosis factor receptor-associated periodic syndrome (TRAPS) in patients in whom systemic juvenile idiopathic arthritis (JIA) had initially been diagnosed or suspected. One patient, given a diagnosis of systemic JIA, was a 10-year-old boy who had presented with recurrent episodes of spike-fever, skin rash, arthritis, and myalgia. The other patient was his 7-year-old sister, who presented with similar symptoms and was suspected of having systemic JIA.

**METHODS:** Serum levels of soluble tumor necrosis factor receptor super family 1A (TNFRSF1A), TNF-alpha, Interleukin (IL) -6, and C-reactive protein (CRP) were

measured in two siblings and JIA patients. In addition, DNA sequencing of the TNFRSF1A gene in two siblings was also performed.

RESULTS: A detailed family history showed that their mother had an episode of recurrent fever, arthritis, and myalgia with an increased serum CRP after the delivery of a daughter. Both siblings had serum levels of soluble TNFRSF1A that were below the normal reference range, and that did not reach a level corresponding to that of systemic JIA. On TNFRSF1A gene analysis, a single missense mutation resulting in C30Y was found in both siblings.

CONCLUSIONS: Based on the clinical features and the TNFRSF1A mutation, both siblings were given a diagnosis of TRAPS. The serum levels of soluble TNFRSF1A, measured along with the CRP level, may be a useful screening marker for differentiating TRAPS from systemic JIA.

DOI: 10.2332/allergolint.55.337

PMID: 17075277 [Indexed for MEDLINE]

4016. Z Rheumatol. 2006 Nov;65(7):595-8, 600-3.

[Periodic fever syndromes].

[Article in German]

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Periodic fever syndromes comprise a group of disorders characterized by attacks of seemingly unprovoked inflammation. The genetic causes of five hereditary autoinflammatory syndromes have been identified in the last few years: familial Mediterranean fever, the cryopyrinopathies [Muckle-Wells, chronic infantile neurological, cutaneous, articular syndrome (CINCA) and familial autoinflammatory syndromes], TNF-receptor associated periodic syndrome, cyclic neutropenia syndrome and periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome. The study of periodic fever syndromes has progressed from clinical characterization to genetic analysis and to the definition of the functional defects linking genes or domains to apoptotic proteins and signal

transduction pathways. This new research opens the way for more specific treatment options with a further improvement in prognosis and outcome.

DOI: 10.1007/s00393-006-0117-5

PMID: 17072571 [Indexed for MEDLINE]

4017. Joint Bone Spine. 2006 Dec;73(6):672-8. Epub 2006 Sep 1.

Colchicine today.

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Colchicine is used chiefly in the treatment of gout but is also valuable in other inflammatory diseases such as familial Mediterranean fever (FMF). Three proteins play pivotal roles in colchicine pharmacokinetics: the colchicine receptor, tubulin, which governs the plasma elimination half-life of the drug; intestinal and hepatic CYP3A4, which is key to the biotransformation of colchicine; and P-glycoprotein, a cell efflux pump that regulates the tissue distribution of colchicine, as well as its excretion via the biliary tract and kidneys.

Pharmacokinetic studies have been performed using a radioimmunity assay to measure blood colchicine levels. Absorption after oral ingestion varies widely (from 24% to 88% of the dose), the volume of distribution is extremely large (7 l/kg), and binding to albumin is moderate. Colchicine is excreted chiefly through the liver and has an elimination half-life of 20-40 hours. With repeated doses of about 1mg/day, the steady-state is achieved within 8 days and concentrations range from 0.3 to 2.5 ng/ml. Studies of associations between pharmacokinetic parameters and pharmacodynamics show that effects are correlated, not to plasma levels, but to levels in leukocytes. Adverse events are not uncommon, most notably when colchicine is used in combination with drugs that interact with CYP3A4 and/or P-glycoprotein, thereby decreasing the renal and/or hepatic elimination of colchicine. Careful monitoring in this situation is effective in preventing the development of toxicity.

DOI: 10.1016/j.jbspin.2006.03.006  
PMID: 17067838 [Indexed for MEDLINE]

4018. Clin Exp Rheumatol. 2006 Sep-Oct;24(5 Suppl 42):S127.

A molecular basis for the absence of familial Mediterranean fever in Ethiopian Jews.

Rozenbaum M, Touitou I, Portnoy E, Morkos S, Rosner I.

Erratum in  
Clin Exp Rheumatol. 2007 May-Jun;25(3):507-8.

PMID: 17067447 [Indexed for MEDLINE]

4019. Clin Exp Rheumatol. 2006 Sep-Oct;24(5 Suppl 42):S120-2.

Are carriers for MEFV mutations "healthy"?

Kalyoncu M(1), Acar BC, Cakar N, Bakkaloglu A, Ozturk S, Dereli E, Tunca M, Kasapcopur O, Yalcinkaya F, Ozen S.

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Erratum in  
Clin Exp Rheumatol. 2007 May-Jun;25(3):507-8.

**OBJECTIVE:** We aimed to compare whether carriers for the MEFV mutations display an increase or decrease in certain features. We compared the frequency of a number of inflammatory symptoms and diseases in carriers and a control population.

**METHODS:** A questionnaire was designed to be applied to parents of children with FMF and a control group of parents. Clinical features and some diseases including the frequency of febrile episodes, abdominal pain, arthralgia, prophylaxis with penicillin, acute rheumatic fever, rheumatoid arthritis, vasculitis,

spondyloarthropathy, urinary tract infection, asthma, allergy, irritable bowel disease, appendectomy and tonsillectomy were inquired. 676 parents of 440 children with FMF were surveyed in this study. Controls (n: 774) were selected as parents of healthy children.

RESULTS: The presence of febrile episodes more than four per year, arthralgia, past diagnosis for acute rheumatic fever, rheumatoid arthritis and prophylaxis of penicillin, acute rheumatic fever, and rheumatoid arthritis were significantly higher in asymptomatic parents for the MEFV mutations compared to controls. The frequency of allergy was found to be significantly lower in the asymptomatic parents as compared to controls. There was no significant difference at the frequency of urinary tract infection and tonsillectomy between the parents of the patents and controls.

CONCLUSIONS: We suggest that one MEFV mutation may indeed be conferring a heightened inflammation as suggested by the increased frequency in inflammatory symptoms. The carrier status for MEFV mutations seem to be unique, in that they cause an alteration in the state of "health".

PMID: 17067442 [Indexed for MEDLINE]

4020. Clin Exp Rheumatol. 2006 Sep-Oct;24(5 Suppl 42):S99-103.

Treatment options in colchicine resistant familial Mediterranean fever patients: thalidomide and etanercept as adjunctive agents.

Seyahi E(1), Ozdogan H, Celik S, Ugurlu S, Yazici H.

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Erratum in

Clin Exp Rheumatol. 2007 May-Jun;25(3):507-8.

OBJECTIVE: Regular colchicine treatment cannot control the typical febrile attacks of FMF in about 5-10% of the compliant patients. Here we report the effect of thalidomide and etanercept in 5 colchicine-resistant cases.

METHODS: Five (4M/ 1F) FMF patients between April 2005 and March 2006, who were



experiencing at least 2 attacks per month, despite regular colchicine were included to the study. Four male patients were given thalidomide 100 mg/d initially. Two of these patients unresponsive to thalidomide were prescribed subcutaneous injections of etanercept 25 mg, twice a week. The female patient received etanercept as the first choice due to potential side effects. She then had to be converted to thalidomide due to a severe injection site reaction.

**RESULTS:** The median follow up period with thalidomide and etanercept was 8 months. Both thalidomide and etanercept lowered the number of the abdominal attacks.

**CONCLUSION:** Thalidomide and etanercept might be effective as additional treatment in colchicine-resistant cases of FMF.

PMID: 17067437 [Indexed for MEDLINE]

4021. Clin Exp Rheumatol. 2006 Sep-Oct;24(5 Suppl 42):S95-8.

Circulating thrombomodulin levels in familial Mediterranean fever.

Ozbalkan Z(1), Ozturk MA, Onat AM, Ureten K, Haznedaroglu IC, Kiraz S, Ertenli AI, Kirazli S, Calguneri M.

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Erratum in

Clin Exp Rheumatol. 2007 May-Jun;25(3):507-8.

Increments in circulating thrombomodulin levels reflect endothelial cell injury. Thrombomodulin can also be synthesized by several inflammatory cells including monocytes, neutrophils, and thrombomodulin itself can modulate the inflammatory response. In this study, we assessed circulating thrombomodulin concentrations in patients with familial Mediterranean fever (FMF). Twenty-five patients with FMF (F/M: 14/11) (mean age: 31.1 +/- 9.7 years) and 25 healthy controls (F/M: 13/12) (mean age: 34.6 +/- 7.0 years) were involved in the study. Thrombomodulin levels were measured by commercially available enzyme-linked immunosorbant assay (ELISA) (Immunoassay of thrombomodulin Diagnostica Stago, Asnieres-Sur-Seine, France).

Twenty of the patients were in attack-free period and the remaining five had been during acute FMF attacks. Thrombomodulin levels were higher in the study group (20.9 +/- 12.1 ng/ml) than healthy controls (14.1 +/- 8.4 ng/ml) ( $p < 0.05$ ). Circulating thrombomodulin levels were also higher in attack-free FMF patients (22.4 +/- 12.9 ng/ml) than controls. This study disclosed for the first time significantly higher increments in the circulating levels of thrombomodulin in FMF. This observation could be a consequence of injured endothelium and/or activated inflammatory cells.

PMID: 17067436 [Indexed for MEDLINE]

4022. Clin Exp Rheumatol. 2006 Sep-Oct;24(5 Suppl 42):S51-2.

The MEFV E148Q allele: a deleterious mutation or harmless variation?

Hershko AY, Ben-Chetrit E.

Erratum in

Clin Exp Rheumatol. 2007 May-Jun;25(3):507-8.

PMID: 17067427 [Indexed for MEDLINE]

4023. Br J Anaesth. 2006 Dec;97(6):866-8. Epub 2006 Oct 24.

Spinal cord stimulation for relief of abdominal pain in two patients with familial Mediterranean fever.

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Familial Mediterranean fever is a hereditary disease characterized by recurrent attacks of fever and serosal inflammation that commonly presents as severe

abdominal pain. Though colchicine remains the mainstay of treatment, a significant proportion of patients are partially responsive, unresponsive or intolerant to it. We present two such cases where spinal cord stimulation (SCS) was used to manage the paroxysmal abdominal pain associated with this disease. Abdominal visceral pain pathways and the application of SCS techniques in its management are discussed.

DOI: 10.1093/bja/ael279

PMID: 17062615 [Indexed for MEDLINE]

4024. Clin Rheumatol. 2007 Sep;26(9):1557-60. Epub 2006 Oct 24.

The expanded clinical spectrum of familial Mediterranean fever.

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The classical clinical features of familial Mediterranean fever (FMF) are recurrent self-limited attacks of fever and serositis. Amyloidosis of the AA type is the major complication of the disease. The diagnosis of FMF is still based on a history of typical acute attacks, ethnic background, and frequently, notable family history. Together with the discovery of MEFV gene, the clinical criteria for the diagnosis of the disease did not change. Although we have learned a great deal about the clinical features and the pathogenesis of FMF in the past few years, many atypical cases emerge, and caution should be exercised during diagnosis. In this report, we present three FMF patients not fulfilling clinical criteria for the diagnosis, discuss rare and unusual presentations of the disease, and emphasize the role of genetic analysis in these suspicious cases.

DOI: 10.1007/s10067-006-0447-3

PMID: 17061155 [Indexed for MEDLINE]

4025. Praxis (Bern 1994). 2006 Sep 20;95(38):1441-8; quiz 1449.

[Hereditary periodic fever. Chief symptoms: recurrent fever, (poly-)serositis and synovitis, exanthema].

[Article in German]

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DOI: 10.1024/1661-8157.95.38.1441

PMID: 17058594 [Indexed for MEDLINE]

4026. Clin Rheumatol. 2007 Jun;26(6):908-10. Epub 2006 Oct 21.

Tumor necrosis factor-alpha gene promoter polymorphism in patients with familial Mediterranean fever.

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The proinflammatory cytokine tumor necrosis factor-alpha (TNF-alpha) plays an important role on the course of disease in familial Mediterranean fever (FMF). TNF-alpha gene promoter polymorphism may be a marker of susceptibility and severity of FMF. The aim of this study is to evaluate both TNF-alpha/238 and TNF-alpha/308 genotypes and allelic distribution in patients with FMF. Forty-one FMF patients and 43 healthy volunteers were included in the study. Genomic DNA was extracted from EDTA-preserved whole blood of whole series of patients and controls. Polymorphism of TNF-alpha promoter at positions -238 and -308 were detected by using amplification refractory mutation system polymerase chain reaction. TNF-alpha/238 and TNF-alpha/308 genotype distributions and allele frequencies of FMF patients and healthy volunteers were found to be similar. Moreover, there was no association between TNF-alpha/238 and TNF-alpha/308 genotypes and the frequency of acute attacks in FMF. TNF-alpha/238 and

TNF-alpha/308 promoter polymorphisms do not seem to be major genetic risk factors for susceptibility to FMF and severity of the disease.

DOI: 10.1007/s10067-006-0430-z

PMID: 17057944 [Indexed for MEDLINE]

4027. Ann N Y Acad Sci. 2006 Aug;1072:19-27.

Innate immune sensing of microbes by Nod proteins.

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Nod1 and Nod2 are proteins involved in innate immune defense. These intracellular surveillance proteins detect bacterial peptidoglycan, although requiring distinct motifs to achieve sensing. Detection through Nod1 and Nod2 initiates proinflammatory signaling via NF-kappaB activation, which is necessary for clearance of infecting pathogens from the host. The peptidoglycan product sensed by Nod1 is a motif characteristic of Gram-negative bacteria plus some Gram-positive bacteria, such as *Bacillus* and *Listeria* spp. The specificity of Nod1 to detect this subset of bacteria might represent a selective advantage for the host in certain cases when Gram-negative bacteria represent the main threat, such as in the epithelial cells lining the intestinal mucosa. In contrast, Nod2 has been implicated as a general sensor for both Gram-positive and Gram-negative bacteria since muramyl dipeptide (MDP), which is the minimal motif in all peptidoglycans, is the structure recognized by Nod2. Mutations in Nod2 have been associated with autoinflammatory disease in humans, including Crohn's disease. Interestingly, the most common mutation in Nod2 associated with Crohn's disease results in protein product that no longer detects MDP. Although the implications of these findings are still not fully understood, it appears that lack of bacterial sensing through a loss of interaction between mutant Nod2 and MDP contributes to the pathology of disease. A loss of surveillance activity by Nod2 may result in the inability of local responses in the intestinal mucosa to control bacterial infection, thereby initiating systemic responses and leading to aberrant inflammation.

DOI: 10.1196/annals.1326.020

PMID: 17057187 [Indexed for MEDLINE]

4028. J Natl Med Assoc. 2006 Oct;98(10):1692-3.

Rubinstein-Taybi syndrome and familial Mediterranean fever in a single patient: two distinct genetic diseases located on chromosome 16p13.3.

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Rubinstein-Taybi syndrome (RTS) is characterized by typical facies, short stature, mental retardation, broad thumbs and broad great toes. The syndrome is at least in part caused by microdeletions at chromosome 16p13.3 or by mutations in the gene for the CREB binding protein (CBP), which is located at 16p13.3. Familial Mediterranean fever (FMF) is an autosomal recessive disease, caused by mutations in the FMF-gene [Mediterranean fever (MEFV)] and characterized by recurrent attacks of fever and peritonitis, arthritis and pleuritis. The FMF gene (MEFV) has recently been cloned by two consortia and 30 point mutations, causing the disease have been identified. MEFV maps to chromosome 16p and encodes a 781-amino-acid protein called pyrin or marenostrin, which is expressed mainly in neutrophils and myeloid bone marrow precursors. Herein, we report a case with RTS and FMF.

PMCID: PMC2569755

PMID: 17052063 [Indexed for MEDLINE]

4029. J Nephrol. 2006 Jul-Aug;19(4):543-9.

A complex case of renal amyloidosis with a rare co-occurrence of 2 mutations in separate hereditary periodic fever syndrome-related genes.

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A 41 year-old male was admitted because of nephrotic syndrome associated with renal impairment and arterial hypertension. Renal biopsy showed a complete subverting of renal architecture with eosinophilic, amorphous deposits which stained positive for Congo red and were positive for antibodies against AA-amyloid. Abdominal fat pad aspirate confirmed the diagnosis of AA amyloidosis. Despite high values of serum amyloid A (SAA), surprisingly medical history, physical examination and all tests failed to identify any underlying inflammatory disease, even asymptomatic, at presentation and during the whole follow-up period. The patient carried a mutation (Glu148Gln) in the MEFV gene, and a mutation (Arg92Gln) in the TNFRSF1A gene, both in heterozygosity. The patient has never complained of the typical features of the Familial Mediterranean fever or of the TNF receptor-associated periodic syndrome. The patient's father carried the same mutations. His father's medical history was unremarkable; renal tests, acute-phase reactants and SAA were normal. During a trial with colchicine (while the patient was also taking atorvastatin) SAA decreased, renal function continued to deteriorate and proteinuria remained high; no cardiac involvement was detected. Six months later our patient developed rhabdomyolysis, thus accelerating the decline of renal function and requiring the start of dialysis.

PMID: 17048217 [Indexed for MEDLINE]

4030. Ther Umsch. 2006 Oct;63(10):667-71.

[Recurrent febrile episodes--normal, periodic fever syndrome or immunodeficiency?].

[Article in German]

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Fever is one of the main symptoms leading to medical evaluation. Not only infections cause fever but also inflammatory disorders. To distinguish one from another, a thorough medical history and clinical evaluation are needed. Sometimes, only the clinical course will reveal the diagnosis. PFAPA-Syndrome (periodic fever, aphthous stomatitis, pharyngitis, adenitis) is the most frequent periodic fever syndrome in Switzerland. No diagnostic test is available to support the diagnosis. Some important diseases have to be ruled out, such as Immunodeficiency, cyclic neutropenia, chronic viral infections and rheumatologic disorders. To know the diagnosis of the PFAPA-Syndrome can help avoiding antibiotic courses for febrile episodes in infants. There is a clinical overlap to hereditary periodic fever syndromes as familial Mediterranean fever (FMF), Hyper-IgD and fever syndrome (HIDS), Tumor-necrosis factor receptor associated periodic syndrome (TRAPS) and others, in which a genetic basis for the disease has already been found.

DOI: 10.1024/0040-5930.63.10.667

PMID: 17048186 [Indexed for MEDLINE]

4031. J Clin Rheumatol. 2004 Jun;10(3):134-7.

Infliximab treatment of Familial Mediterranean fever and its effect on secondary AA amyloidosis.

Metyas S(1), Arkfeld DG, Forrester DM, Ehresmann GR.

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We describe a patient with a long history of familial Mediterranean fever who developed proteinuria as a result of secondary AA amyloidosis. In this patient, the inflammatory process, including recurrent attacks of arthritis, abdominal pain, nephrotic syndrome secondary to amyloidosis, and high sedimentation rate, was rapidly suppressed by treatment with infliximab and there was remarkable improvement of the proteinuria. Because TNF-alpha is a proinflammatory cytokine



that plays a major role in FMF and secondary amyloid, it is an appropriate target for therapy. Our case is the first case of reactive systemic amyloidosis secondary to familial Mediterranean fever, which responded favorably to infliximab.

DOI: 10.1097/01.rhu.0000128856.13595.eb

PMID: 17043487

4032. Ann Rheum Dis. 2006 Nov;65(11):1530-1.

Refractory auto-inflammatory syndrome associated with digenic transmission of low-penetrance tumour necrosis factor receptor-associated periodic syndrome and cryopyrin-associated periodic syndrome mutations.

Touitou I, Perez C, Dumont B, Federici L, Jorgensen C.

DOI: 10.1136/ard.2006.054312

PMCID: PMC1798361

PMID: 17038455 [Indexed for MEDLINE]

4033. Mod Rheumatol. 2005;15(5):358-60.

An unusual complication of familial Mediterranean fever: protracted arthritis with bilateral coxarthrosis and intraosseous amyloidosis of femoral head.

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Protracted arthritis is uncommon in familial Mediterranean fever (FMF) and rarely may result in degenerative joint damage, a well-known complication of FMF, usually affecting kidneys. We present an unusual case of FMF involving severe bilateral coxarthrosis leading to residual incapacity that was treated by total hip arthroplasty, and an unusual presentation of amyloidosis - intraosseous

amyloidosis of the femoral head.

DOI: 10.1007/s10165-005-0415-9

PMID: 17029093

4034. J Clin Rheumatol. 2006 Oct;12(5):265-6.

Histologic signs of inflammatory myopathy in familial Mediterranean fever.

Gdynia HJ, Sperfeld AD, Haerter G.

Comment on

J Clin Rheumatol. 2006 Apr;12(2):93-6.

DOI: 10.1097/01.rhu.0000240149.96221.ed

PMID: 17023819 [Indexed for MEDLINE]

4035. J Rheumatol. 2006 Dec;33(12):2498-500. Epub 2006 Oct 1.

Arg753Gln TLR-2 polymorphism in familial mediterranean fever: linking the environment to the phenotype in a monogenic inflammatory disease.

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**OBJECTIVE:** Familial Mediterranean fever (FMF) is an autoinflammatory disease common in eastern Mediterranean populations. The most severe complication is the development of secondary amyloidosis. Toll-like receptor (TLR-2) plays a critical role in linking the recognition of microbes to immune activation. We investigated whether the Arg753Gln TLR2 polymorphism affected the development of secondary amyloidosis in patients with FMF.

**METHODS:** We studied 75 patients with FMF, 40 patients with FMF who developed secondary amyloidosis, and 116 healthy controls. TLR2 gene Arg753Gln mutations

were analyzed with a polymerase chain reaction-restriction fragment length polymorphism method.

RESULTS: The frequency of the Arg753Gln TLR2 polymorphism among the Turkish population was 6%, whereas it was 25.2% among patients with FMF ( $p < 0.01$ ). The difference of the frequency of the polymorphism between FMF patients with and without amyloidosis was significant: 15/40 (37.5%) and 14/75 (18.6%), respectively ( $p = 0.02$ ).

CONCLUSION: The Arg753Gln polymorphism may affect the severity of this monogenic disease by influencing the innate immune response to pathogens. The presence of the polymorphism may influence the phenotype of FMF in geographic areas where bacterial insult is more common.

PMID: 17013994 [Indexed for MEDLINE]

4036. Rheumatol Int. 2007 Feb;27(4):395-8. Epub 2006 Sep 28.

Changes in the liver function tests during the attacks of familial Mediterranean fever.

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The present study aims to investigate whether or not FMF patients display abnormal liver functions during attack periods. About 41 consecutive FMF patients with attacks were enrolled on this study. Bilirubin levels, liver transaminases, erythrocyte sedimentation rate and C-reactive protein (C-RP) levels were determined within the first 72 h after the onset of attacks. This procedure could be performed on only 28 of these 41 FMF patients, 4 weeks after the attack of the patients' had completely disappeared. As for the disease control group, 44 patients were determined to be eligible for the study. Another 31 healthy individuals were also included. Hyperbilirubinemia was determined in 11 of the 41 patients (26.8%) with FMF. The number of FMF patients with hyperbilirubinemia was significantly higher than in DC and HC ( $P < 0.001$ ,  $P = 0.03$ , respectively).

Levels of liver transaminases slightly increased in four patients with FMF during

the attack and two of these four patients had also mild hyperbilirubinemia. A significant correlation was found between C-RP levels and total and unconjugated bilirubin levels in FMF patients with attack ( $r = 0.43$ ,  $P = 0.01$ ;  $r = 0.40$ ,  $P = 0.02$ , respectively). In conclusion, mild hyperbilirubinemia may occur in one-fourth of the patients with FMF during the attack period.

DOI: 10.1007/s00296-006-0226-0

PMID: 17006702 [Indexed for MEDLINE]

4037. Med Hypotheses. 2007;68(3):499-501. Epub 2006 Sep 26.

Goats, germs, and fever: Are the pyrin mutations responsible for familial Mediterranean fever protective against Brucellosis?

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Mutations in the MEFV gene are highly prevalent in the Middle East and Mediterranean basin, with carrier rates of up to 1:3 in some populations. More than 50 mutations in the MEFV gene have been described. The high prevalence, multiple mutations, and geographic localization to the Middle East suggest a positive selection advantage for the abnormal gene operating in this area over the last several thousand years. To date, no satisfactory explanation of this phenomenon has been made. Rather, many harmful effects of these mutations have been described. MEFV gene mutations cause familial Mediterranean fever in homozygotes, a disease associated with recurrent febrile inflammatory episodes, and death from renal failure and amyloidosis. Heterozygotes with MEFV mutations are predisposed to premature coronary disease, and rheumatologic conditions such as Behçet's disease. MEFV mutations do not appear to protect against tuberculosis. Brucellosis is still highly endemic in the Middle East because of the traditional reliance for meat and dairy production on goats and sheep, the major vectors for this zoonosis. Brucellosis causes a prolonged febrile illness lasting for months and even years, and it may have exacted a major toll among Bronze Age peasant populations in the Middle East. The gene product for MEFV, pyrin, normally inhibits interleukin-1 $\beta$  production. Mutations in MEFV result

in a pro-inflammatory state, with a Th1 polarization and high levels of interferon-gamma. This may actually be protective against intracellular pathogens such as brucellosis. The possible heterozygote advantage of MEFV mutations against brucellosis may therefore be a balanced polymorphism, analogous to the protective effect against malaria that maintains high levels of sickle cell trait in sub-Saharan Africa.

DOI: 10.1016/j.mehy.2006.07.027

PMID: 17005326 [Indexed for MEDLINE]

4038. Can J Anaesth. 2006 Oct;53(10):1062-3.

Meningismus after metamamol administration in a patient with Familial Mediterranean fever.

Kapur S, Mutagi H, Raphael J.

DOI: 10.1007/BF03022538

PMID: 16987863 [Indexed for MEDLINE]

4039. J Rheumatol. 2006 Oct;33(10):2085-7. Epub 2006 Sep 15.

Anakinra prevents symptoms of familial cold autoinflammatory syndrome and Raynaud's disease.

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(1)Division of Rheumatology, University of Southern California, Los Angeles, California 90033, USA. metyas@usc.edu

**OBJECTIVE:** Familial cold autoinflammatory syndrome (FCAS) is a rare, hereditary disorder characterized by cold-induced inflammation. We describe the successful longterm treatment of a patient with FCAS with anakinra, an interleukin 1 receptor antagonist (IL-1Ra). The remarkable response of FCAS and associated Raynaud's disease in this patient suggests that IL-1 is an important mediator of these inflammatory diseases. Our report supports increasing evidence that

anakinra plays an important role in the treatment of select chronic inflammatory diseases.

PMID: 16981288 [Indexed for MEDLINE]

4040. Best Pract Res Clin Rheumatol. 2006 Oct;20(5):879-96.

Is IL-1 a good therapeutic target in the treatment of arthritis?

Burger D(1), Dayer JM, Palmer G, Gabay C.

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Inflammation is an important homeostatic mechanism that limits the effects of infectious agents. However, inflammation might be self-damaging and therefore has to be tightly controlled or even abolished by the organism. Interleukin 1 (IL-1) is a crucial mediator of the inflammatory response, playing an important part in the body's natural responses and the development of pathological conditions leading to chronic inflammation. While IL-1 production may be decreased or its effects limited by so-called anti-inflammatory cytokines, in vitro IL-1 inflammatory effects are inhibited and can be abolished by one particularly powerful inhibitor, IL-1 receptor antagonist (IL-1Ra). Recent research has shown that in the processes of rheumatoid arthritis (RA) IL-1 is one of the pivotal cytokines in initiating disease, and IL-1Ra has been shown conclusively to block its effects. In laboratory and animal studies the inhibition of IL-1 by either antibodies to IL-1 or IL-1Ra proved beneficial to the outcome. Because of its beneficial effects in many animal disease models, IL-1Ra has been used as a therapeutic agent in human patients. The recombinant form of IL-1Ra, anakinra (Kineret, Amgen) failed to show beneficial effects in septic shock and displays weak effects in RA patients. However, IL-1 blockade by anakinra is dramatically effective in systemic-onset juvenile idiopathic arthritis, in adult Still's disease and in several autoinflammatory disorders, most of the latter being caused by mutations of proteins controlling IL-1 $\beta$  secretion. Importantly, to be efficacious, anakinra required daily injections, suggesting that administered

IL-1Ra displays very short-term effects. Better IL-1 antagonists are in the process of being developed.

DOI: 10.1016/j.berh.2006.06.004

PMID: 16980212 [Indexed for MEDLINE]

4041. Cell Death Differ. 2007 Jan;14(1):10-22. Epub 2006 Sep 15.

Inflammatory caspases and inflammasomes: master switches of inflammation.

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Fifteen years have passed since the cloning and characterization of the interleukin-1 $\beta$ -converting enzyme (ICE/caspase-1), the first identified member of a family of proteases currently known as caspases. Caspase-1 is the prototypical member of a subclass of caspases involved in cytokine maturation termed inflammatory caspases that also include caspase-4 caspase -5, caspase -11 and caspase -12. Efforts to elucidate the molecular mechanisms involved in the activation of these proteases have uncovered an important role for the NLR family members, NALPs, NAIP and IPAF. These proteins promote the assembly of multiprotein complexes termed inflammasomes, which are required for activation of inflammatory caspases. This article will review some evolutionary aspects, biochemical evidences and genetic studies, underlining the role of inflammasomes and inflammatory caspases in innate immunity against pathogens, autoinflammatory syndromes and in the biology of reproduction.

DOI: 10.1038/sj.cdd.4402038

PMID: 16977329 [Indexed for MEDLINE]

4042. Clin Exp Rheumatol. 2006 Jul-Aug;24(4):435-7.

Etanercept in the treatment of arthritis in a patient with familial Mediterranean fever.

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Familial Mediterranean fever (FMF) patients may present with different joint complaints, one being the 'protracted attack' that lasts for weeks. We present a 15 year-old boy with polyarthritis (right wrist, knee, shoulder, and both ankles) while on colchicine treatment for FMF. His polyarthritis was resistant to treatment with prednisolone and methotrexate, and etanercept was instituted (0.8 mg/kg/week). He responded dramatically to etanercept and remained in full remission, although the drug was stopped at 4 months due to social and financial causes. We suggest that anti-TNF drugs may be an alternative for resistant attacks. However the timing and dosage, as well as efficacy, need to be further studied.

PMID: 16956436 [Indexed for MEDLINE]

4043. Rheumatol Int. 2007 Jan;27(3):309-10. Epub 2006 Sep 2.

Acute renal failure in a patient with familial Mediterranean fever.

Ozçakar ZB, Yüksel S, Ensari A, Ekim M, Yalçinkaya F.

DOI: 10.1007/s00296-006-0205-5

PMID: 16951944 [Indexed for MEDLINE]

4044. Mediators Inflamm. 2006;2006(3):41783.

Genetic analysis of MEFV gene pyrin domain in patients with Behçet's disease.

Dursun A(1), Durakbasi-Dursun HG, Zamani AG, Gulbahar ZG, Dursun R, Yakicier C.

Author information:



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**OBJECTIVES:** Behçet's disease (BD) is a systemic vasculitis with recurrent oral and genital ulcers and uveitis. MEFV gene, which is the main factor in familial Mediterranean fever (FMF), is also reported to be a susceptibility gene for BD. The pyrin domain of MEFV gene is a member of death-domain superfamily and has been proposed to regulate inflammatory signaling in myeloid cells. This study was designed to determine if mutations in pyrin domain of MEFV gene are involved in BD.

**METHODS:** We analyzed the pyrin domain of MEFV gene in 54 Turkish patients with BD by PCR-analysis and direct sequencing.

**RESULTS:** Neither deletion or insertion mutations nor point mutations in pyrin domain were found in any patient.

**CONCLUSION:** Although pyrin gene mutations have been reported in patients with BD, pyrin domain is not mutated. However, alterations in other regions of MEFV gene and interaction between pyrin domains are needed to be further investigated.

DOI: 10.1155/MI/2006/41783

PMCID: PMC1592598

PMID: 16951489 [Indexed for MEDLINE]

4045. Rheumatol Int. 2006 Dec;27(2):197-9. Epub 2006 Aug 31.

Successful treatment of nephrotic syndrome due to FMF amyloidosis with azathioprine: report of three Turkish cases.

Sayarlioglu H(1), Erkoc R, Sayarlioglu M, Dogan E, Soyoral Y.

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Secondary amyloidosis is a well-known complication of certain familial Mediterranean fever (FMF). We presented three Turkish patients with FMF and biopsy proven amyloidosis. These patients were treated with colchicine 1.5 mg/day. They have experienced five to six peritonitis attacks with fever within 1

year. On admission, the laboratory test results were as follows: serum creatinine 2.3, 0.6, and 0.5 mg/dl; albumin 4.2, 1.9, and 1.8 g/dl; and urinary protein excretion 4, 15, and 10 g/day, respectively. All the patients were started azathioprine (AZA) 100 mg/day and attacks were completely stopped. Laboratory findings were as follows after 1 year of AZA treatment: serum creatinine 1, 0.8, and 0.6 mg/dl; albumin 4.3, 3, and 3.5 g/dl; and urinary protein excretion 3, 8, and 1.5 g/day, respectively. Treatment with azathioprine in addition to colchicine could ameliorate the nephrotic syndrome and control the attacks very effectively in these cases.

DOI: 10.1007/s00296-006-0188-2

PMID: 16944160 [Indexed for MEDLINE]

4046. Anadolu Kardiyol Derg. 2006 Sep;6(3):272-4.

Familial Mediterranean fever and acute anterior myocardial infarction in a young patient.

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(1)Department of Cardiology, Siyami Ersek Cardiovascular and Thoracic Surgery Center, Istanbul, Turkey. uyarel@yahoo.com

PMID: 16943116 [Indexed for MEDLINE]

4047. Turk J Gastroenterol. 2006 Sep;17(3):231-2.

An unusual complication of familial Mediterranean fever: intestinal volvulus and necrosis.

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Familial Mediterranean fever is an autosomal recessive disease characterized by recurring inflammatory attacks of synovial membranes. More than 95% of patients show peritoneal involvement which mimics acute abdomen and can sometimes cause unnecessary surgical intervention. The authors present two patients with the diagnosis of familial Mediterranean fever who underwent surgery because of rare abdominal complication of the disease. Two patients with the diagnosis of familial Mediterranean fever underwent laparotomy, and segmental small bowel resection was done because of the necrosis. Adhesive intestinal obstruction with associated bowel strangulation and volvulus is a rare complication of familial Mediterranean fever, and this life-threatening emergency must be kept in mind.

PMID: 16941262 [Indexed for MEDLINE]

4048. Rheumatology (Oxford). 2007 Jul;46(7):1211-2. Epub 2006 Aug 25.

Failure of anti-TNF therapy in TNF Receptor 1-Associated Periodic Syndrome (TRAPS).

Jacobelli S, André M, Alexandra JF, Dodé C, Papo T.

Comment in

Rheumatology (Oxford). 2008 Feb;47(2):228-9.

Rheumatology (Oxford). 2007 Dec;46(12):1865-6.

DOI: 10.1093/rheumatology/kel298

PMID: 16935919 [Indexed for MEDLINE]

4049. Eur J Pediatr. 2007 Apr;166(4):383-4. Epub 2006 Aug 24.

Incomplete attack and protracted sacroiliitis: an unusual manifestation of FMF in a child.

Eifan AO(1), Ozdemir C, Aydogan M, Gocmen I, Bahceciler NN, Barlan IB.

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DOI: 10.1007/s00431-006-0245-6

PMID: 16932947 [Indexed for MEDLINE]

4050. Am J Physiol Regul Integr Comp Physiol. 2007 Jan;292(1):R86-98. Epub 2006 Aug 24.

Pathogenesis of familial periodic fever syndromes or hereditary autoinflammatory syndromes.

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Familial periodic fever syndromes, otherwise known as hereditary autoinflammatory syndromes, are inherited disorders characterized by recurrent episodes of fever and inflammation. The general hypothesis is that the innate immune response in these patients is wrongly tuned, being either too sensitive to very minor stimuli or turned off too late. The genetic background of the major familial periodic fever syndromes has been unraveled, and through research into the pathophysiology, a clearer picture of the innate immune system is emerging. After an introduction on fever, interleukin-1 $\beta$  and inflammasomes, which are involved in the majority of these diseases, this manuscript offers a detailed review of the pathophysiology of the cryopyrin-associated periodic syndromes, familial Mediterranean fever, the syndrome of pyogenic arthritis, pyoderma gangrenosum and acne, Blau syndrome, TNF-receptor-associated periodic syndrome and hyper-IgD and periodic fever syndrome. Despite recent major advances, there are still many questions to be answered regarding the pathogenesis of these disorders.

DOI: 10.1152/ajpregu.00504.2006

PMID: 16931648 [Indexed for MEDLINE]

4051. Am J Kidney Dis. 2006 Sep;48(3):e41-5.

Hereditary periodic fever with systemic amyloidosis: is hyper-IgD syndrome really a benign disease?

Siewert R(1), Ferber J, Horstmann RD, Specker C, Heering PJ, Timmann C.

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(1)Department of Nephrology, Solingen General Hospital, University of Cologne, Solingen, Germany. siewert@klinikumsolingen.de

We report a case of amyloidosis in association with hyperimmunoglobulinemia D syndrome (HIDS). The patient showed typical clinical features of HIDS. He had crescentic glomerulonephritis progressing to end-stage renal disease at age 13 years. Eight years later, he developed an AA-type amyloidosis with extensive involvement of the intestine, respiratory tract, and thyroid gland. These unusual complications of HIDS seriously challenge the assumption that the disease is associated with a good prognosis.

DOI: 10.1053/j.ajkd.2006.05.027

PMID: 16931207 [Indexed for MEDLINE]

4052. Eur Rev Med Pharmacol Sci. 2006 Jul-Aug;10(4):173-8.

The pharmacologic basis of treatment with colchicine in children with familial Mediterranean fever.

Rigante D(1), La Torraca I, Avallone L, Pugliese AL, Gaspari S, Stabile A.

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Familial Mediterranean fever (FMF) is the prototype of auto-inflammatory disorders and is ethnically restricted to people living in the Mediterranean basin and Middle-East. Pyrin, the protein product of the FMF gene, expressed in myeloid cells and fibroblasts, interacts with the cytoskeletal machinery and may modulate leukocyte effector functions. At present colchicine, an alkaloid with antimetabolic activity interfering with microtubule formation, which has been used to alleviate acute gout, is the only available drug for patients with FMF to

prevent both acute attacks and long-term complications such as amyloidosis. The anti-inflammatory effect of colchicine may be mediated not only through direct interaction with microtubules, but also through changes at the transcriptional level influencing cell cycle regulation and leukocyte migration. Gastrointestinal side effects may occur early and are the most frequent manifestations of colchicine toxicity in children, whilst multiple organ failure is very rarely reported as overdose expression.

PMID: 16910346 [Indexed for MEDLINE]

4053. Eur Rev Med Pharmacol Sci. 2006 Jul-Aug;10(4):163-71.

The multi-face expression of familial Mediterranean fever in the child.

Rigante D(1), La Torraca I, Ansuini V, Compagnone A, Sallì A, Stabile A.

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Familial Mediterranean fever (FMF) is characterized by recurrent self-limiting flares of fever in the absence of pathogens, autoantibodies or antigen specific T cells and is inherited as an autosomal recessive trait probably deriving from common ancestors of Armenian, Jew, Turk and Arab origin. The underlying pathogenetic mechanisms of FMF have not been fully interpreted, but mutations in the gene MEFV encoding pyrin, a natural repressor of proinflammatory molecules, result in uncontrolled relapsing systemic inflammation, increased leukocyte migration to serosal membranes or joints and inappropriate response to inflammatory stimuli. FMF heterogeneous phenotypic expression could originate both from allelic heterogeneity or from the existence of modulating genes. Proper diagnosis of FMF is needed to begin both specific clinical management and treatment based on continuous prophylactic administration of colchicine, preventing flares or at least the onset of amyloidosis.

PMID: 16910345 [Indexed for MEDLINE]

4054. N Engl J Med. 2006 Aug 10;355(6):581-92.

Neonatal-onset multisystem inflammatory disease responsive to interleukin-1beta inhibition.

Goldbach-Mansky R(1), Dailey NJ, Canna SW, Gelabert A, Jones J, Rubin BI, Kim HJ, Brewer C, Zalewski C, Wiggs E, Hill S, Turner ML, Karp BI, Aksentijevich I, Pucino F, Penzak SR, Haverkamp MH, Stein L, Adams BS, Moore TL, Fuhlbrigge RC, Shaham B, Jarvis JN, O'Neil K, Vehe RK, Beitz LO, Gardner G, Hannan WP, Warren RW, Horn W, Cole JL, Paul SM, Hawkins PN, Pham TH, Snyder C, Wesley RA, Hoffmann SC, Holland SM, Butman JA, Kastner DL.

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Comment in

Nat Clin Pract Rheumatol. 2006 Dec;2(12):646-7.

**BACKGROUND:** Neonatal-onset multisystem inflammatory disease is characterized by fever, urticarial rash, aseptic meningitis, deforming arthropathy, hearing loss, and mental retardation. Many patients have mutations in the cold-induced autoinflammatory syndrome 1 (CIAS1) gene, encoding cryopyrin, a protein that regulates inflammation.

**METHODS:** We selected 18 patients with neonatal-onset multisystem inflammatory disease (12 with identifiable CIAS1 mutations) to receive anakinra, an interleukin-1-receptor antagonist (1 to 2 mg per kilogram of body weight per day subcutaneously). In 11 patients, anakinra was withdrawn at three months until a flare occurred. The primary end points included changes in scores in a daily diary of symptoms, serum levels of amyloid A and C-reactive protein, and the erythrocyte sedimentation rate from baseline to month 3 and from month 3 until a disease flare.

**RESULTS:** All 18 patients had a rapid response to anakinra, with disappearance of rash. Diary scores improved ( $P<0.001$ ) and serum amyloid A (from a median of 174 mg to 8 mg per liter), C-reactive protein (from a median of 5.29 mg to 0.34 mg per deciliter), and the erythrocyte sedimentation rate decreased at month 3 (all  $P<0.001$ ), and remained low at month 6. Magnetic resonance imaging showed improvement in cochlear and leptomeningeal lesions as compared with baseline.

Withdrawal of anakinra uniformly resulted in relapse within days; retreatment led to rapid improvement. There were no drug-related serious adverse events.

CONCLUSIONS: Daily injections of anakinra markedly improved clinical and laboratory manifestations in patients with neonatal-onset multisystem inflammatory disease, with or without CIAS1 mutations. (ClinicalTrials.gov number, NCT00069329 [ClinicalTrials.gov].).

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DOI: 10.1056/NEJMoa055137

PMCID: PMC4178954

PMID: 16899778 [Indexed for MEDLINE]

4055. Isr Med Assoc J. 2006 Jul;8(7):509-11.

Familial Mediterranean fever and peritoneal malignant mesothelioma: a possible association?

Hershcovici T(1), Chajek-Shaul T, Hasin T, Amar S, Hiller N, Prus D, Peleg H.

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Comment in

Isr Med Assoc J. 2006 Jul;8(7):501-2.

PMID: 16889173 [Indexed for MEDLINE]

4056. Isr Med Assoc J. 2006 Jul;8(7):469-72.

Colchicine therapy and the cognitive status of elderly patients with familial Mediterranean fever.

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**BACKGROUND:** [corrected] Colchicine is widely used for treating gout and familial Mediterranean fever. However, studies in animal models have reported ill effects of colchicine on the central nervous system, including cognitive function.

**OBJECTIVES:** To evaluate the cognitive status of elderly FMF patients on long-term colchicine treatment.

**METHODS:** The study group consisted of 55 FMF patients aged 74 +/- 5, attending an FMF outpatient clinic and receiving colchicine treatment for 25.1 +/- 8.9 years.

The Mini-Mental State Examination was used for cognitive evaluation. Patients' scores were compared with accepted age- and education-adjusted cutoff scores, population-based norms, and scores of a matched control group of 56 subjects.

**RESULTS:** Individually, all colchicine-treated FMF patients scored well above the age- and education-corrected cutoff scores. Overall, there was a large difference, 5.0 +/- 1.6, from the expected cutoff points, in favor of the study group scores ( $P < 0.001$ ). The individual scores of the control group were also above the cutoff points, however with a lower but still statistically significant difference (3.71 +/- 1.15 points,  $P < 0.001$ ). Compared to population-based norms adjusted by age and education, the study group had significantly higher mean MMSE scores (27.2 +/- 2.2 vs. 25.5 +/- 2.4,  $P < 0.001$ ). The control group's scores were also somewhat higher than expected, but not significantly so.

**CONCLUSIONS:** Our results do not support the view that prolonged colchicine treatment may be associated with cognitive impairment. On the contrary, it is possible that long-term colchicine treatment may even confer protection against cognitive decline in patients with FMF.

PMID: 16889161 [Indexed for MEDLINE]

4057. J Immunol. 2006 Aug 15;177(4):2601-9.

Inflammation-responsive transcription factor SAF-1 activity is linked to the development of amyloid A amyloidosis.

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Abundantly expressed serum amyloid A (SAA) protein under chronic inflammatory conditions gives rise to insoluble aggregates of SAA derivatives in multiple organs resulting in reactive amyloid A (AA) amyloidosis, a consequence of rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, familial Mediterranean fever, and Castleman's disease. An inflammation-responsive transcription factor, SAF (for SAA activating factor), has been implicated in the sustained expression of amyloidogenic SAA under chronic inflammatory conditions. However, its role in the pathogenesis of AA amyloidosis has thus far remained obscure. In this paper we have shown that SAF-1, a major member of the SAF family, is abundantly present in human AA amyloidosis patients. To assess whether SAF-1 is directly linked to the pathogenesis of AA amyloidosis, we have developed a SAF-1 transgenic mouse model. SAF-1-overexpressing mice spontaneously developed AA amyloidosis at the age of 14 mo or older. Immunohistochemical analysis confirmed the nature of the amyloid deposits as an AA type derived from amyloidogenic SAA1. Furthermore, SAF-1 transgenic mice rapidly developed severe AA amyloidosis in response to azocasein injection, indicating increased susceptibility to inflammation. Also, during inflammation SAF-1 transgenic mice exhibited a prolonged acute phase response, leading to an extended period of SAA synthesis. Together, these results provide direct evidence that SAF-1 plays a key role in the development of AA amyloidosis, a consequence of chronic inflammation.

PMID: 16888022 [Indexed for MEDLINE]

4058. J Clin Invest. 2006 Aug;116(8):2073-5.

Gout: new insights into an old disease.

Martinon F(1), Glimcher LH.

Author information:

(1)Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, Massachusetts 02115, USA.

Comment on

J Clin Invest. 2006 Aug;116(8):2262-71.

Gout is an autoinflammatory disorder associated with deposition of monosodium urate (MSU) crystals in joints and periarticular tissues. Recent advances suggest that the innate immune system may drive the gouty inflammatory response to MSU. These findings prompt questions concerning how the innate immune system recognizes MSU and the identities of the receptors involved. In this issue of the JCI, Chen et al. show that the IL-1 receptor and its signaling protein myeloid differentiation primary response protein 88 (MyD88) but not the "classical" innate immune receptors, TLRs, are central for MSU-induced inflammation (see the related article beginning on page 2262).

DOI: 10.1172/JCI29404

PMCID: PMC1523387

PMID: 16886051 [Indexed for MEDLINE]

4059. Mediators Inflamm. 2006;2006(2):62868.

Serum leptin is not a diagnostic marker for familial Mediterranean fever attacks.

Toy B(1), Tarçin O, Bağcı S, Ustündağ Y, Inal A, Tiftikçi A.

Author information:

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The aim of our study is to determine whether there is a relationship between familial Mediterranean fever (FMF) attacks and serum leptin levels. We enrolled 25 patients (22 males and 3 females) and 25 healthy controls (21 males and 4 females) with a mean age of  $24.42 \pm 1.22$  (Mean  $\pm$  SEM) years and  $24.30 \pm 1.19$  years (Mean  $\pm$  SEM), respectively. We investigated serum levels of leptin, interleukin-6 (IL-6) erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen, and leukocyte counts before the attack and 8-12 hours after the attack started. The same parameters have been investigated in the control subjects. The mean serum leptin levels before the attacks were  $6.45 \pm 1.05$  (Mean  $\pm$  SEM) and during the attacks were  $7.59 \pm 1.3$  (Mean  $\pm$  SEM) in FMF group, respectively. There was a slight increase in serum leptin levels during the attacks but it was not statistically significant ( $P > .05$ ). The mean serum leptin

levels were 16.12 +/- 2.81 in the control group which were not different from the mean serum leptin levels before and during the attack periods in the study group ( $P > .05$ ). However, there were statistical differences in the serum levels of IL-6, ESR, CRP, fibrinogen, and leukocyte counts before and during the attack periods ( $P > .05$ ). No correlation was found between serum leptin levels and IL-6, ESR, CRP, fibrinogen, and leukocyte counts ( $P > .05$ ). Serum leptin levels do not increase during FMF attacks and therefore it is not useful for diagnostic purposes and follow-up during treatment.

DOI: 10.1155/MI/2006/62868

PMCID: PMC1592591

PMID: 16883064 [Indexed for MEDLINE]

4060. Acta Clin Belg. 2006 May-Jun;61(3):147-51.

Pulmonary amyloidosis in familial Mediterranean fever.

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Familial Mediterranean Fever (FMF) is a hereditary periodic fever syndrome expressed by acute episodes of fever and painful manifestations. The gravest consequence of FMF is kidney involvement by secondary amyloidosis of AA type, which gradually leads to nephrotic syndrome and uremia. Nephropathic amyloidosis of the AA type, which complicates FMF in most untreated patients, may progress to affect other organs, including the lungs. This kind of organ involvement rarely produces noticeable symptoms and is associated with symptomatic involvement of other organs while remaining subclinical in itself. In this report, one case who had nephropathic and pulmonary amyloidosis of the secondary amyloidosis of AA type, which complicates the FMF was presented and the pulmonary manifestations of FMF were reviewed.

DOI: 10.1179/acb.2006.024

PMID: 16881565 [Indexed for MEDLINE]

4061. Intern Med. 2006;45(13):805-6. Epub 2006 Aug 1.

Behcet's disease and familial Mediterranean fever.

Takeno M, Ishigatsubo Y.

PMID: 16880703 [Indexed for MEDLINE]

4062. Rheumatology (Oxford). 2006 Oct;45(10):1307-8. Epub 2006 Jul 31.

Clinical improvement with infliximab in a child with amyloidosis secondary to familial Mediterranean fever.

Yüksel S, Yalçinkaya F, Acar B, Ozçakar ZB, Oztürk B, Ekim M.

DOI: 10.1093/rheumatology/kel250

PMID: 16880190 [Indexed for MEDLINE]

4063. J Nephrol. 2006 May-Jun;19(3):318-21.

Serum amyloid A1 -13 T/C alleles in Turkish familial Mediterranean fever patients with and without amyloidosis.

Akar N(1), Hasipek M, Oztürk A, Akar E, Tekin M.

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Previously reported studies concerning the effect of homozygosity of the 1.1 allele of the SAA gene found a correlation between this haplotype and susceptibility to amyloidosis in FMF patients. Another report revealed a strong association between SAA1 -13T/C and secondary amyloidosis in the rheumatoid arthritis patient group. In this study, we aimed to determine the effect of SAA1 -13T/C in FMF patients with and without amyloidosis. The study cohort, consisting

of 166 patients with FMF was divided into two groups, according to the presence (n=66) or absence (n=100) of renal amyloidosis at study entry. MEFV gene mutation analysis and allelic variant of SAA1 gene -13 T/C was analyzed according to the previously described techniques. SAA1 -13 T allele frequencies were 0.5816, 0.23 and 0.4242 in controls, FMF patients and FMF-amyloidosis patients respectively. The difference between controls vs. FMF patients and FMF-amyloidosis patients were 0.0002 and 0.1673 respectively. It was 0.0071 for FMF-patients vs. FMF-amyloidosis. When 694 M/V homozygous nonamyloid-FMF group was compared with 694 M/V carriers of the FMF-amyloidosis group, the difference was 0.049. When carrying TT allele was considered, the difference between controls vs. FMF patients and FMF-amyloidosis patients were 0.0001 and 0.58. It was 0.0003 for FMF patients vs. FMF-amyloidosis. When 694 M/V homozygous nonamyloid-FMF group was compared with 694 M/V carriers of the FMF-amyloidosis group, the difference was 0.03. Carrying SAA -13T in homozygote state revealed a 7.9 (95% CI 3.6 -17.5) fold risk for the occurrence of amyloidosis when compared with FMF patients without amyloidosis. This was 8.75 (95% CI 3.0 - 25.1) when 694 M/V homozygotes were taken into consideration. Our data revealed that the genotype SAA1 -13T has at least an effect on the development of amyloidosis. As more data on this polymorphism accumulate, we will understand its effect on the pathogenesis of amyloidosis in FMF.

PMID: 16874691 [Indexed for MEDLINE]

4064. Arthritis Rheum. 2006 Aug;54(8):2674-87.

Modeling of tumor necrosis factor receptor superfamily 1A mutants associated with tumor necrosis factor receptor-associated periodic syndrome indicates misfolding consistent with abnormal function.

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**OBJECTIVE:** To investigate the effect of mutations in the tumor necrosis factor receptor superfamily 1A (TNFRSF1A) gene on the conformation and behavior of the

TNFRSF1A protein. Mutations in TNFRSF1A cause the autosomal-dominant, autoinflammatory TNFR-associated periodic syndrome (TRAPS).

**METHODS:** The expression of recombinant TNFRSF1A was compared in SK-HEp-1 endothelial cells and HEK 293 epithelial cells stably transfected with full-length R347A or Deltasig constructs of wild-type or TRAPS-associated mutant TNFRSF1A. TNF binding was assessed in HEK 293 cell lines expressing R347A wild-type or mutant TNFRSF1A. Homology modeling of the 3-dimensional structure of the ectodomains of wild-type and mutant TNFRSF1A was performed.

**RESULTS:** TRAPS-associated mutant and wild-type TNFRSF1A behaved differently and had different localization properties within the cell, as a direct result of mutations in the ectodomains of TNFRSF1A. From a structural perspective, mutants with a predicted structure similar to that of the wild-type protein (e.g., R92Q) behaved similarly to wild-type TNFRSF1A, whereas forms of TNFRSF1A with mutations predicted to drastically destabilize the protein structure (e.g., cysteine mutations) showed defects in cell surface expression and TNF binding.

**CONCLUSION:** The results obtained from the in vitro experiments, in combination with the modeled structures, indicate that the phenotype and clinical differences between different TRAPS-associated mutants of TNFRSF1A result from different conformations of the TNFRSF1A ectodomains.

DOI: 10.1002/art.21964

PMID: 16871532 [Indexed for MEDLINE]

4065. Rheumatol Int. 2006 Nov;27(1):97-100. Epub 2006 Jul 27.

Treatment with anakinra in the hyperimmunoglobulinemia D/periodic fever syndrome.

Rigante D(1), Ansuini V, Bertoni B, Pugliese AL, Avallone L, Federico G, Stabile A.

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Hyperimmunoglobulinemia D/periodic fever syndrome is caused by recessively inherited mutations in the mevalonate kinase gene and is characterized by persistently high polyclonal serum IgD titre and recurrent febrile attacks. No conventional therapy exists for preventing the typical recurrent inflammatory

picture of patients. A host of studies have evidenced that elevated levels of various cytokines, such as interleukin-1 (IL-1), mark febrile attacks in this disease and that IL-1 might represent a suitable therapeutic target. We describe the case of a 7-year-old female-child with an established diagnosis of hyperimmunoglobulinemia D/periodic fever syndrome in whom anakinra, IL-1 receptor antagonist, was daily administered at the dosage of 1 mg/kg/day by subcutaneous injection for 18 months after numerous disappointing attempts with non-steroidal anti-inflammatory drugs, steroids, colchicine and etanercept through the years. The clinical response under anakinra treatment was recorded through a standardized diary, whilst inflammation parameters were serially measured in comparison with the half-year before starting anakinra. Frequency and severity of fever attacks were totally reduced by anakinra and this is the first child demonstrating that symptoms of hyperimmunoglobulinemia D/periodic fever syndrome might be at least extenuated by anakinra, though not abolished.

DOI: 10.1007/s00296-006-0164-x

PMID: 16871408 [Indexed for MEDLINE]

4066. Eur J Hum Genet. 2006 Dec;14(12):1295-305. Epub 2006 Jul 26.

An intronic variable number of tandem repeat polymorphisms of the cold-induced autoinflammatory syndrome 1 (CIAS1) gene modifies gene expression and is associated with essential hypertension.

Omi T(1), Kumada M, Kamesaki T, Okuda H, Munkhtulga L, Yanagisawa Y, Utsumi N, Gotoh T, Hata A, Soma M, Umemura S, Ogihara T, Takahashi N, Tabara Y, Shimada K, Mano H, Kajii E, Miki T, Iwamoto S.

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Cold-induced autoinflammatory syndrome 1 (CIAS1) gene is a member of the NALP subfamily of the CATERPILLER protein family that is expressed predominantly in peripheral blood leukocytes, which is to regulate apoptosis or inflammation through the activation of NF-kappaB and caspase. Recent genetic analyses suggested an association between inflammation and oxidative stress-related genes in the development of hypertension. This is the first genetic study indicating an



association between the CIAS1 gene and susceptibility to essential hypertension (EH). The frequency of subject with the homozygote of 12 repeat allele was significantly higher in patients with hypertension compared with control subjects (987 cases, 924 controls) ( $P=0.030$ ; odds ratio=1.24) at a novel VNTR polymorphism of CIAS1 intron 4 loci. We also found that the mean of systolic blood pressure of homozygotes of 12 repeat allele was 6.4 mmHg higher than those of homozygotes of non-12 repeat allele in male random population ( $P=0.009$ ). The frequency of six SNPs spanning of the CIAS1 gene was not significantly between patients and controls. The real-time PCR analysis showed that among healthy young adults, 12-12 subjects expressed CIAS1 mRNA in peripheral leukocytes significantly more abundantly than homozygote of non-12 repeat alleles subjects ( $P<0.05$ ). Reporter gene assay of the CIAS1-VNTR in HL60 stimulated by lipopolysaccharides showed that the intronic sequence involving 12 repeat increased the expression of luciferase compared with 9, 7, and 6 repeats. Thus, we propose here the CIAS1 is associated with EH through the dominant expression of transcripts, which may depend on the CIAS1-VNTR genotype.

DOI: 10.1038/sj.ejhg.5201698

PMID: 16868559 [Indexed for MEDLINE]

4067. Anaesthesia. 2006 Aug;61(8):815.

Use of metaraminol in patients with Familial Mediterranean Fever.

Kapur S, Mutagi H, Raphael J.

DOI: 10.1111/j.1365-2044.2006.04731.x

PMID: 16867110 [Indexed for MEDLINE]

4068. Dig Dis Sci. 2006 Jun;51(6):1061-2.

Intestinal pseudo-obstruction as a manifestation of tumor necrosis factor receptor-associated periodic syndrome.

Marie I(1), Hervé F, Dodé C, Bernet J, Levesque H.

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DOI: 10.1007/s10620-006-8009-8

PMID: 16865571 [Indexed for MEDLINE]

4069. Am Fam Physician. 2006 Jul 1;74(1):43; author reply 43.

Genetic predisposition of familial Mediterranean fever.

Greenfield WR.

Comment on

Am Fam Physician. 2005 Aug 1;72(3):441-8.

PMID: 16848379 [Indexed for MEDLINE]

4070. Intern Med. 2006;45(12):799-800. Epub 2006 Jul 18.

Coexistence of familial Mediterranean fever and Behçet's disease in a Japanese patient.

Matsuda M(1), Nakamura A, Tsuchiya S, Yoshida T, Horie S, Ikeda S.

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PMID: 16847372 [Indexed for MEDLINE]

4071. Ned Tijdschr Geneesk. 2006 Jun 24;150(25):1407-12.

[Intestinal perforation caused by tuberculosis in a kidney transplant patient who was extensively evaluated for tuberculosis prior to transplant].

[Article in Dutch]

Rendering H(1), Zijlstra JG, van Son WJ, de Maar EF, Manson WL, van der Werf TS.

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A 47-year-old man from Armenia presented at the emergency department with abdominal pain. He had had a kidney transplant 2 years earlier for renal failure caused by amyloidosis that was secondary to familial Mediterranean fever. He was also known to have chronic hepatitis B with persistent viraemia. He had not received any prophylactic anti-tuberculosis treatment due to impaired liver function, but an extensive work-up was performed prior to transplant, including chest radiography, a Mantoux tuberculin skin test and cultures from 3 consecutive fasting gastric lavage samples, which were all negative for active or latent tuberculosis infection. The patient had presented at the emergency department repeatedly with abdominal pain that was attributed to the familial Mediterranean fever. During his last visit his complaints were accompanied by vomiting, coughing, night sweats and weight loss. He was diagnosed with an intestinal perforation with faecal peritonitis and underwent several laparotomies to treat the faecal peritonitis. Histopathological examination of resected bowel tissue revealed granulomatous inflammation, and acid-fast bacilli were seen with appropriate staining. Later, cultures appeared to be positive for normally sensitive *Mycobacterium tuberculosis*. The patient died as a result of the disseminated tuberculosis. In immunocompromised patients, tuberculosis often has an atypical course and an increased chance of dissemination that may be difficult to recognize.

PMID: 16841591 [Indexed for MEDLINE]

4072. J Cardiovasc Electrophysiol. 2006 Jul;17(7):724-32.

Familial pseudo-Wolff-Parkinson-White syndrome.

Sternick EB(1), Oliva A, Magalhães LP, Gerken LM, Hong K, Santana O, Brugada P, Brugada J, Brugada R.

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Comment in

J Cardiovasc Electrophysiol. 2006 Dec;17(12):E9; author reply E10.

J Cardiovasc Electrophysiol. 2006 Jul;17(7):733-4.

**INTRODUCTION:** PRKAG2 plays a role in regulating metabolic pathways, and mutations in this gene are associated with familial ventricular preexcitation, hypertrophic cardiomyopathy, and atrioventricular conduction disturbances. Clinico-pathologic and experimental data suggest the hypothesis of a glycogen storage disease.

**OBJECTIVE:** To report a unique pattern of clinical features observed in individuals with a mutant PRKAG2 from two unrelated families.

**METHODS AND RESULTS:** We studied two large families and found a total of 20 affected individuals showing a combination of sinus bradycardia, short PR interval, RBBB, intra and infrahisian conduction disturbances often requiring a pacemaker, and atrial tachyarrhythmias. Three individuals died suddenly at a young age. No patient had the Wolff-Parkinson-White (WPW) syndrome, and only two patients (10%) had myocardial hypertrophy. We performed screening of the exons and exon-intron boundaries of PRKAG2. Genetic analysis revealed a missense mutation (Arg302Gln) in the affected individuals from both families. This mutation had been described before and has been associated with the familial form of the WPW syndrome and with a high prevalence of left ventricular hypertrophy.

**CONCLUSION:** PRKAG2 mutations are responsible for a diverse phenotype and not only the familial form of the WPW syndrome. Familial occurrence of right bundle branch block, sinus bradycardia, and short PR interval should raise suspicion of a mutant PRKAG2 gene.

DOI: 10.1111/j.1540-8167.2006.00485.x

PMID: 16836667 [Indexed for MEDLINE]

4073. Hum Mutat. 2006 Aug;27(8):796-802.

Mutational spectrum and genotype-phenotype correlations in mevalonate kinase deficiency.

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Mevalonate kinase deficiency (MKD) is an autosomal recessive autoinflammatory disorder caused by mutations in the MVK gene resulting in deficient activity of mevalonate kinase (MK). Depending on the clinical severity, MKD may present as hyper-IgD and periodic fever syndrome (HIDS) or the more severe mevalonic aciduria (MA). We analyzed the MVK gene in 57 patients with MKD and found 39 different mutations including 15 novel mutations, expanding the total mutational spectrum of MKD to 63 mutations. To get more insight into the genotype-phenotype correlation in MKD, we studied the effect of selected missense mutations on MK protein stability and activity in various patient fibroblast cell lines. All MKD cell lines showed markedly decreased MK activities that correlated well with the clinical severity and, for most of the cell lines, with the amount of MK protein. When fibroblasts of MKD patients were cultured under conditions known to promote a more controlled protein folding, all cell lines of patients with the HIDS phenotype and few cell lines of patients with the MA phenotype showed an increase in the residual MK activity. This increase in enzyme activity correlates well with an increase in the MK protein levels in these cell lines, indicating that most of the mutations in MKD affect stability and/or folding of the MK protein rather than affecting the catalytic properties of the enzyme. The finding that the residual activity in MKD can be manipulated by environmental conditions may offer therapeutic options to alleviate or prevent the clinical symptoms associated with MKD.

DOI: 10.1002/humu.20361

PMID: 16835861 [Indexed for MEDLINE]

4074. Arch Orthop Trauma Surg. 2007 May;127(4):229-34. Epub 2006 Jul 8.

Arthroscopy of the knee in pre-adolescent children.

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**INTRODUCTION:** Arthroscopic operations performed in the pediatric age group constitute less than 5% of all arthroscopies. Diagnostic accuracy is reported to be lower than the procedures in adult patients. The incidence of pathologies also varies in the literature. We aimed at assessing the diagnostic accuracy of arthroscopy and review the incidence of pathologies in pre-adolescent patients.

**MATERIALS AND METHODS:** In the period April 1990-January 2002, 50 pre-adolescent patients underwent knee arthroscopy after clinical and radiological assessment.

Average age was 10.24 (1-13) with a male-to-female ratio of 34:16.

**RESULTS:** Discoid lateral meniscus was found to be the most common pathology encountered in 17 cases followed by infection and synovitis in 8 cases each.

Diagnostic accuracy of arthroscopy correlated with preoperative clinical and radiologic evaluation was 90%. Arthroscopy findings were negative in two cases. Two cases of plica syndrome and one case of chondral injury were mistaken for medial meniscal tear. Final diagnosis was familial Mediterranean fever in one case of synovitis and knee fusion was performed at follow-up due to progressive degenerative changes. No other patient required reoperation.

**CONCLUSION:** Arthroscopy is a safe procedure with minor morbidity allowing treatment of various intraarticular knee disorders. Diagnostic accuracy of the procedure may increase with careful preoperative work-up.

DOI: 10.1007/s00402-006-0138-1

PMID: 16830144 [Indexed for MEDLINE]

4075. Am J Cardiol. 2006 Jul 15;98(2):267-71. Epub 2006 Jun 5.

Long-term outcomes in difficult-to-treat patients with recurrent pericarditis.

Brucato A(1), Brambilla G, Moreo A, Alberti A, Munforti C, Ghirardello A, Doria A, Shinar Y, Livneh A, Adler Y, Shoenfeld Y, Mauri F, Palmieri G, Spodick DH.

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Patients with many recurrences of acute pericarditis are commonly alarmed by the

fear of constriction. We studied their long-term outcome and the possible presence of systemic diseases. Sixty-one Italian patients (36 men) were followed for an average of 8.3 years according to a predefined protocol, including testing for autoimmune diseases and familial Mediterranean fever. Symptomatic pericarditis lasted from 1 to 43 years (mean 5.4 years). Fifty-two patients had been referred to us after failure of previous therapies, including steroids. We observed 378 attacks with a mean of 1.6 per patient per year and 156 hospital admissions. Thirteen patients had a post-cardiac injury syndrome. In 43 (70.5%), the pericarditis remained idiopathic, whereas we made a new diagnosis of rheumatoid arthritis in 1 and of Sjogren's syndrome in 4 patients, but in these patients pericarditis represented the dominant clinical manifestation. Cardiac tamponade occurred during the initial attacks in 4 patients (6.5%) but never recurred. Pleural effusions were present during the first attack in 22 patients (36.0%) and liver involvement in 5 (8%). No patients developed constrictive pericarditis. Echocardiographic examination produced no evidence of chronic myocardial disease. Response to therapy was good. Thirty-one patients (50.8%) are in sustained remission, without any therapy; their total observation period has averaged 10.3 years. In idiopathic patients, antinuclear antibodies were present in 56.2% and anti-Ro/SSA in 8.3%. Mutations linked to familial Mediterranean fever were absent. In conclusion, in this large series of difficult patients with recurrent acute pericarditis and a very long follow-up, the long-term prognosis is good.

DOI: 10.1016/j.amjcard.2006.01.086

PMID: 16828606 [Indexed for MEDLINE]

4076. Ter Arkh. 2006;78(4):76-8.

[Immunogenetic blood markers as a risk factor of development of periodic disease in Armenian population].

[Article in Russian]

Nersisian VM, Astvatsatrian VA, Zakharian AG, Musaelian NO, Martirosian IG.

AIM: To reveal characteristic associations between various markers of immunogenetic (HLA--A, B, C, DR), erythrocytic (ABO, Rh-Hr, MNSs, Pp, Kell-Chellano, Lewis), serum (Gm, Inv) systems and familial Mediterranean fever

(FMF) in Armenian population.

**MATERIAL AND METHODS:** From 41 to 125 patients (depending on systems studied) were examined. HLA-antigens of A-, B-, C-classes were detected by the microcytotoxic test in a total population of lymphocytes, HLA-DR antigens--by a prolonged test in B-lymphocytes, erythrocytic antigens--by hemagglutination technique and indirect Coombs' reaction, serum antigens--by the method of hemagglutination suppression.

**RESULTS:** Confidential positive associative relations between antigens HLA-A1 and A9 (RR = 2.2 and 2.4), HLA B5 and B35 (RR = 3.03 and 3.2), HLA-Cw4 (RR = 4.3), HLA-DR3 (RR = 2.6), phenotypes AB (RR = 2.86) and MN (RR = 2.2), serum antigen Gmx+ (RR = 2.87) were demonstrated. Simultaneous expression of phenotype MN and antigen Gmx+ is a marker of high predisposition to the disease (RR = 4.7).

Negative associative relations were found between FMF and antigens HLA-B12 and B18 (RR = 0.6 and 0.1), HLA DR4 (RR = 0.1) and phenotype MM (RR = 0.37).

**CONCLUSION:** A simultaneous complex investigation of the markers of various immunogenetic systems allows detection of genetic markers of predisposition to FMF (HLA-B5, B35, Cw4, DR3, AB, Gmx+, MN) and the resistance to this disease (HLA-B12, B18, DR4) in a population of Armenians.

PMID: 16821429 [Indexed for MEDLINE]

4077. Isr Med Assoc J. 2006 May;8(5):359-60.

Small bowel obstruction by a carcinoid tumor in a patient with familial Mediterranean fever.

Gabizon I(1), Giladi H, Ovnat A, Dukhno O, Flusser D, Sukenik S.

Author information:

(1)Department of Internal Medicine D, Soroka University Medical Center, Beer Sheva, Israel.

PMID: 16805241 [Indexed for MEDLINE]

4078. Arthritis Rheum. 2006 Jul;54(7):2314-20.



A severe case of chronic infantile neurologic, cutaneous, articular syndrome treated with biologic agents.

Matsubara T(1), Hasegawa M, Shiraishi M, Hoffman HM, Ichiyama T, Tanaka T, Ueda H, Ishihara T, Furukawa S.

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Comment in

Arthritis Rheum. 2007 Jun;56(6):2099-101; author reply 2101-2.

In this report we describe a case of severe chronic infantile neurologic, cutaneous, articular (CINCA) syndrome with a novel G307V cryopyrin mutation and all of the characteristic clinical and laboratory features of this autoinflammatory disease. There was no clear response to standard therapies, including human interleukin-1 (IL-1) receptor antagonist (anakinra) and soluble tumor necrosis factor receptor (etanercept). The patient finally had a partial clinical response (reduction in fever and irritability) and complete laboratory response (improved C-reactive protein and serum amyloid A levels) to humanized anti-IL-6 receptor antibody (MRA), but died from congestive heart failure and interstitial pneumonia 2 months after initiation of therapy. We serially measured the serum cytokine levels and expression of NF-kappaB activation in the patient's peripheral blood mononuclear cells before and during consecutive therapies. Pathologic examination of autopsy specimens was also performed. This case illustrates the continued difficulty in management of patients with CINCA syndrome and the complexity of the inflammatory pathways in this disorder.

DOI: 10.1002/art.21965

PMID: 16802372 [Indexed for MEDLINE]

4079. Arthritis Rheum. 2006 Jul;54(7):2306-13.

Manipulation of isoprenoid biosynthesis as a possible therapeutic option in mevalonate kinase deficiency.

Schneiders MS(1), Houten SM, Turkenburg M, Wanders RJ, Waterham HR.

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**OBJECTIVE:** In cells from patients with the autoinflammatory disorder mevalonate kinase (MK) deficiency, which includes the hyperimmunoglobulin D with periodic fever syndrome, MK becomes the rate-limiting enzyme in the isoprenoid biosynthesis pathway. This suggests that up-regulation of residual MK activity in these patients could be a way in which to prevent or alleviate the associated symptoms. We studied the effect of 2 specific inhibitors of isoprenoid biosynthetic enzymes on the residual activity of MK in cells from patients with MK deficiency.

**METHODS:** Skin fibroblasts from MK-deficient patients and from controls were cultured for 7 days with either simvastatin, an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, or zaragozic acid A, an inhibitor of squalene synthase. Following culture, MK activity, MK protein levels, MVK messenger RNA levels, and the effect on the pathway flux toward non-sterol isoprenoid biosynthesis were determined.

**RESULTS:** Treatment of the fibroblasts with either of the inhibitors led to a marked increase in residual MK enzyme activity, which was largely attributable to increased MVK gene transcription. This effect was even more pronounced when the cells were cultured in lipoprotein-depleted medium. The flux toward nonsterol isoprenoid end-product synthesis was reduced when cells were treated with simvastatin but was partly restored by concomitant treatment with zaragozic acid A.

**CONCLUSION:** Our results indicate that manipulations of the isoprenoid biosynthesis pathway that promote the synthesis of nonsterol isoprenoids may provide an interesting therapeutic option for the treatment of MK deficiency.

DOI: 10.1002/art.21960

PMID: 16802371 [Indexed for MEDLINE]

4080. Rheumatology (Oxford). 2006 Sep;45(9):1171-3. Epub 2006 Jun 26.

Successful treatment using tacrolimus (FK506) in a patient with TNF

receptor-associated periodic syndrome (TRAPS) complicated by monocytic fasciitis.

Ida H, Aramaki T, Arima K, Origuchi T, Kawakami A, Eguchi K.

DOI: 10.1093/rheumatology/kel178

PMID: 16801330 [Indexed for MEDLINE]

4081. Surg Today. 2006;36(7):651-4.

Left-sided paraduodenal hernia: report of a case.

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(1)Department of General Surgery, Marmara University School of Medicine, Tophanelioglu cad Altunizade, Istanbul, Turkey.

Paraduodenal hernias are rare congenital malformations consisting of incomplete rotation of the midgut, which may lead to intestinal obstruction or simply be detected as an incidental finding at autopsy or laparotomy. We report a case of left paraduodenal hernia diagnosed preoperatively by computed tomography and operated on in an emergency setting for signs of peritoneal irritation. A misdiagnosis had been made when the patient suffered his first attack 6 months earlier and he had been treated for familial Mediterranean fever. We reduced the small bowel loops from the left paraduodenal hernia sac with ligation and transection of the inferior mesenteric vessels. The patient was discharged from hospital on postoperative day 4 after an uneventful recovery.

DOI: 10.1007/s00595-006-3205-x

PMID: 16794804 [Indexed for MEDLINE]

4082. Pathobiology. 2006;73(1):26-39.

Impaired endotoxin tolerance induction in patients with familial Mediterranean fever.

Davtyan TK(1), Hakopyan GS, Avetisyan SA, Mkrtchyan NR.

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**OBJECTIVE:** To investigate periodic disturbances in proinflammatory activation of neutrophils and monocytes in patients with familial Mediterranean fever (FMF) both during an attack and in remission.

**METHODS:** 20 FMF patients, who were naive to colchicine treatment and did not have amyloidosis, and 10 patients with Behçet's disease (BD) were enrolled in this study. Phagocytosis, respiratory burst, CD11a/CD18 expression and intracellular cytokine synthesis were determined by flow cytometry. Endotoxin tolerance induction was defined by a reduced capacity of monocytes to respond to lipopolysaccharide (LPS) activation following a first exposure to LPS.

**RESULTS:** In FMF patients, we observed upregulation of neutrophil and monocyte phagocytic activity and oxidative burst during remission and downregulation of phagocytic activity and stimulus-dependent oxidative burst during an attack. A comparative analysis of oxidative burst has revealed that while the neutrophil population shows a certain periodicity in the increase (during remission) and decrease (during attacks) in the spontaneous and inducible respiratory burst, periodicity in the monocyte population is very poor. In addition, LPS-induced oxidative burst and CD11a/CD18 integrin surface expression is higher in patients during an attack compared to patients in remission. The induction of homologous tolerance of monocytes to the repeated action of LPS is observed in FMF patients during an attack, normal donors and patients with BD, whereas monocytes from patients in remission failed to induce LPS homologous tolerance and exhibited heightened sensitivity to bacterial endotoxin. We found that colchicine is able to restore impaired LPS homologous tolerance induction in FMF patients in remission upon increased synthesis of IL-4 in FMF patient monocytes.

**CONCLUSION:** Chronic inflammation during FMF is characterized by periodic changes in monocyte and neutrophil activation and heightened sensitivity to endotoxin, which is associated with the episodic nature of FMF. Increased endotoxin sensitivity in the period of remission could result from a shift in the monocyte activation program from 'alternatively' into 'classically' activated monocytes, which may have important implications for the treatment of FMF.

DOI: 10.1159/000093089

PMID: 16785765 [Indexed for MEDLINE]

4083. Proc Natl Acad Sci U S A. 2006 Jun 27;103(26):9982-7. Epub 2006 Jun 19.

The B30.2 domain of pyrin, the familial Mediterranean fever protein, interacts directly with caspase-1 to modulate IL-1beta production.

Chae JJ(1), Wood G, Masters SL, Richard K, Park G, Smith BJ, Kastner DL.

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Familial Mediterranean fever (FMF) is a recessively inherited autoinflammatory disorder with high carrier frequencies in the Middle East. Pyrin, the protein mutated in FMF, regulates caspase-1 activation and consequently IL-1beta production through cognate interaction of its N-terminal PYRIN motif with the ASC adaptor protein. However, the preponderance of mutations reside in pyrin's C-terminal B30.2 domain. Here we demonstrate direct interaction of this domain with caspase-1. In lysates from cells not expressing ASC, reciprocal GST pull-downs demonstrated the interaction of pyrin with the p20 and p10 catalytic subunits of caspase-1. Coimmunoprecipitations of pyrin and caspase-1 from THP-1 human monocytic cells were consistent with the interaction of endogenous proteins. The C-terminal B30.2 domain of pyrin is necessary and sufficient for the interaction, and binding was reduced by FMF-associated B30.2 mutations. Full-length pyrin attenuated IL-1beta production in cells transfected with a caspase-1/IL-1beta construct, an effect diminished by FMF-associated B30.2 mutations and in B30.2 deletion mutants. Modeling of the crystal structure of caspase-1 with the deduced structure of the pyrin B30.2 domain corroborated both the interaction and the importance of M694V and M680I pyrin mutations. Consistent with a net inhibitory effect of pyrin on IL-1beta activation, small interfering RNA (siRNA)-mediated pyrin knockdown in THP-1 cells augmented IL-1beta production in response to bacterial LPS. Moreover, the IL-1 receptor antagonist anakinra suppressed acute-phase proteins in a patient with FMF and amyloidosis. Our data support a direct, ASC-independent effect of pyrin on IL-1beta activation and suggest heightened IL-1 responsiveness as one factor selecting for pyrin mutations.

DOI: 10.1073/pnas.0602081103

4084. Am J Med Sci. 2006 Jun;331(6):295-303.

Patterns of hypocapnia on tilt in patients with fibromyalgia, chronic fatigue syndrome, nonspecific dizziness, and neurally mediated syncope.

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**OBJECTIVES:** To assess whether head-up tilt-induced hyperventilation is seen more often in patients with chronic fatigue syndrome (CFS), fibromyalgia, dizziness, or neurally mediated syncope (NMS) as compared to healthy subjects or those with familial Mediterranean fever (FMF).

**PATIENTS AND METHODS:** A total of 585 patients were assessed with a 10-minute supine, 30-minute head-up tilt test combined with capnography. Experimental groups included CFS (n = 90), non-CFS fatigue (n = 50), fibromyalgia (n = 70), nonspecific dizziness (n = 75), and NMS (n = 160); control groups were FMF (n = 90) and healthy (n = 50). Hypocapnia, the objective measure of hyperventilation, was diagnosed when end-tidal pressure of CO<sub>2</sub> (PETCO<sub>2</sub>) less than 30 mm Hg was recorded consecutively for 10 minutes or longer. When tilting was discontinued because of syncope, one PETCO<sub>2</sub> measurement of 25 or less was accepted as hyperventilation.

**RESULTS:** Hypocapnia was diagnosed on tilt test in 9% to 27% of patients with fibromyalgia, CFS, dizziness, and NMS versus 0% to 2% of control subjects. Three patterns of hypocapnia were recognized: supine hypocapnia (n = 14), sustained hypocapnia on tilt (n = 76), and mixed hypotensive-hypocapnic events (n = 80). Hypocapnia associated with postural tachycardia syndrome (POTS) occurred in 8 of 41 patients.

**CONCLUSIONS:** Hyperventilation appears to be the major abnormal response to postural challenge in sustained hypocapnia but possibly merely an epiphenomenon in hypotensive-hypocapnic events. Our study does not support an essential role

for hypocapnia in NMS or in postural symptoms associated with POTS. Because unrecognized hypocapnia is common in CFS, fibromyalgia, and nonspecific dizziness, capnography should be a part of the evaluation of patients with such conditions.

PMID: 16775435 [Indexed for MEDLINE]

4085. Clin Exp Rheumatol. 2006 Mar-Apr;24(2):213.

Selective pressures for the high prevalence of MEFV variants induced by smallpox infection in the "Old World": A hypothesis.

Gül A.

PMID: 16762167 [Indexed for MEDLINE]

4086. Ann Saudi Med. 2006 Mar-Apr;26(2):157-8.

Remission of nephrotic syndrome in amyloidosis of familial Mediterranean fever following colchicine treatment.

Odabas H.

PMCID: PMC6074157

PMID: 16761461 [Indexed for MEDLINE]

4087. J Rheumatol. 2006 Jun;33(6):1210-1.

A boy with fever and whorl keratopathy.

Halligan C, Heese BA, Mellor G, Michels VV, Reed A.

PMID: 16755678 [Indexed for MEDLINE]

4088. J Rheumatol. 2006 Jun;33(6):1089-92.

The prodrome: a prominent yet overlooked pre-attack manifestation of familial Mediterranean fever.

Lidar M(1), Yaqubov M, Zaks N, Ben-Horin S, Langevitz P, Livneh A.

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**OBJECTIVE:** To identify and characterize pre-attack symptoms (prodrome) in patients with familial Mediterranean fever (FMF).

**METHODS:** Forty-eight patients with FMF whose attacks are preceded by a prodromal period composed the study population. Clinical, demographic, and genetic characteristics of the study group were compared to those of a control group of 48 patients with FMF whose attacks begin without a premonitory phase. Patients of both groups were recruited consecutively, during their routine followup visit to the FMF clinic.

**RESULTS:** A prodrome was found to be a common manifestation of FMF, experienced by about 50% of the patients. Overall, demographic, clinical, and genetic variables were comparable between study and control groups. In affected patients prodrome recurs in most attacks, lasts a mean of 20 hours, and manifests with either a mildly unpleasant sensation at the site of the forthcoming spell (discomfort prodrome), or with a spectrum of physical, emotional, and neuropsychological complaints (variant prodrome). The 2 types of prodromata are frequently accompanied by a host of constitutional symptoms.

**CONCLUSIONS:** A prodromal period heralding attacks is a newly defined and reliable FMF manifestation that reproducibly predicts attacks and may help prevent attacks and elucidate the pathogenesis of the disease.

PMID: 16755655 [Indexed for MEDLINE]

4089. Springer Semin Immunopathol. 2006 Jun;27(4):494-508. Epub 2006 May 4.



Hereditary auto-inflammatory disorders and biologics.

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The term auto-inflammatory disorders has been coined to describe a group of conditions characterized by spontaneously relapsing and remitting bouts of systemic inflammation without apparent involvement of antigen-specific T cells or significant production of auto-antibodies. The hereditary periodic fever syndromes are considered as the prototypic auto-inflammatory diseases, and genetic studies have yielded important new insights into innate immunity. DNA analysis has greatly enhanced the clinical characterization of these conditions, and elucidation of their molecular aetiopathogenesis has suggested that therapies may be aimed at specific targets within the immune cascade. The availability of biologic response modifiers such as inhibitors of tumour necrosis factor (TNF) and interleukin-1beta has greatly improved the outlook for some of these disorders, although effective therapies remain elusive in patients with certain conditions, including hyperimmunoglobulinaemia-D with periodic fever syndrome (HIDS) and a proportion of those with TNF-receptor associated periodic syndrome (TRAPS). Indeed, outstanding challenges and the unique potential to further elucidate molecular mechanisms in innate immunity are illustrated by the dashed early hope that TNF blockade would be a panacea for TRAPS: not only is etanercept (Enbrel) ineffective in some cases, but there are anecdotal reports of this condition being greatly exacerbated by infliximab (Remicade).

DOI: 10.1007/s00281-006-0015-6

PMID: 16738958 [Indexed for MEDLINE]

4090. Skeletal Radiol. 2007 Jun;36 Suppl 1:S105-7.

Familiar Mediterranean fever mimicking septic arthritis: distinguishing with diffusion weighted imaging.

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FMF arthritis is generally monoarticular in origin. The affected joint is hot, tender, red and mimics septic arthritis. Conventional imaging findings, including magnetic resonance imaging (MRI) and ultrasound, do not help differentiate between these two entities. The final diagnosis depends on culture of the synovial fluid, and therefore initiation of proper drug therapy can be delayed. Diffusion weighted imaging (DWI), with its ability to detect altered water-proton mobility, might play an important role as a fast and non-invasive problem-solving tool in this setting. We here present MRI and DWI findings of a case of FMF arthritis mimicking septic arthritis.

DOI: 10.1007/s00256-006-0153-x

PMID: 16738914 [Indexed for MEDLINE]

4091. J Nephrol. 2006 Mar-Apr;19(2):189-91.

SAA1 alpha/alpha alleles in amyloidosis.

Kelkitli E(1), Bilgici B, Tokgöz B, Dilek M, Bedir A, Akpolat I, Utaş C, Akpolat T.

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**BACKGROUND:** Amyloidosis, mainly AA type, is one of the common diseases in nephrology clinics in Turkey. AA type amyloidosis is a complication of various chronic infections or inflammatory diseases such as familial Mediterranean fever (FMF), rheumatoid arthritis (RA), tuberculosis and bronchiectasis. A controversy exists in the literature regarding the relationship between SAA1 genotypes and AA type amyloidosis. This study aimed to investigate SAA1 gene polymorphism in different patient groups: 1) amyloidosis, 2) FMF and 3) healthy controls.

**METHODS:** Eighty-two patients from the three groups were included in the study: 1) amyloidosis, 2) FMF without amyloidosis, and 3) healthy controls. SAA1 genotypes were studied by the polymerase chain reaction/restriction fragment length

polymorphism (PCR-RFLP) method.

RESULTS: The homozygous alpha/alpha genotype is the most common SAA1 genotype among patient groups with amyloidosis, and the alpha/alpha genotype frequency is significantly higher than in healthy controls (68 vs. 38%,  $p < 0.05$ ).

CONCLUSIONS: The SAA1 alpha/alpha genotype is a risk factor for AA type amyloidosis in Caucasoid populations and more studies are needed to investigate why the gamma/gamma genotype is associated with AA type amyloidosis in Japan.

PMID: 16736418 [Indexed for MEDLINE]

4092. Nephrol Dial Transplant. 2006 Oct;21(10):3000-1. Epub 2006 May 30.

Familial Mediterranean fever triggered by renal transplantation.

Khosroshahi HT, Tubbs RS, Shoja MM.

DOI: 10.1093/ndt/gfl282

PMID: 16735383 [Indexed for MEDLINE]

4093. Arthritis Rheum. 2006 Jun;54(6):2010-4.

AA amyloidosis complicating hyperimmunoglobulinemia D with periodic fever syndrome: a report of two cases.

Lachmann HJ(1), Goodman HJ, Andrews PA, Gallagher H, Marsh J, Breuer S, Rowczenio DM, Bybee A, Hawkins PN.

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AA amyloidosis is the most serious potential complication of the inherited autoinflammatory syndromes and frequently results in end-stage renal failure. Although this complication is well recognized in familial Mediterranean fever, tumor necrosis factor receptor-associated periodic syndrome, and Muckle-Wells syndrome, there is only 1 previous published report of its occurrence in

hyperimmunoglobulinemia D with periodic fever syndrome (HIDS). We report 2 further cases of patients with AA amyloidosis in HIDS, both of whom developed dialysis-dependent renal failure, and we describe the outcome of the first renal transplant in this setting.

DOI: 10.1002/art.21901

PMID: 16732551 [Indexed for MEDLINE]

4094. Biochem Biophys Res Commun. 2006 Jul 14;345(4):1326-32. Epub 2006 May 15.

Mutational analysis of the PRYSPRY domain of pyrin and implications for familial mediterranean fever (FMF).

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Familial Mediterranean fever (FMF) is an autosomal, recessively inherited disease, characterized by recurrent fever and serositis that affects mainly patients of the Mediterranean basin. The gene responsible for FMF, named MEFV, was cloned and several missense mutations were found to be responsible for the disease. Based on a recent molecular analysis of MEFV gene mutations in 43 patients from Crete aiming to correlate specific genotypes and clinical manifestations of FMF, we were prompted to construct a three-dimensional model (3-D model) of the PRYSPRY domain of pyrin. The majority of the known MEFV mutations located on this domain have been classified, according to disease severity, and localized on this 3-D model. The functional consequences of these mutations and their implications on disease severity are discussed. Moreover, we report a putative novel missense mutation, S702C, which we identified in exon 10 of the MEFV gene and localized on the constructed 3-D model.

DOI: 10.1016/j.bbrc.2006.04.185

PMID: 16730661 [Indexed for MEDLINE]

4095. Curr Top Microbiol Immunol. 2006;305:127-60.

The systemic autoinflammatory diseases: inborn errors of the innate immune system.

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The autoinflammatory syndromes are a newly recognized group of immune disorders that lack the high titers of self-reactive antibodies and T cells characteristic of classic autoimmune disease. Nevertheless, patients with these illnesses experience unprovoked inflammatory disease in the absence of underlying infection. Here we discuss recent advances in eight Mendelian autoinflammatory diseases. The causative genes and the proteins they encode play a critical role in the regulation of innate immunity. Both pyrin and cryopyrin, the proteins mutated in familial Mediterranean fever and the cryopyrinopathies, respectively, are involved in regulation of the proinflammatory cytokine, IL-1 $\beta$ , and may influence the activity of the transcription factor, NF $\kappa$ B. NOD2, the Blau syndrome protein, shares certain domains with cryopyrin and appears to be a sensor of intracellular bacteria. PSTPIP1, mutated in the syndrome of pyogenic arthritis with pyoderma gangrenosum and acne, interacts both with pyrin and a protein tyrosine phosphatase to regulate innate and adaptive immune responses. Somewhat unexpectedly, mutations in the p55 TNF receptor lead not to immunodeficiency but to dramatic inflammatory disease, the mechanisms of which are still under investigation. Finally, the discovery of the genetic basis of the hyperimmunoglobulinemia D with periodic fever syndrome has provided a fascinating but incompletely understood link between cholesterol biosynthesis and autoinflammation. In this manuscript, we summarize the current state of the art with regard to the diagnosis, pathogenesis, and treatment of these inborn errors of the innate immune system.

PMID: 16724804 [Indexed for MEDLINE]

4096. Clin Rheumatol. 2007 Jul;26(7):1183-5. Epub 2006 Jul 6.

Vasculitis in siblings with familial Mediterranean fever: a report of three cases and review of the literature.

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Familial Mediterranean Fever (FMF) is characterized by recurrent attacks of self-limited polyserositis and fever. Several types of vasculitis are associated with FMF: polyarteritis nodosa, Henoch-Schonlein purpura (HSP), and protracted febrile myalgia (PFM). We describe three cases of vasculitis in four siblings of a Sephardic Jewish family with FMF and reviewed the literature. One brother and one sister developed severe HSP with intestinal involvement while another brother developed PFM. Genetic tests in three brothers confirmed the M694V mutation on both alleles. Vasculitides may be a clinical feature of FMF with a higher familial prevalence. MEFV mutations may act as a genetic susceptibility factor for vasculitides in FMF patients.

DOI: 10.1007/s10067-006-0323-1

PMID: 16721494 [Indexed for MEDLINE]

4097. Clin Rheumatol. 2007 Mar;26(3):366-70. Epub 2006 May 24.

Hypercoagulability: interaction between inflammation and coagulation in familial Mediterranean fever.

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Familial Mediterranean fever (FMF) patients in clinical remission are reported to have increased baseline inflammation. Normal function of the natural

anticoagulant pathways is particularly needed in diminishing inflammatory responses. In the presence of subclinical inflammation, natural anticoagulant response may be exaggerated. We aimed to observe the anticoagulant-procoagulant status in attack-free FMF patients. Twenty-seven FMF patients diagnosed in accordance with Tel-Hashomer criteria, and 26 healthy controls were included. All patients were attack-free under regular colchicine treatment. Amyloidosis, autoimmunity, accompanying liver and renal disease, and vasculitis were excluded. Predisposing factors for thrombosis were not present. Acute phase reactants (APRs), anticardiolipin antibody positivity, prothrombin time (PT), activated prothrombin time, thrombin time (TT) and d-dimer, protein C activity, activated protein C resistance, free protein S, antithrombin, lupus anticoagulant, human prothrombin fragment F 1 + 2, and human thrombin/antithrombin III complex were analyzed for all subjects. APRs were comparable with controls. Autoimmune markers were negative in all. Anti-streptolysin titers were significantly different than the control group. PT, TT, protein C activity, and F 1 + 2 levels were significantly different from those of healthy controls. Shortened PT and TT, decreased protein C activity vs increased levels of F 1 + 2 suggested a hypercoagulable state in our patients. The hypercoagulable state detected in FMF patients suggests that screening with abnormal coagulation tests may be beneficial for tracing the future consequences of subclinical inflammation in these patients. Studies covering larger groups of patients are needed to verify the currently observed hypercoagulable status in FMF.

DOI: 10.1007/s10067-006-0334-y

PMID: 16721492 [Indexed for MEDLINE]

4098. J Paediatr Child Health. 2006 May;42(5):240-3.

Adrenomedullin and total nitrite levels in children with familial Mediterranean fever.

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AIM: Familial Mediterranean fever (FMF) is the most frequent periodic syndrome

characterised by recurrent attacks of polyserositis. However, recent studies revealed that there might be an ongoing subclinical inflammation between the attacks. As nitric oxide (NO) and adrenomedullin (AM) are both synthesised in the endothelium, and mediates many functions within immune system, we considered them to be an interesting target of investigation in FMF.

**METHODS:** Fifteen children with FMF receiving regular colchicine, ranging in age from 3 to 16 years, were investigated in comparison with 15 healthy age- and sex-matched controls. The mean age of the patients was 9.7 +/- 3.9 years. Total nitrite, a stable product of NO, was quantitated by means of the Griess reaction, while AM was measured by HPLC.

**RESULTS:** Plasma-urinary AM and total nitrite levels were significantly higher in children with FMF. Plasma AM levels (pmol/mL) in patients and controls were 40.95 +/- 5.99 vs. 34.86 +/- 5.24,  $P < 0.05$ , and urinary AM excretion (pmol/mg creatinine) was 51.16 +/- 28.15 vs. 37.5 +/- 24.26,  $P < 0.05$  respectively. Plasma total nitrite levels (micromol/L) in patients and controls were 44.80 +/- 10.36 vs. 32.13 +/- 9.28,  $P < 0.05$ , and urinary nitrite excretion (micromol/mg creatinine) was 2.24 +/- 1.71 vs. 1.09 +/- 0.96,  $P < 0.05$  respectively.

**CONCLUSION:** This study considered that AM and NO may have a role in the immuno-inflammatory process of FMF, although, whether these act to preserve, or protect against, further inflammatory injury is not clear. Our results further supports the hypothesis that these patients have subclinical inflammation between attacks.

DOI: 10.1111/j.1440-1754.2006.00845.x

PMID: 16712551 [Indexed for MEDLINE]

4099. Pol Arch Med Wewn. 2005 Sep;114(3):913-7.

[Fever of unknown origin].

[Article in Polish]

Jankiewicz-Ziobro K(1), Lewicki M, Kotulska A, Kucharz EJ.

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4100. Ann Rheum Dis. 2006 Nov;65(11):1427-32. Epub 2006 May 17.

A decision tree for genetic diagnosis of hereditary periodic fever in unselected patients.

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**BACKGROUND:** The diagnostic value of molecular analysis of the familial Mediterranean fever (FMF) gene (Mediterranean fever (MEFV)) has been well established only in patients selected on the basis of ethnic background or clinical criteria. Genetic diagnosis for other hereditary periodic fever syndromes has been poorly evaluated.

**OBJECTIVE:** To determine the diagnostic contribution of genetic tests for hereditary periodic syndromes in a large, unselected series of patients.

**METHODS:** A retrospective study was conducted on 1941 patients referred to us for FMF genetic tests between 1997 and 2005. MEFV genotypes were compared with clinical data to appraise criteria for FMF diagnosis. Genetic tests for tumour necrosis factor receptor-associated periodic syndrome (TRAPS), hyperimmunoglobulinaemia D syndrome (HIDS) and cryopyrin-associated periodic syndromes (CAPS) were also reviewed.

**RESULTS:** 71% of the 1574 patients with enough data had a clinical diagnosis of FMF according to the widely used Israeli criteria. Two MEFV mutations were found in only 409 patients of this subgroup (sensitivity = 37%) and in 15 (3.3%) of the patients with an improbable clinical diagnosis of FMF (specificity = 97%).

Molecular diagnosis for alternate hereditary periodic syndromes was carried out in 456 of the patients having a non-conclusive FMF genetic test. A positive diagnosis was obtained in 31 of these patients (TRAPS (n = 19), HIDS (n = 4) and CAPS (n = 8)).

**CONCLUSIONS:** First-line MEFV mutation screening in patients with clinically typical FMF may be appropriate only in particular areas. To optimise genetic diagnosis, we propose a decision tree, which, with the advice of an expert

practitioner, could help redirect test indications towards non-FMF hereditary periodic syndromes.

DOI: 10.1136/ard.2006.054304

PMCID: PMC1798342

PMID: 16707534 [Indexed for MEDLINE]

4101. Br J Dermatol. 2006 Jun;154(6):1190-3.

Early and severe amyloidosis in a patient with concurrent familial Mediterranean fever and pseudoxanthoma elasticum.

Cattan D(1), Bouali B, Chassaing N, Martinez F, Dupont JM, Dode C, Martin L.

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A young woman patient had early and extensive familial Mediterranean fever (FMF)-related amyloidosis and pseudoxanthoma elasticum (PXE). She had the novel G1042S mutation in the ATP-binding cassette subfamily C member 6 (ABCC6) gene, responsible for PXE, and the mutation M694I in MEFV, the FMF gene. Both mutations were homozygous, in agreement with consanguinity in the parents. ABCC6 deficiency may have increased the severity of amyloidosis by increasing the deposition in target tissues of heparan sulphate, which colocalizes spatially and temporally with amyloid proteins, and/or by decreasing the therapeutic activity of colchicine.

DOI: 10.1111/j.1365-2133.2006.07187.x

PMID: 16704654 [Indexed for MEDLINE]

4102. Intern Med. 2006;45(8):515-7. Epub 2006 May 15.

A Japanese case of familial Mediterranean fever with onset in the fifties.

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(1)Division of Gastroenterology and Hepatology, Department of Internal Medicine, The Jikei University Kashiwa Hospital, Kashiwashita, Chiba.

The patient was a 63-year-old woman with attacks of fever and abdominal pain, starting from the age of 53 years and recurring every month. Despite various examinations at another hospital, the etiology remained unclear. She was under symptomatic treatment, and was referred to our department for further evaluation. Although she had onset in middle age, the clinical symptoms and examination findings suggested familial Mediterranean fever, and administration of colchicine inhibited the attacks completely. Therefore, the patient was diagnosed as having the disease. We were not able to analyze the entire MEFV gene, but detected only a heterozygous M694I mutation. Amyloidosis did not develop as a complication. The disease is rare in Japan, and its onset in the fifties is extremely rare in the world.

PMID: 16702743 [Indexed for MEDLINE]

4103. Arch Pediatr. 2006 Jun;13(6):601-3. Epub 2006 May 12.

[Renal involvement in systemic diseases].

[Article in French]

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DOI: 10.1016/j.arcped.2006.03.071

PMID: 16697604 [Indexed for MEDLINE]

4104. Blood. 2006 Aug 15;108(4):1320-7. Epub 2006 May 9.

Abnormal disulfide-linked oligomerization results in ER retention and altered signaling by TNFR1 mutants in TNFR1-associated periodic fever syndrome (TRAPS).

Lobito AA(1), Kimberley FC, Muppidi JR, Komarow H, Jackson AJ, Hull KM, Kastner DL, Screaton GR, Siegel RM.

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Tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is an autosomal dominant systemic autoinflammatory disease associated with heterozygous mutations in TNF receptor 1 (TNFR1). Here we examined the structural and functional alterations caused by 9 distinct TRAPS-associated TNFR1 mutations in transfected cells and a mouse "knock-in" model of TRAPS. We found that these TNFR1 mutants did not generate soluble versions of the receptor, either through membrane cleavage or in exosomes. Mutant receptors did not bind TNF and failed to function as dominant-negative inhibitors of TNFR1-induced apoptosis. Instead, TRAPS mutant TNFR1 formed abnormal disulfide-linked oligomers that failed to interact with wild-type TNFR1 molecules through the preligand assembly domain (PLAD) that normally governs receptor self-association. TRAPS mutant TNFR1 molecules were retained intracellularly and colocalized with endoplasmic reticulum (ER) markers. The capacity of mutant receptors to spontaneously induce both apoptosis and nuclear factor kappaB (NF-kappaB) activity was reduced. In contrast, the R92Q variant of TNFR1 behaved like the wild-type receptor in all of these assays. The inflammatory phenotype of TRAPS may be due to consequences of mutant TNFR1 protein misfolding and ER retention.

DOI: 10.1182/blood-2005-11-006783

PMCID: PMC1895878

PMID: 16684962 [Indexed for MEDLINE]

4105. Joint Bone Spine. 2006 Oct;73(5):514-7. Epub 2006 Mar 31.

Sonographic evaluation of the tendons in familial Mediterranean fever and Behçet's disease.

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**OBJECTIVES:** There have been some studies on the burden of certain rheumatological disorders on the tendons; however, patients with familial Mediterranean fever (FMF) and Behçet's disease (BD) have not, up to now, been studied in this regard in the literature. Thus, this current study centers on ensuing changes in the tendons of these patients.

**METHODS:** The study comprised 32 patients with FMF (13 male, 19 female), 31 with BD (18 male, 13 female) and 35 control subjects (17 male, 18 female).

Sonographical evaluations were performed from the triceps, quadriceps and Achilles tendons on the non-dominant extremities of the individuals using a linear array probe of 8-16 MHz.

**RESULTS:** The mean triceps tendon (TT) thickness value of FMF patients was greater than that of BD patients ( $P=0.03$ ) or the controls' ( $P=0.02$ ). The mean quadriceps tendon (QT) thickness value of BD patients was greater than that of FMF patients ( $P=0.00$ ) or the controls' ( $P=0.01$ ). The mean Achilles tendon (AT) thickness value of BD patients was greater than that of controls' ( $P=0.05$ ) only. There was not any difference between the tendon thickness measurements of either group of patients with and without arthritic involvement.

**CONCLUSION:** Our first and preliminary findings pertaining to increased tendon thicknesses in FMF (TT) and BD (QT and AT) patients should be complemented with future histological and clinical studies. The functional relevance of tendon thickening, its probable reflection on the rupture risk and the role of each disease related contributing factor remain to be uncovered.

DOI: 10.1016/j.jbspin.2006.01.009

PMID: 16650792 [Indexed for MEDLINE]

4106. Arthritis Rheum. 2006 May;54(5):1697-700.

Recovery from deafness in a patient with Muckle-Wells syndrome treated with anakinra.

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Muckle-Wells syndrome (MWS) is a dominantly inherited autoinflammatory disease characterized by rashes, fever, arthralgia, sensorineural deafness, and the possible development of systemic AA amyloidosis. We used anakinra to treat a 22-year-old patient with MWS who had deafness and a high serum level of C-reactive protein (CRP). Following treatment with anakinra, the patient's CRP level normalized, and she recovered from deafness. The fact that this occurrence has never been previously reported strengthens the role of anakinra in MWS but also raises new questions about the physiopathology of such deafness.

DOI: 10.1002/art.21807

PMID: 16646042 [Indexed for MEDLINE]

4107. Reumatismo. 2006 Jan-Mar;58(1):1-4.

[The Italian Society of Rheumatology's registry for systemic autoinflammatory syndromes].

[Article in Italian]

Punzi L, Galeazzi M, Modena V, Bombardieri S.

PMID: 16639481 [Indexed for MEDLINE]

4108. Pediatr Int. 2006 Apr;48(2):169-71.

A new low-penetrance TNFRSF1A mutation causing atypical periodic fever.

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DOI: 10.1111/j.1442-200X.2006.02194.x

PMID: 16635178 [Indexed for MEDLINE]

4109. Clin Imaging. 2006 May-Jun;30(3):153-9.

Imaging findings of familial Mediterranean fever.

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**PURPOSE:** The aim of this study was to study the imaging findings of familial Mediterranean fever (FMF).

**MATERIALS AND METHODS:** We performed a retrospective review of the medical records and imaging studies of 38 patients with proven FMF, diagnosed between 1992 and 2002.

**RESULTS:** The most common clinical manifestation was recurrent peritoneal attacks with abdominal pain (76.3%) and fever (42.1%). Abdominal imaging findings included ileus (n=12), splenomegaly (n=5), hepatomegaly (n=2), ascitis (n=2), focal peritonitis (n=2), mesenteric streaking (n=1), and enlarged mesenteric lymph node (n=1). One patient developed fatal peritoneal mesothelioma, and 13.1% of the patients developed amyloidosis with sonographic findings of renal parenchymal disease or cardiomyopathy. Arthritis was second in frequency, occurring in 34.2% of patients; radiographs were normal (n=4) or showed joint effusion and periarticular soft tissue swelling (n=4) due to synovitis. One patient developed seronegative destructive arthropathy. Skin lesions were noted in 23.6% of patients. Pleuritis was encountered in 13.1% and pericarditis in 5.2%. Polyarteritis nodosa (PAN) was present in two patients, multiple sclerosis in one, and autoimmune hemolytic anemia in one patient.

**CONCLUSION:** FMF predominantly involves abdominal viscera but can affect other organs. The majority of patients have nonspecific imaging findings, and the radiologic diagnosis is rarely considered. Amyloidosis, mesothelioma, and

destructive arthropathy are potential serious complications of FMF. PAN, multiple sclerosis, and autoimmune hemolytic anemia are probably rare associations or rather than coincident with FMF.

DOI: 10.1016/j.clinimag.2005.07.002

PMID: 16632148 [Indexed for MEDLINE]

4110. Clin Biochem. 2006 Jul;39(7):688-91. Epub 2006 Apr 24.

Classical pathway complement activity in Familial Mediterranean fever.

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**OBJECTIVES:** The present study emphasizes the important role of the immune reactions in the pathogenesis of Familial Mediterranean fever. In the present study, the total hemolytic activity of the complement and the activities of individual complement components, C1, C2, C3, and C4, were determined in the blood serum of 32 patients with FMF and 28 healthy subjects.

**DESIGN AND METHODS:** Hemolytic assay was applied, measuring THAC and individual complement components' activities. The patients were divided into 3 groups upon the regularity of colchicine therapy: patients receiving regular, irregular and not receiving colchicine treatment for at least 1 year.

**RESULTS:** No significant changes in the hemolytic activities of the C1, C2, C3, and C4 complement components were found between the healthy subjects and those FMF patients, who were receiving regular colchicine treatment.

**CONCLUSIONS:** Our data obtained have raised a number of important questions relevant to FMF pathogenesis and once again confirms the efficiency of regular colchicine treatment.

DOI: 10.1016/j.clinbiochem.2006.02.016

PMID: 16631629 [Indexed for MEDLINE]

4111. Eur J Med Genet. 2006 Nov-Dec;49(6):481-6. Epub 2006 Apr 3.



Familial Mediterranean fever in the Syrian population: gene mutation frequencies, carrier rates and phenotype-genotype correlation.

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(1)Biochemistry Department, Faculty of Pharmacy, Damascus University, Damascus, Syria.

**BACKGROUND:** Familial Mediterranean fever (FMF) is an autosomal recessive disease mainly affecting particularly Arabs, Non-Ashkenazi Jews, Armenians, and Turks. It is an autoinflammatory periodic disorder characterized by febrile and painful attacks due to inflammation involving the serosal membranes in the abdomen, chest or joints. Over 50 mutations have been identified in the MEFV gene responsible for FMF.

**OBJECTIVE:** To identify the distribution and the frequency of the MEFV gene mutations in Syrian FMF patients and population and perform a genotype/phenotype correlation in the patients' cohort.

**PATIENTS AND METHODS:** The study was carried out on 83 clinically diagnosed Syrian FMF patients and 242 healthy subjects. The tested individuals were screened for the most common five MEFV mutations (M694V, M694I, M680I, V726A and E148Q) by restriction fragment length polymorphism. Sequencing of exon 10 was performed only for the patients' DNA where just one or no mutation was detected.

**RESULTS AND DISCUSSION:** Of the 83 patients studied, 74 (89%) were positive either for one, two or three mutations and nine (11%) had no mutations detected. Of those positive for mutations, 25 were homozygous, 30 were compound heterozygotes, three had complex alleles, and 16 patients had only one mutation. The M694V, V726A, M694I, M680I and E148Q mutations accounted for 45.8%, 26%, 13.9%, 4.8% and 6% of the alleles, respectively. The carrier rate in the Syrian population for the tested mutations was 17.5%, E148Q being the most common mutation, followed by V726A and M694V. The severity of the disease and development of amyloidosis seem to have an association with M694V, the most common mutation in Syrian FMF patients.

DOI: 10.1016/j.ejmg.2006.03.002

PMID: 16627024 [Indexed for MEDLINE]

4112. Dig Dis Sci. 2006 Apr;51(4):687-92.

Increased frequency of mutations in the gene responsible for familial Mediterranean fever (MEFV) in a cohort of patients with ulcerative colitis: evidence for a potential disease-modifying effect?

Giaglis S(1), Mimidis K, Papadopoulos V, Thomopoulos K, Sidiropoulos P, Rafail S, Nikolopoulou V, Fragouli E, Kartalis G, Tzioufas A, Boumpas D, Ritis K.

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The MEFV gene, responsible for familial Mediterranean fever (FMF), is involved in inflammatory reactions through altered leukocyte apoptosis, secretion of interleukin (IL)-1 $\beta$ , and activation of the NF- $\kappa$ B pathway. Ulcerative Colitis (UC) and FMF are both characterized by a recurrent pattern of presentation with periods of remission and flares associated with neutrophilic infiltration at the site of injury. The aim of this study was to investigate the possible correlation between UC and MEFV gene alterations. Twenty-five consecutive, first-diagnosed and untreated UC patients, 28 control patients with rheumatoid arthritis, and 65 normal individuals were analyzed. Nonisotopic RNase Cleavage Assay (NIRCA) was applied as a first-step mutational screening method of exons 10 and 2 of MEFV gene; direct sequencing was subsequently performed to confirm the results. MEFV mutations were identified in 7 (3 M694V/0, 2 M680I/0, 1 E148Q/E148Q, and 1 A744S/0) out of 25 UC patients versus 1 (M694V/0) out of 28 rheumatoid arthritis patients ( $P = .0199$ ) and 1 (M694V/0) out of 65 healthy controls ( $P = .0004$ ). Four out of 7 patients with MEFV mutations had inflammatory arthritis, a clinical finding that was not observed in the 18 UC patients with unmutated MEFV ( $P = .0028$ ). Patients with UC almost universally carried the T A C G MEFV exon 2 haplotype in contrast with normal individuals ( $P < .0001$ ) and FMF patients ( $P = .0310$ ). In conclusion the increased frequency of mutations of MEFV in UC patients, especially in those with episodic arthritis, suggests a possible modifying effect of MEFV in the disease process and its localization within the joint. The difference in distribution of MEFV exon 2 haplotypes between UC patients and both FMF patients and normal individuals, suggests that UC patients constitute a genetically distinct population. Larger, longitudinal studies are needed to confirm these initial findings.

DOI: 10.1007/s10620-006-3192-1

PMID: 16614989 [Indexed for MEDLINE]

4113. Patol Fiziol Eksp Ter. 2006 Jan-Mar;(1):11-3.

[Modulation of endotoxin-induced respiratory splash of granulocytes and monocytes in patients with Familial Mediterranean Fever by iodine-lithium-alpha-dextrin and sodium thiosulfate].

[Article in Russian]

Avetisian SA, Akopian GS, Davtian TK.

The effect of an endotoxin--E. coli liposaccharide (LPS) of serotype 026:B6--on the respiratory splash (RS) of neutrophils and monocytes in peripheral blood of patients with Familial Mediterranean Fever (FMF) was studied. It is shown that FMF patients have a periodic increase (during an attack) and a decrease (in the period of remission) in endotoxin-induced RS of neutrophils and monocytes. LPS stimulates chemotoxis-induced RS of neutrophils and monocytes in patients both in the period of remission and during the attack equally effectively.

Iodine-lithium-alpha-dextrin and sodium thiosulfate have a marked anti-endotoxic effect which manifests with quick neutralization of endotoxin activity on RS of monocytes and neutrophils in FMF patients both during the attack and remission.

PMID: 16607886 [Indexed for MEDLINE]

4114. Ann Rheum Dis. 2006 Jul;65(7):961-4. Epub 2006 Apr 10.

Familial Mediterranean fever (FMF) and beyond: a new horizon. Fourth International Congress on the Systemic Autoinflammatory Diseases held in Bethesda, USA, 6-10 November 2005.

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Autoinflammatory diseases are characterised by seemingly unprovoked inflammation. They can be categorised as: hereditary (monogenic) autoinflammatory diseases, complex (polygenic/multifactorial) autoinflammatory diseases, and diseases where the course is affected by mutations in the defined autoinflammatory disease genes. Identification of the inflammatory pathways involved has opened up new areas of research which have implications for the treatment of these disorders and the pathogenesis of common inflammatory diseases.

DOI: 10.1136/ard.2006.052688

PMCID: PMC1798229

PMID: 16606647 [Indexed for MEDLINE]

4115. J Clin Rheumatol. 2006 Apr;12(2):93-6.

Febrile myalgia syndrome in familial Mediterranean fever.

Soylu A(1), Kasap B, Türkmen M, Saylam GS, Kavukçu S.

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Comment in

J Clin Rheumatol. 2006 Oct;12(5):265-6.

Familial Mediterranean fever is characterized by recurrent polyserositis episodes associated with fever. However, the clinical spectrum of this disease has been expanded recently and myalgia is now a frequently recognized component. Protracted febrile myalgia syndrome was first described in patients with familial Mediterranean fever in 1994. This syndrome is characterized by severe paralyzing myalgia, high fever, abdominal pain, diarrhea, arthritis/arthralgia, and transient vasculitic rashes mimicking Henoch-Schonlein purpura. Recently, we evaluated 6 patients with the clinical picture of protracted febrile myalgia syndrome in our clinic. One of them was a patient with known familial Mediterranean fever, but the others were subsequently diagnosed to have familial

Mediterranean fever by mutational analyses. Thus, introduction of genetic analysis would possibly change the diagnostic criteria for familial Mediterranean fever. In addition, all 6 patients presented in the spring months when streptococcal infections are at their peak rate and 3 of them had elevated ASO levels indicating that streptococci could be one of the agents triggering protracted febrile myalgia syndrome.

DOI: 10.1097/01.rhu.0000208635.64537.10

PMID: 16601545 [Indexed for MEDLINE]

4116. J Rheumatol. 2006 Apr;33(4):810-1.

Recurrent transient synovitis of the hip in childhood. Longterm outcome among 39 patients.

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**OBJECTIVE:** To describe the outcome of children with recurrent transient synovitis (TS) of the hip.

**METHODS:** A retrospective chart review of children with at least 2 separate episodes of TS between 1986 and 2003. We described the diagnostic investigations and outcome of these patients. A followup telephone survey for disability and pain scores was performed in 2004.

**RESULTS:** We studied 39 children, 26 boys and 13 girls, from 6 pediatric rheumatology centers. The mean age at initial episode was 6 +/- 2.6 years. There were a total of 102 episodes (mean 2.9 +/- 1.6, median 2, range 2-10). All but 2 children had normal plain radiographs of the hip. All patients were contacted 4.2 +/- 2.5 years after the first episode. None developed clinical Perthes disease or other chronic orthopedic condition. Three (8%) patients developed chronic disease: one had familial Mediterranean fever and 2 developed spondyloarthropathies, 0.5, 2, and 6 years after presentation. At followup 26 of 36 patients were asymptomatic, and 10 reported rare hip pain after intensive physical effort.

CONCLUSION: Children with recurrent TS usually have a benign course. In some patients recurrent TS may be the presenting feature of a chronic inflammatory condition. No progression to chronic orthopedic conditions was observed.

PMID: 16583482 [Indexed for MEDLINE]

4117. Cell Death Differ. 2006 Nov;13(11):1938-49. Epub 2006 Mar 31.

The estrogen-responsive B box protein: a novel enhancer of interleukin-1beta secretion.

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The estrogen-responsive B box protein (EBBP) and Pyrin belong to a family of structurally related proteins. While mutations in the pyrin gene cause an autoinflammatory disease, the biological function of EBBP is unknown. In this study, we identified the proinflammatory cytokine interleukin-1beta (IL-1beta) as an EBBP-binding partner. Furthermore, caspase-1 and NACHT, LRR and Pyrin domain containing protein (NALP) 1, two components of the recently identified inflammasome, a platform for the activation of caspase-1, also interact with EBBP. These proteins bind to the RFP domain of EBBP, suggesting that this domain of so far unknown function is an important protein-binding domain. EBBP was secreted in a caspase-1-dependent manner from cultured cells, and its secretion was enhanced by IL-1beta. Vice versa, endogenous and overexpressed EBBP increased IL-1beta secretion. These results provide evidence for a role of EBBP in innate immunity by enhancing the alternative secretion pathway of IL-1beta.

DOI: 10.1038/sj.cdd.4401896

PMID: 16575408 [Indexed for MEDLINE]

4118. Pediatr Nephrol. 2006 Jun;21(6):877-9. Epub 2006 Mar 29.

Renal amyloidosis in a child with sickle cell anemia.

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The kidney is frequently affected in patients with sickle cell syndrome, i.e., homozygous and heterozygous patients, with a consequently large spectrum of renal abnormalities that may range from minimal functional changes to chronic renal failure. Here, we present a 13-year-old boy with sickle cell anemia (SCA) (HbSS) who was referred to our unit with nephrotic syndrome. Renal biopsy revealed AA type amyloidosis on the basis of light microscopic findings, indicating Congo red staining and immunohistochemistry. He had neither a family history of familial Mediterranean fever (FMF) nor any complaint of recurrent abdominal pain, arthritis, and fever, but frequent painful vaso-occlusive crises. The patient was found to have no MEFV gene (Mediterranean fever) mutations either. Painful episodic attacks might provoke recurrent acute inflammation, leading to repeated stimulation of acute phase responses and cause secondary amyloidosis. To our knowledge, this boy is the first case of SCA complicated by renal amyloidosis observed in childhood.

DOI: 10.1007/s00467-006-0069-7

PMID: 16570202 [Indexed for MEDLINE]

4119. Ann Rheum Dis. 2006 Sep;65(9):1158-62. Epub 2006 Mar 28.

Clinical significance of P46L and R92Q substitutions in the tumour necrosis factor superfamily 1A gene.

Ravet N(1), Rouaghe S, Dodé C, Bienvenu J, Stirnemann J, Lévy P, Delpech M, Grateau G.

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**OBJECTIVE:** Tumour necrosis factor receptor-associated periodic syndrome (TRAPS) has been associated with several mutations in the TNF receptor super family 1A (TNFRSF1A), including most cysteine substitutions. However, the nature of two substitutions, P46L and R92Q, remains a topic of discussion. The aim of this study was to assess the actual role of these two sequence variations in a series of patients with TRAPS.

**METHODS:** The main clinical data of 89 patients with TRAPS have been prospectively registered on a standard form. 84 patients or members of families with recurrent episodes of inflammatory symptoms spanning a period of more than 6 months and harbouring a TNFRSF1A mutation were studied. Clinical data have been analysed according to the nature of the mutation-P46L, R92Q or others.

**RESULTS:** P46L is often seen in patients from Maghreb and is associated with a mild phenotype. P46L appears as a polymorphism with a non-specific role in inflammation. R92Q is associated with a variable phenotype and presents as a low-penetrance mutation. Interpreting these results will require a comparison with clinical signs and genetic background.

DOI: 10.1136/ard.2005.048611

PMCID: PMC1798274

PMID: 16569687 [Indexed for MEDLINE]

4120. Lancet. 2006 Mar 25;367(9515):1016-24.

Familial mediterranean fever in Arabs.

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Autoinflammatory diseases are a group of disorders characterised by seemingly unprovoked inflammation in the absence of high-titre autoantibodies or antigen-specific T cells, and include the hereditary periodic fever syndromes. Familial Mediterranean fever (FMF) is an archetypal autoinflammatory disorder, which is autosomal recessive and has a high prevalence in non-Ashkenazi Jews, Armenians, Turks, and Arabs. The classic clinical picture is recurrent acute short-lived febrile and painful attacks with variable periods of remission. In a



subset of patients, the disorder is complicated by amyloidosis that leads to renal failure. The gene responsible for FMF--MEFV--has been identified and its role in inflammation is being assessed. There seems to be a distinctive clinical picture in Arab patients with FMF, and the range and distribution of MEFV mutations is different from that noted in other affected ethnic groups. Here, we discuss the clinical and molecular aspects of FMF in Arabs.

DOI: 10.1016/S0140-6736(06)68430-4

PMID: 16564365 [Indexed for MEDLINE]

4121. Rev Med Interne. 2006 Jun;27(6):502-3. Epub 2006 Mar 3.

[Pseudo-autoinflammatory attacks of temporal arteritis].

[Article in French]

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INTRODUCTION: Usually, temporal arteritis progresses as a chronic disease.

CASE REPORT: The authors report the observation of a 74-year-old woman who presented with two acute flares of temporal arteritis with headache, fever and inflammatory syndrome, which have spontaneously resolved.

DISCUSSION: The observations of auto-inflammatory attacks of arteritis disease are rare, but maybe underestimated. The pathophysiology remains unclear.

DOI: 10.1016/j.revmed.2006.02.002

PMID: 16563572 [Indexed for MEDLINE]

4122. J Pediatr Endocrinol Metab. 2006 Feb;19(2):155-60.

Familial Mediterranean fever and growth: effect of disease severity and colchicine treatment.

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**OBJECTIVE:** To evaluate the effect of disease severity and colchicine treatment on height and weight parameters in children with familial Mediterranean fever (FMF).

**METHODS:** Thirty prepubertal children (19 M, 11 F) were studied retrospectively.

Z-score values of height, growth velocity, weight and body mass index were obtained over 1.84 +/- 1.14 years before and 2.58 +/- 1.55 years during colchicine therapy. Disease severity was evaluated by a specific score for FMF.

**RESULTS:** By comparison to growth before treatment, during colchicine therapy height SDS increased from -1.00 +/- 1.17 to -0.54 +/- 0.96 ( $p < 0.001$ ) and weight SDS increased from -0.74 +/- 1.09 to -0.47 +/- 1.06 ( $p = 0.008$ ). An effect of disease severity on growth pattern could not be detected. Height SDS during therapy was negatively correlated with age at colchicine initiation.

**CONCLUSIONS:** Colchicine therapy has a positive effect on both height and weight parameters in children with FMF. Early initiation of treatment is beneficial for height gain.

PMID: 16562589 [Indexed for MEDLINE]

4123. Nat Rev Immunol. 2006 Apr;6(4):308-17.

Caspases at the crossroads of immune-cell life and death.

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Caspases are responsible for crucial aspects of inflammation and immune-cell death that are disrupted in a number of genetic autoimmune and autoinflammatory diseases. The caspase family of proteases can be divided into pro-apoptotic and pro-inflammatory members based on their substrate specificity and participation

in separate signalling cascades. However, as discussed here, evidence has emerged over the past few years that a number of the caspases thought to be involved solely in apoptosis also contribute to specific aspects of immune-cell development, activation and differentiation, and can even protect cells from some forms of cell death.

DOI: 10.1038/nri1809

PMID: 16557262 [Indexed for MEDLINE]

4124. J Clin Epidemiol. 2006 Apr;59(4):358-64. Epub 2006 Feb 14.

Population screening for single genes that codetermine common diseases in adulthood had limited effects.

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**BACKGROUND AND OBJECTIVE:** Familial hemochromatosis (FHEM), familial hypercholesterolemia (FH), familial mediterranean fever (FMF), and familial thrombophilia (FT) are relatively common genetically determined diseases of (early) adulthood. Chances, shortcomings, and practical aspects of population screening were considered.

**METHODS:** The literature, as well as existing data concerning the treatment of these diseases in The Netherlands, were studied.

**RESULTS:** In these four diseases there are so many modifying genes and environmental and lifestyle influences that accurate predictive testing at the population level is currently not sufficiently effective. The data indicate that the implementation of family clinics for FHEM and FH are necessary. There is need for further sociologic studies in the moslim population of Mediterranean and North African origin about acceptance of DNA diagnostics in relation to consanguinity and into the problem of "pseudodominance." There seems no need for early detection and preventive measures for FT in asymptomatic persons.

**CONCLUSION:** No population screening for these four genetically determined diseases of (early) adulthood is sufficiently effective at the present time. We propose to call these diseases "chronic diseases with a single gene component."

DOI: 10.1016/j.jclinepi.2005.09.006

PMID: 16549257 [Indexed for MEDLINE]

4125. Transplant Proc. 2006 Mar;38(2):473-6.

Does colchicine have an antifibrotic effect on development of interstitial fibrosis in renal allografts of recipients with familial Mediterranean fever?

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Colchicine, which has been reported to inhibit fibrosis, has been successfully used to treat fibrotic disorders, such as liver cirrhosis, scleroderma, and idiopathic pulmonary fibrosis. We hypothesized that besides its ability to prevent amyloid deposition, colchicine may prevent the development of interstitial fibrosis (IF) in amyloidosis patients who had undergone renal transplantation. We evaluated the influence of colchicine therapy on the development of IF in 25 patients with systemic amyloidosis secondary to familial Mediterranean fever (group 1). Twenty-five nonamyloidotic patients who did not receive colchicine therapy served as controls (group 2). The incidences of recurrence and development of IF in the first, second, and third years after transplantation were evaluated from follow-up allograft biopsies. Only four patients showed amyloid recurrence in their renal allografts. IF developed in 44% (11/25) of group 1 patients and 80% (20/25) of group 2 patients during the 36 months posttransplantation ( $P < .01$ ). Development of IF in the first, second, and third years posttransplantation was significantly greater among group 2 recipients than group 1 recipients ( $P < .01$ ). The overall 1-, 2-, and 3-year graft survival rates for group 1 recipients were 96%, 92%, and 80%, and those for group 2 recipients were 96%, 88%, and 60%, respectively. Our results support the thesis that colchicine therapy may help prevent the development of interstitial fibrosis in renal allografts.

DOI: 10.1016/j.transproceed.2005.12.049

PMID: 16549151 [Indexed for MEDLINE]

4126. Transplant Proc. 2006 Mar;38(2):435-9.

Outcome of kidney transplantation for renal amyloidosis:a single-center experience.

Celik A(1), Saglam F, Dolek D, Sifil A, Soylu A, Cavdar C, Temizkan A, Bora S, Gulay H, Camsari T.

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The aim of this retrospective study was to investigate the results of kidney transplantation in patients with renal amyloidosis. We analyzed the results of renal transplantation in 13 amyloidotic transplant recipients compared with those in a control group of 13 nonamyloidotic patients. While the etiology of amyloidosis was rheumatoid arthritis in one patient, in all of the others it was secondary to familial Mediterranean fever. Acute rejection episodes developed once in six and twice in one patient. The renal function in these patients was improved by antirejection treatment. Chronic rejection did not develop in any patient. However six patients (46%) died due to various complications despite functional grafts. The others are still being followed with well-functioning grafts. Among the control group, acute and chronic rejection were diagnosed in three and two patients, respectively: one patient returned to hemodialysis after 26 months of transplantation, while the others are still alive with functional grafts. There was no death in the control group. The 5- and 10-year actuarial patient survival rates of the amyloidosis and control groups were 52.2%, 26.6%, and 100%, 100%, respectively ( $P = .002$ ). However, the graft survivals of the amyloidosis versus control groups were 100%, 100%, versus 87.5%, 87.5%, respectively ( $P = .47$ ). In conclusion, we observed a high rate of early mortality among recipients with amyloidosis associated with infectious complications. Moreover, patient survivals were lower among amyloidotic renal recipients.

DOI: 10.1016/j.transproceed.2006.01.003

PMID: 16549141 [Indexed for MEDLINE]

4127. Immunity. 2006 Mar;24(3):317-27.

Critical role for NALP3/CIAS1/Cryopyrin in innate and adaptive immunity through its regulation of caspase-1.

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Comment in

Immunity. 2006 Mar;24(3):241-3.

Mutations in the NALP3/CIAS1/cryopyrin gene are linked to three autoinflammatory disorders: Muckle-Wells syndrome, familial cold autoinflammatory syndrome, and chronic infantile neurologic cutaneous and articular syndrome. NALP3, with the adaptor molecule ASC, has been proposed to form a caspase-1-activating "inflammasome," a complex with pro-IL1beta-processing activity. Here, we demonstrate the effect of NALP3 deficiency on caspase-1 function. NALP3 was essential for the ATP-driven activation of caspase-1 in lipopolysaccharide-stimulated macrophages and for the efficient secretion of the caspase-1-dependent cytokines IL-1alpha, IL-1beta, and IL-18. IL-1beta has been shown to play a key role in contact hypersensitivity; we show that ASC- and NALP3-deficient mice also demonstrate an impaired contact hypersensitivity response to the hapten trinitrophenylchloride. NALP3, however, was not required for caspase-1 activation by *Salmonella typhimurium*, and NALP3 deficiency only partially protects mice from the lethal effects of endotoxin. These data suggest that NALP3 plays a specific role in the caspase-1 activation pathway.

DOI: 10.1016/j.immuni.2006.02.004

PMID: 16546100 [Indexed for MEDLINE]

4128. Immunity. 2006 Mar;24(3):241-3.

Cryopyrin: in from the cold.

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Comment on

Immunity. 2006 Mar;24(3):317-27.

Mutations in CIAS1/cryopyrin are linked to several autoinflammatory diseases. In this issue of Immunity, a critical role for cryopyrin in the caspase-1/IL-1beta axis and reveal a broader role for cryopyrin than anticipated is uncovered.

DOI: 10.1016/j.immuni.2006.03.004

PMID: 16546091 [Indexed for MEDLINE]

4129. Isr Med Assoc J. 2006 Feb;8(2):142-4.

Expansion of CD28-CD27-NKG2D+ effector memory T cells and predominant Th1-type response during febrile attacks in tumor necrosis factor-associated periodic syndrome.

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PMID: 16544745 [Indexed for MEDLINE]

4130. Eur Ann Allergy Clin Immunol. 2006 Jan;38(1):5-9.

Inherited autoinflammatory recurrent fevers.

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Autoinflammatory diseases have a quite similar clinical picture and are characterised by recurrent episodes of fever, joint features, abdominal features and skin features. Auto-inflammatory syndrome are related to mutations in genes implied in apoptosis or inflammation. FMF's gene is MEFV, present on the short arm of the chromosom 6, encoding the pyrin or marenostrie which is widely expressed in neutrophils and monocyts and implied in the control of the inflammation. Muckle wells syndrome and Familial cold urticaria are related to CIAS1 gene mutations which are located on the long arm of the chromosome 1 and encodes cryopyrine involved in apoptosis. TRAPS gene is present on the chromosome 12, the majority of mutations are located in the extra cellular region of the receptor.

PMID: 16544581 [Indexed for MEDLINE]

4131. Ann Rheum Dis. 2006 Apr;65(4):533-4.

Hearing improvement in a patient with variant Muckle-Wells syndrome in response to interleukin 1 receptor antagonism.

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BACKGROUND: Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome, and neonatal onset multisystem inflammatory disease, also called chronic, infantile, neurological, cutaneous, and articular syndrome, are three hereditary autoinflammatory syndromes caused by mutations affecting the CIAS1/NALP3 gene on chromosome 1q44. The proinflammatory cytokine, interleukin 1beta, is believed to have a fundamental role in their pathogenesis.

CASE REPORT: The case is described of a 59 year old white woman who presented



with increasingly severe MWS-type features over a 15 year period. The response to interleukin 1beta inhibition with anakinra was dramatic, including a reduction in intracranial pressure with associated auditory improvement, as demonstrated by serial audiometry.

**CONCLUSIONS:** The confirmed improvement in hearing after initiation of interleukin 1 receptor antagonism corroborates previous reports that specific blockade of this single cytokine reverses most of the symptoms of this group of CIAS1/NALP3 related autoinflammatory conditions, including the sensorineural deafness, which has not been previously reported.

DOI: 10.1136/ard.2005.038091

PMCID: PMC1798106

PMID: 16531551 [Indexed for MEDLINE]

4132. Rheumatology (Oxford). 2006 Sep;45(9):1140-3. Epub 2006 Mar 9.

Peculiarities of PAPA syndrome.

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**OBJECTIVES:** To describe a family from New Zealand with the pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome, an autoinflammatory, variably expressed, erosive destructive form of arthritis.

**METHODS:** Information was gained through medical records and interviews of the affected patients and wider family. DNA sequencing was performed at Seay Center for Musculoskeletal Research Texas Scottish Rite Hospital for Children.

**RESULTS:** Five patients were affected over three generations with an E250Q mutation found on the CD2BP1 gene on chromosome 15. Common features included a severe, pauciarticular-onset, destructive peripheral arthritis, beginning at ages 5, 5, 2, 3 and 1(1/2) years. This combination marked cervical ankylosis (in two members), micrognathia and a more severe phenotype is unique. A third-generation family member treated early with DMARDs is following a less severe course. The skin involvement was variable, all with degrees of acne from puberty, though only one patient displayed pyoderma gangrenosum. A clear pattern of the arthritis switching off in adolescence and the triggering of skin disease was observed.

**CONCLUSIONS:** Differing degrees of joint destruction, and cervical ankylosis in this family with the E250Q mutation demonstrate PAPA syndrome's variable expression. Further understanding of this rare condition and its pathway may allow better targeting of treatments, not just for families with this specific syndrome but also for other, more common, forms of arthritis.

DOI: 10.1093/rheumatology/kei178

PMID: 16527883 [Indexed for MEDLINE]

4133. Childs Nerv Syst. 2006 Apr;22(4):334-7. Epub 2006 Mar 9.

Hydrocephalus in CINCA syndrome treated with anakinra.

Rigante D(1), Ansuini V, Caldarelli M, Bertoni B, La Torraca I, Stabile A.

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**INTRODUCTION:** Chronic infantile neurologic, cutaneous, articular (CINCA) syndrome is a rare congenital autoinflammatory disease characterized by neonatal-onset chronic meningitis, hydrocephalus, sensorineural hearing loss, persistent urticarial rash, deforming arthritis, and recurrent fever. This clinical entity is believed to result from dysregulation of cytokine production. No recommended treatment protocol exists so far for CINCA syndrome.

**CASE REPORT:** We report a 7-year-old child affected with CINCA syndrome in whom no therapy had resulted effective. Anakinra, an interleukin-1-receptor antagonist, was administered in a 1-year period with complete inflammatory symptom remission and dramatically ameliorated laboratory tests. This optimal response has been supported by the demonstration of a stabilized hydrocephalus upon magnetic resonance imaging and by an overall improvement of the neurodevelopmental issues.

**DISCUSSION:** This paper emphasizes and discusses the medical approach with anakinra in CINCA syndrome presenting with hydrocephalus in which a consistent control of the neurological picture can be obtained.

DOI: 10.1007/s00381-006-1280-3

PMID: 16525848 [Indexed for MEDLINE]

4134. J Nephrol. 2006 Jan-Feb;19(1):119-20.

Is MEFV P706 polymorphism important in familial Mediterranean fever patients?

Akar N, Ozturk A, Ozel D, Akar E, Ekim M.

PMID: 16523438 [Indexed for MEDLINE]

4135. J Nephrol. 2006 Jan-Feb;19(1):104-7.

Two sisters with familial Mediterranean fever: lack of correlation between genotype and phenotype?

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Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by attacks of fever and serositis. The most important complication of FMF is renal amyloidosis, which determines the prognosis. The gene coding the disease (MEFV) is identified on the 16th chromosome. The most common MEFV mutations are M694V, M680I, V726A and M694I located on exon 10 and E148Q located on exon 2. Unfortunately, genotype-phenotype correlation is not well established and there are unexplained ethnic differences in amyloidosis rates. We report two sisters with a common genotype (M694V/M694V) presenting with different phenotypic characteristics: one complaining of intermittent abdominal pain, arthritis and fever, while the other was suffering from intermittent pleuritis and fever during attacks. The observation of different phenotypic presentations with a common genotype in two family members shows that different phenotypes cannot be explained by particular mutations. To understand the correlation between genotypic and phenotypic FMF variants the existence of complex alleles, modifier loci, genetic heterogeneity and possible epigenetic factors should be studied

extensively.

PMID: 16523434 [Indexed for MEDLINE]

4136. Ter Arkh. 2005;77(12):39-43.

[A respiratory splash of monocytes and neutrophils in familial Mediterranean fever].

[Article in Russian]

Davtian TK, Avetisian SA, Akopian GS, Arutiunian VM.

AIM: To study spontaneous chemotaxis-, phagocytosis-, and proteinkinase C-mediated respiratory splash (RS) of neutrophils and monocytes in colchicin-untreated patients with familial Mediterranean fever (FMF).

MATERIAL AND METHODS: Of 17 FMF patients, 8 ones were examined during the attack, 9 patients--in fever-free period. Spontaneous and induced RS of peripheral blood neutrophils and monocytes was investigated with quantitative flow-cytofluorimetric method.

RESULTS: Compared to healthy donors, RS is characterized with activation of both spontaneous and induced production of free radicals. The activity and intensity of the RS in FMF was low in the attack vs in the attack-free period but monocytes population has a stable high activity of the RS.

CONCLUSION: Activation of neutrophilic RS in FMF patients is characterized by periodicity the direction of which is opposite to induced monocyte activation in the attack and in attack-free interval.

PMID: 16514818 [Indexed for MEDLINE]

4137. Klin Lab Diagn. 2006 Jan;(1):11-5.

[Study of volatile fatty acids in the blood of patients with periodic disease].

[Article in Russian]

Karagezian KG, Beloborodova NV, Ktsoian ZhA, Khachatryan ZA, Bořko NB, Kazarian KA, Sarkisian NN, Akopian GS.

Microecological "failures" are an important pathogenetic factor of different diseases and, in the authors' opinion, periodic disease (PD) is one of them. PD is a recessive disease characterized by fever attacks and neutrophil-mediated serous inflammation. A genetic factor has been established to be responsible for half the cases of PD, the influence of non-hereditary factors, particularly a role of the host automicroflora in the genesis of an inflammatory process, has been little studied. The authors' early studies indicate that there are changes in the qualitative and quantitative composition of microbial molecules in the blood of patients with PD. The anaerobic bacterial metabolites that are volatile fatty acids (VFAs) represent biologically active substances that affect the growth of the microflora, on the one hand, and the host's immunological responsiveness, on the other. Out of VFAs, only is acetic acid detectable in small quantities in the blood of healthy individuals. The other VFAs, namely propionic, valeric, butyric, and caproic acids and their isomers, are absent. Gas chromatography was used for qualitative and quantitative determination of the metabolites of anaerobic microorganisms in the blood of patients with PD (n = 13) during an attack and remission and in that of healthy volunteers (Armenians) (n = 5) of a control group from one Yerevan region. The blood samples from all the patients with PD displayed a significantly higher concentration of caproic acid while the latter was absent in the blood of the controls. This finding suggests that there is a specific shift in the structure of the microbiocenosis in patients with PD. It is conceivable that caproic acid plays a certain role in the pathogenesis of the disease under study. Further studies will deal with the association of some microbial molecules with the manifestation of an attack of PD, which may provide the key to the goal-oriented regulation of detected homeostatic disorders and to the management of the frequency of its attacks.

PMID: 16512475 [Indexed for MEDLINE]

4138. J Neurol. 2006 Jul;253(7):928-34. Epub 2006 Mar 6.

Inflammatory/demyelinating central nervous system involvement in familial Mediterranean fever (FMF): coincidence or association?

Akman-Demir G(1), Gul A, Gurol E, Ozdogan H, Bahar S, Oge AE, Gurvit H, Saruhan-Direskeneli G, Yazici H, Eraksoy M.

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**BACKGROUND AND OBJECTIVE:** Familial Mediterranean fever (FMF) is an inherited inflammatory disease characterized by recurrent febrile polyserositis. Central nervous system (CNS) involvement in FMF is uncommon, but recently cases with multiple sclerosis (MS) and FMF have been reported. Here we assess patients with both FMF and MS, in order to clarify any relationship between FMF and MS, and to evaluate disease characteristics.

**PATIENTS AND METHODS:** Our MS database between 1986-2005 was screened retrospectively, and patients with both FMF and inflammatory/demyelinating CNS disease were evaluated among a total of 2800 patients including definite MS (n = 2268) and other demyelinating disorders.

**RESULTS:** There were 12 patients with FMF, who developed a CNS disorder with multifocal white matter lesions. Median age at onset of FMF was 7 years, and median age at neurological onset was 26.8 years. Nine patients (including two siblings) had definite MS according to clinical and MRI findings, whereas 3 patients had atypical features suggesting other demyelinating disorders. Disease severity varied among the patients between very mild to a fatal course. All 8 patients evaluated for oligoclonal IgG bands in CSF were positive.

**CONCLUSION:** The rate of FMF among our patients with definite MS is almost 4 times the expected prevalence in Turkey. Our series including a sibling pair concordant for FMF and MS may suggest that similar genetic susceptibility and environmental factors might be responsible, although coincidence still remains a possibility. A prospective study on a larger sample seems to be justified.

DOI: 10.1007/s00415-006-0137-8

PMID: 16511642 [Indexed for MEDLINE]

4139. Arthritis Rheum. 2006 Mar;54(3):998-1008.

Neutrophils from patients with TNFRSF1A mutations display resistance to tumor necrosis factor-induced apoptosis: pathogenetic and clinical implications.

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**OBJECTIVE:** To explore tumor necrosis factor (TNF)-induced apoptosis in neutrophils from patients with TNF receptor-associated periodic syndrome (TRAPS) and to correlate the results with the different kinds of TNFRSF1A mutations.

**METHODS:** Two hundred sixty-five patients with clinically suspected inherited autoinflammatory syndrome were screened for mutations of the TNFRSF1A gene. Neutrophils were isolated from heparinized blood by dextran sedimentation and incubated with and without cycloheximide (CHX) and TNFalpha. Cell apoptosis was assessed by human annexin V binding, and caspase 8 activation was assessed by flow cytometry.

**RESULTS:** Twenty-one patients were found to carry a variant of the TNFRSF1A gene: 13 patients had an R92Q substitution, and 8 patients presented other missense substitutions, 1 splicing mutation, and 1 in-frame interstitial deletion.

Neutrophil stimulation with TNF and CHX was associated with induction of apoptosis in 12 normal controls and in 10 subjects with the R92Q mutation. Conversely, neutrophils from 8 TRAPS patients with mutations of cysteine or threonine residues or interstitial deletion did not show any induction of apoptosis after stimulation. The incidence of the R92Q mutation among patients with recurrent autoinflammatory syndromes was similar to that observed in the normal population.

**CONCLUSION:** Resistance to TNF-mediated apoptosis is a feature in TRAPS patients who have mutations of cysteine residues or interstitial deletion, and may play a pathogenic role. The R92Q mutation does not appear to be significantly associated with TRAPS.

DOI: 10.1002/art.21657

PMID: 16508982 [Indexed for MEDLINE]

4140. Nat Rev Immunol. 2006 Mar;6(3):183-95.

CATERPILLERS, pyrin and hereditary immunological disorders.

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The newly described CATERPILLER family (also known as NOD-LRR or NACHT-LRR) is comprised of proteins with a nucleotide-binding domain and a leucine-rich region. This family has gained rapid prominence because of its demonstrated and anticipated roles in immunity, cell death and growth, and diseases. CATERPILLER proteins are structurally similar to a subgroup of plant-disease-resistance (R) proteins and to the apoptotic protease activating factor 1 (APAF1). They provide positive and negative signals for the control of immune and inflammatory responses, and might represent intracellular sensors of pathogen products. Most importantly, they are genetically linked to several human immunological disorders.

DOI: 10.1038/nri1788

PMID: 16498449 [Indexed for MEDLINE]

4141. Nat Rev Immunol. 2006 Mar;6(3):173-82.

Neutrophils and immunity: challenges and opportunities.

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Scientists who study neutrophils often have backgrounds in cell biology, biochemistry, haematology, rheumatology or infectious disease. Paradoxically, immunologists seem to have a harder time incorporating these host-defence cells into the framework of their discipline. The recent literature discussed here indicates that it is appropriate for immunologists to take as much interest in



neutrophils as in their lymphohaematopoietic cousins with smooth nuclei. Neutrophils inform and shape immune responses, contribute to the repair of tissue as well as its breakdown, use killing mechanisms that enrich our concepts of specificity, and offer exciting opportunities for the treatment of neoplastic, autoinflammatory and autoimmune disorders.

DOI: 10.1038/nri1785

PMID: 16498448 [Indexed for MEDLINE]

4142. EMBO J. 2006 Mar 22;25(6):1353-63. Epub 2006 Feb 23.

Structural and functional insights into the B30.2/SPRY domain.

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The B30.2/SPRY domain is present in approximately 700 eukaryotic (approximately 150 human) proteins, including medically important proteins such as TRIM5alpha and Pyrin. Nonetheless, the functional role of this modular domain remained unclear. Here, we report the crystal structure of an SPRY-SOCS box family protein GUSTAVUS in complex with Elongins B and C, revealing a highly distorted two-layered beta-sandwich core structure of its B30.2/SPRY domain. Ensuing studies identified one end of the beta-sandwich as the surface interacting with an RNA helicase VASA with a 40 nM dissociation constant. The sequence variation in TRIM5alpha responsible for HIV-1 restriction and most of the mutations in Pyrin causing familial Mediterranean fever map on this surface, implicating the corresponding region in many B30.2/SPRY domains as the ligand-binding site. The amino acids lining the binding surface are highly variable among the B30.2/SPRY domains, suggesting that these domains are protein-interacting modules, which recognize a specific individual partner protein rather than a consensus sequence motif.

DOI: 10.1038/sj.emboj.7600994

PMCID: PMC1422157

PMID: 16498413 [Indexed for MEDLINE]

4143. Clin Rheumatol. 2006 Nov;25(6):885. Epub 2006 Jul 7.

Endocrine function and dysfunction in familial Mediterranean fever.

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DOI: 10.1007/s10067-006-0209-2

PMID: 16496077 [Indexed for MEDLINE]

4144. Proc Natl Acad Sci U S A. 2006 Feb 28;103(9):3292-7. Epub 2006 Feb 21.

Involvement of a tissue-specific autoantibody in skin disorders of murine systemic lupus erythematosus and autoinflammatory diseases.

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Human systemic lupus erythematosus (SLE) and its murine model, MRL lpr/lpr mice, are well known to develop a wide range of symptoms, such as glomerulonephritis, dermatitis, and arthritis, as an immune-complex disease. However, the deposition of circulating immune complex does not fully explain the tissue specificity of disease. Tissue-specific autoantigens may also be involved in tissue inflammation. In this study, desmoglein 3 (Dsg3), a major component of epidermal desmosomes, was identified as a skin-specific autoantigen. Several murine models of skin inflammation were found to develop autoantibodies to Dsg3 tightly correlated with disease aggravation, especially in MRL lpr/lpr mice. Furthermore, SLE-prone skin disease-free FcgammaRIIb-deficient mice developed skin inflammation upon immunization with Dsg3. Taken together with histological

studies, we concluded that skin-specific Dsg3 serves as an autoantigen in chronic skin inflammatory diseases accompanied by mast cell degranulation, including both murine SLE and other autoinflammatory diseases.

DOI: 10.1073/pnas.0510756103

PMCID: PMC1413900

PMID: 16492738 [Indexed for MEDLINE]

4145. Joint Bone Spine. 2006 May;73(3):334-6. Epub 2005 Dec 1.

Lack of association between familial Mediterranean fever and angiotensin converting enzyme gene polymorphism.

Calgüneri M, Oztürk MA, Kiraz S, Ertenli I, Onat AM, Ureten K, Ozbalkan Z, Haznedaroğlu IC.

Erratum in

Joint Bone Spine. 2006 Oct;73(5):579. Calgüneri, Oztürk Meral [corrected to Calgüneri, Meral].

DOI: 10.1016/j.jbspin.2005.08.001

PMID: 16488647 [Indexed for MEDLINE]

4146. J Clin Rheumatol. 2006 Feb;12(1):34-6.

Diffuse pulmonary amyloidosis that mimics interstitial lung disease in a patient with familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is an autosomal-recessive disorder characterized by recurrent attacks of fever, serositis, and arthritis.

Amyloidosis, which mostly affects the kidneys, represents the most serious

complication of the disease. The lungs, particularly after the onset of renal failure, may be asymptotically involved in some of the patients with AA amyloidosis secondary to FMF. However, clinically detectable pulmonary amyloidosis is quite rare, and only 2 cases of pulmonary amyloidosis secondary to FMF have been reported so far. We describe a patient with pulmonary amyloidosis who had pulmonary hypertension and presented with clinical and radiologic features highly suggestive of interstitial lung disease. Amyloidosis was diagnosed only after lung biopsy. FMF was confirmed by molecular analysis.

DOI: 10.1097/01.rhu.0000200424.58122.38

PMID: 16484879 [Indexed for MEDLINE]

4147. Clin Exp Rheumatol. 2006 Jan-Feb;24(1 Suppl 40):S79-85.

Autoinflammatory syndromes.

Galeazzi M(1), Gasbarrini G, Ghirardello A, Grandemange S, Hoffman HM, Manna R, Podswiadek M, Punzi L, Sebastiani GD, Touitou I, Doria A.

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The autoinflammatory disorders are a new and expanding classification of inflammatory diseases characterized by recurrent episodes of systemic inflammation in the absence of pathogens, autoantibodies or antigen specific T cells. These disorders are caused by primary dysfunction of the innate immune system, without evidence of adaptive immune dysregulation. Innate immune abnormalities include aberrant responses to pathogen associated molecular patterns (PAMPs) like lipopolysaccharide and peptidoglycan, prominent neutrophilia in blood and tissues, and dysregulation of inflammatory cytokines (IL-1 $\beta$ , TNF- $\alpha$ ) or their receptors. The autoinflammatory diseases comprise both hereditary (Familial Mediterranean Fever, FMF; Mevalonate Kinase Deficiency, MKD; TNF Receptor Associated Periodic Syndrome, TRAPS; Cryopyrin Associated Periodic Syndrome, CAPS; Blau syndrome; Pyogenic sterile Arthritis, Pyoderma gangrenosum and Acne syndrome, PAPA; Chronic Recurrent Multifocal Osteomyelitis, CRMO) and multifactorial (Crohn's and Behçet's diseases) disorders. Mutations responsible for FMF, TRAPS, CAPS, PAPA are in proteins involved in modulation of inflammation and apoptosis.

PMID: 16466630 [Indexed for MEDLINE]

4148. Arthritis Rheum. 2006 Feb;54(2):508-14.

PYPAF1 nonsense mutation in a patient with an unusual autoinflammatory syndrome: role of PYPAF1 in inflammation.

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**OBJECTIVE:** To gain insight into the pathophysiology of an unusual autoinflammatory syndrome, in a patient of Armenian origin, that mimicked familial Mediterranean fever (FMF) but with episodes triggered by generalized exposure to cold, and to further elucidate the controversial function of the protein encoded by PYPAF1, whose mutations (exclusively missense to date) have been identified in 3 hereditary recurrent fever syndromes.

**METHODS:** The patient's DNA was screened for mutations in both MEFV, the gene responsible for FMF, and PYPAF1. The ability of different recombinant PYPAF1 isoforms, expressed in HEK 293 cells, to regulate NF-kappaB signaling was subsequently assessed.

**RESULTS:** No disease-causing mutation was found in MEFV. However, a nonsense mutation (p.Arg554X) was identified in PYPAF1; this defect resulted in a truncated protein lacking all leucine-rich repeats. Study of the wild-type and mutant PYPAF1 recombinant proteins revealed that PYPAF1 inhibited NF-kappaB proinflammatory pathways, and that the identified nonsense mutation impaired this property.

**CONCLUSION:** These molecular and clinical findings, together with the clinical manifestations in the patient, which call into question the current nosology of the hereditary recurrent fever syndromes, are consistent with the hypothesis that PYPAF1 acts as an inhibitor of NF-kappaB signaling. They also provide a clear elucidation of the functional consequences of this nonsense PYPAF1 mutation not previously described in the literature, which result in a partial loss of function and may thereby explain the pathophysiology of the autoinflammatory syndrome observed in this patient.

DOI: 10.1002/art.21618

PMID: 16447225 [Indexed for MEDLINE]

4149. Clin Rheumatol. 2006 Nov;25(6):773-7. Epub 2006 Jan 26.

TNF-receptor-associated periodic syndrome (TRAPS): an autosomal dominant multisystem disorder.

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The TNF-receptor-associated periodic syndrome (TRAPS) is an autosomal dominant auto-inflammatory disorder, characterized by recurrent febrile attacks and localized inflammation. TRAPS is caused by mutations in the gene encoding the TNF Receptor Super Family 1A (TNFRSF1A) on chromosome 12p13. However, the incomplete penetrance and genetic heterogeneity have been reported in this syndrome. Although the ethnic diversity and clinical heterogeneity may propose the role of other genes in the pathogenesis of TRAPS, some low-penetrance TNFRSF1A variants contribute to atypical inflammatory responses in other autoimmune diseases. Furthermore, molecular studies on TRAPS and other auto-inflammatory disorders could be suggested to identify additional genes coding the molecules in the TNF signalling process.

DOI: 10.1007/s10067-005-0198-6

PMID: 16447098 [Indexed for MEDLINE]

4150. J Am Acad Dermatol. 2006 Feb;54(2):318-21.

A recurrent rash with fever and arthropathy.

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DOI: 10.1016/j.jaad.2005.07.007

PMID: 16443062 [Indexed for MEDLINE]

4151. Ann Rheum Dis. 2006 Sep;65(9):1154-7. Epub 2006 Jan 26.

Intrafamilial segregation analysis of the p.E148Q MEFV allele in familial Mediterranean fever.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is the most frequent of the recurrent inherited fevers. This autosomal recessive disorder is characterised by periodic episodes of fever and serositis that commonly affect the people of Arab, Armenian, Sephardic Jewish and Turkish origin. Most of the described MEFV gene anomalies responsible for the disease are missense mutations. In the absence of any functional test, epidemiological studies or pedigree analyses are the only means of proving the deleterious character of these sequence variations. Evidence was provided by our recent study using a population-based approach, that the p.E148Q allele is probably a benign polymorphism and not a disease-causing mutation. Its implication in FMF remains, however, controversial.

**OBJECTIVE:** To evaluate the segregation of the p.E148Q MEFV allele with FMF disease by using pedigree analysis.

**PARTICIPANTS:** 21 patients and 48 unaffected relatives belonging to 18 independent families with FMF.

**RESULTS:** Segregation analysis of the p.E148Q allele was compatible with a Mendelian autosomal recessive transmission of the disease phenotype in only three families. In 15 of 18 families, segregation was partly or completely defective. The p.E148Q allele was not transmitted to 14 of 19 (74%) affected children.

**CONCLUSIONS:** No evidence of preferential transmission of p.E148Q from heterozygous parents to their affected offspring was observed. MEFV is not

associated with the clinical manifestations of several patients carrying this variant. Considering p.E148Q to be a benign polymorphism should reduce the possibility of false-positive diagnoses, while highlighting genetic heterogeneity in FMF.

DOI: 10.1136/ard.2005.048124

PMCID: PMC1798299

PMID: 16439437 [Indexed for MEDLINE]

4152. C R Biol. 2006 Feb;329(2):71-4. Epub 2006 Jan 10.

Prevalence and distribution of MEFV mutations among Arabs from the Maghreb patients suffering from familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is an autosomal recessive inherited disease caused by mutations in MEFV. This disease is characterized by recurrent episodes of fever accompanied with topical signs of inflammation. Some patients can develop renal amyloidosis. We prospectively investigated MEFV mutations in a cohort of 209 unrelated Arab patients from Maghreb (85 Algerians, 87 Moroccans, and 37 Tunisians) with a clinical suspicion of FMF. FMF is the main cause of periodic fever syndrome in Maghreb. The most frequent MEFV mutations in this cohort were M694V and M694I. These mutations account for different proportions of the MEFV mutations in Algeria (5%, 80%), Morocco (49%, 37%), and Tunisia (50%, 25%) patients. M694I mutation is specific to the Arab population from Maghreb. Other rare mutations were observed: M680L, M680I, A744S, V726A, and E148Q. We estimated the frequency of MEFV mutation carriers among the Arab Maghrebian population at around 1%, which is significantly lower than in non-Ashkenazi Jews, Armenians or Turks.

DOI: 10.1016/j.crv.2005.11.005

PMID: 16439335 [Indexed for MEDLINE]



4153. Bull Acad Natl Med. 2005 Jun;189(6):1235-46; discussion 1246-8.

[Hereditary recurrent fever syndromes].

[Article in French]

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Four diseases presenting mainly as intermittent bouts of inflammatory symptoms have been clinically and genetically characterized. At the head of this group is familial Mediterranean fever, which affects thousands of patients of Mediterranean ancestry. The other three entities are the tumor necrosis factor receptor superfamily 1A-associated periodic fever syndrome (TRAPS) with a dominant mode of inheritance; hyperimmunoglobulinemia D and periodic fever syndrome (HIDS); and the most recently recognized entity, which includes Muckle Wells syndrome, familial cold urticaria, and the chronic infantile neurological cutaneous and articular (CINCA) syndrome. Proper diagnosis of these entities is needed to begin specific clinical and therapeutic management.

PMID: 16433446 [Indexed for MEDLINE]

4154. J Intern Med. 2006 Feb;259(2):209-13.

Intra-abdominal abscess in a patient with tumour necrosis factor receptor-associated periodic syndrome.

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Tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is an

autoinflammatory disorder characterized by periodic attacks of fever and inflammation, due to mutations in the gene coding for the TNF type I receptor (TNFRSF1A). A 16-year-old patient with the diagnosis of TRAPS was admitted to hospital because of fever and abdominal pain. Initially, the symptoms were interpreted as manifestations of another TRAPS attack, but the patient's condition worsened, despite treatment with corticosteroids and antibiotics. A repeated computer tomography revealed an intra-abdominal abscess, which necessitated urgent surgical intervention. This case stresses the importance of differential diagnostic vigilance when dealing with patients with rare genetic diseases.

DOI: 10.1111/j.1365-2796.2005.01601.x

PMID: 16420550 [Indexed for MEDLINE]

4155. Pigment Cell Res. 2006 Feb;19(1):51-7.

HLA class II haplotype DRB1\*04-DQB1\*0301 contributes to risk of familial generalized vitiligo and early disease onset.

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Generalized vitiligo is a common autoimmune disorder characterized by white patches of skin and overlying hair caused by loss of pigment-forming melanocytes from involved areas. Familial clustering of vitiligo is not uncommon, and patients and their relatives are at increased risk for a specific complex of other autoimmune diseases. Compared with sporadic vitiligo, familial vitiligo is characterized by earlier disease onset and greater risk and broader repertoire of autoimmunity, suggesting a stronger genetic component, and perhaps stronger associations with specific alleles. To determine whether the major histocompatibility complex (MHC) contributes to the familial clustering of vitiligo and vitiligo-associated autoimmune/autoinflammatory diseases, we performed case-control and family-based association analyses of HLA class II-DRB1 and -DQB1 alleles and haplotypes in affected probands and their parents from 76 European-American Caucasian families with familial vitiligo. Affected probands

showed a significantly increased frequency of DRB1\*04-DQB1\*0301 and a significantly decreased frequency of DRB1\*15-DQB1\*0602 compared with a large sample of reference chromosomes. Family-based association analyses confirmed these results. Probands with DRB1\*04-DQB1\*0301 developed vitiligo an average of 13.32 yr earlier than probands with DRB1\*15-DQB1\*0602. Overall, our results indicate that specific MHC-linked genetic variation contributes to risk of familial vitiligo, although HLA does not completely explain familial clustering of vitiligo-associated autoimmune/autoinflammatory diseases.

DOI: 10.1111/j.1600-0749.2005.00279.x

PMID: 16420246 [Indexed for MEDLINE]

4156. J Child Neurol. 2005 Dec;20(12):990-3.

Reversible posterior leukoencephalopathy syndrome: report of three cases.

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Reversible posterior leukoencephalopathy syndrome is characterized clinically by headache, abnormalities of mental status and visual perception, and seizures. Despite its diverse causes, common precipitating factors are defined as abrupt elevations of blood pressure, renal decompensation, fluid retention, and immunosuppressive therapy. We report three children with reversible posterior leukoencephalopathy syndrome presenting with generalized seizures and headache. The causes of reversible posterior leukoencephalopathy syndrome were considered to be acute hypertension and immunosuppressive therapy in case 1 with systemic lupus erythematosus, chemotherapy (vincristine and/or actinomycin-D) and hyponatremia in case 2, and acute hypertension in case 3, admitted with a familial Mediterranean fever attack. In light of these cases, we review the literature for the etiology, clinical and laboratory findings, and pathogenetic mechanisms of the disease.

DOI: 10.1177/08830738050200121201

PMID: 16417849 [Indexed for MEDLINE]

4157. Microvasc Res. 2006 Mar;71(2):103-7. Epub 2006 Jan 18.

Human endothelial cells express NOD2/CARD15 and increase IL-6 secretion in response to muramyl dipeptide.

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Mutations in the human NOD2/CARD15 gene cause Blau syndrome, an autoinflammatory disorder involving the joints, skin and eyes. Insights into the mechanism of this association may be gained by a further understanding of where NOD2 is expressed. The objective of this study was to analyze ocular endothelial cells for NOD2 expression. Human ocular tissue was analyzed by immunohistology using anti-NOD2 antisera. RNA isolated from iris, choroid and endothelial cell lines was analyzed by reverse transcription-PCR and real-time quantitative PCR. Gene regulation was studied by treating endothelial cells with TNF-alpha and IFN-gamma. Functional responses were assessed by measuring IL-6 release from endothelial cells treated with muramyl dipeptide (MDP), synthetic lipopeptide (Pam3CSK4) and lipopolysaccharide (LPS). Immunohistological analysis revealed staining of endothelial cells in the uveal tract. NOD2 expression was detected in primary ocular endothelial cell cultures, and levels increased in response to inflammatory cytokines. Endothelial cells from choroid demonstrated enhanced release of IL-6 in response to MDP, and synergy was observed following treatment with MDP and either Pam3CSK4 or LPS. The observations that endothelial cells express NOD2, upregulate NOD2 in response to stimuli known to promote NOD2 expression and show synergistic cytokine responses to MDP and TLR ligands previously shown to be mediated by NOD2 are informative since they may be relevant to pathogenic mechanisms leading to the spectrum of inflammation seen in Blau syndrome.

DOI: 10.1016/j.mvr.2005.11.010

PMID: 16414084 [Indexed for MEDLINE]

4158. Nature. 2006 Mar 9;440(7081):228-32. Epub 2006 Jan 11.

Cryopyrin activates the inflammasome in response to toxins and ATP.

Mariathasan S(1), Weiss DS, Newton K, McBride J, O'Rourke K, Roose-Girma M, Lee WP, Weinrauch Y, Monack DM, Dixit VM.

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A crucial part of the innate immune response is the assembly of the inflammasome, a cytosolic complex of proteins that activates caspase-1 to process the proinflammatory cytokines interleukin (IL)-1 $\beta$  and IL-18. The adaptor protein ASC is essential for inflammasome function, binding directly to caspase-1 (refs 3, 4), but the triggers of this interaction are less clear. ASC also interacts with the adaptor cryopyrin (also known as NALP3 or CIAS1). Activating mutations in cryopyrin are associated with familial cold autoinflammatory syndrome, Muckle-Wells syndrome and neonatal onset multisystem inflammatory disease, diseases that are characterized by excessive production of IL-1 $\beta$ . Here we show that cryopyrin-deficient macrophages cannot activate caspase-1 in response to Toll-like receptor agonists plus ATP, the latter activating the P2X7 receptor to decrease intracellular K<sup>+</sup> levels. The release of IL-1 $\beta$  in response to nigericin, a potassium ionophore, and maitotoxin, a potent marine toxin, was also found to be dependent on cryopyrin. In contrast to Asc<sup>-/-</sup> macrophages, cells deficient in the gene encoding cryopyrin (Cias1<sup>-/-</sup>) activated caspase-1 and secreted normal levels of IL-1 $\beta$  and IL-18 when infected with Gram-negative *Salmonella typhimurium* or *Francisella tularensis*. Macrophages exposed to Gram-positive *Staphylococcus aureus* or *Listeria monocytogenes*, however, required both ASC and cryopyrin to activate caspase-1 and secrete IL-1 $\beta$ . Therefore, cryopyrin is essential for inflammasome activation in response to signalling pathways triggered specifically by ATP, nigericin, maitotoxin, *S. aureus* or *L. monocytogenes*.

DOI: 10.1038/nature04515

PMID: 16407890 [Indexed for MEDLINE]

4159. Nature. 2006 Mar 9;440(7081):237-41. Epub 2006 Jan 11.

Gout-associated uric acid crystals activate the NALP3 inflammasome.

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Development of the acute and chronic inflammatory responses known as gout and pseudogout are associated with the deposition of monosodium urate (MSU) or calcium pyrophosphate dihydrate (CPPD) crystals, respectively, in joints and periarticular tissues. Although MSU crystals were first identified as the aetiological agent of gout in the eighteenth century and more recently as a 'danger signal' released from dying cells, little is known about the molecular mechanisms underlying MSU- or CPPD-induced inflammation. Here we show that MSU and CPPD engage the caspase-1-activating NALP3 (also called cryopyrin) inflammasome, resulting in the production of active interleukin (IL)-1 $\beta$  and IL-18. Macrophages from mice deficient in various components of the inflammasome such as caspase-1, ASC and NALP3 are defective in crystal-induced IL-1 $\beta$  activation. Moreover, an impaired neutrophil influx is found in an in vivo model of crystal-induced peritonitis in inflammasome-deficient mice or mice deficient in the IL-1 $\beta$  receptor (IL-1R). These findings provide insight into the molecular processes underlying the inflammatory conditions of gout and pseudogout, and further support a pivotal role of the inflammasome in several autoinflammatory diseases.

DOI: 10.1038/nature04516

PMID: 16407889 [Indexed for MEDLINE]

4160. Nature. 2006 Mar 9;440(7081):233-6. Epub 2006 Jan 11.

Bacterial RNA and small antiviral compounds activate caspase-1 through cryopyrin/Nalp3.

Kanneganti TD(1), Ozören N, Body-Malapel M, Amer A, Park JH, Franchi L, Whitfield J, Barchet W, Colonna M, Vandenabeele P, Bertin J, Coyle A, Grant EP, Akira S, Núñez G.

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Missense mutations in the CIAS1 gene cause three autoinflammatory disorders: familial cold autoinflammatory syndrome, Muckle-Wells syndrome and neonatal-onset multiple-system inflammatory disease. Cryopyrin (also called Nalp3), the product of CIAS1, is a member of the NOD-LRR protein family that has been linked to the activation of intracellular host defence signalling pathways. Cryopyrin forms a multi-protein complex termed 'the inflammasome', which contains the apoptosis-associated speck-like protein (ASC) and caspase-1, and promotes caspase-1 activation and processing of pro-interleukin (IL)-1 $\beta$  (ref. 4). Here we show the effect of cryopyrin deficiency on inflammasome function and immune responses. Cryopyrin and ASC are essential for caspase-1 activation and IL-1 $\beta$  and IL-18 production in response to bacterial RNA and the imidazoquinoline compounds R837 and R848. In contrast, secretion of tumour-necrosis factor- $\alpha$  and IL-6, as well as activation of NF- $\kappa$ B and mitogen-activated protein kinases (MAPKs) were unaffected by cryopyrin deficiency. Furthermore, we show that Toll-like receptors and cryopyrin control the secretion of IL-1 $\beta$  and IL-18 through different intracellular pathways. These results reveal a critical role for cryopyrin in host defence through bacterial RNA-mediated activation of caspase-1, and provide insights regarding the pathogenesis of autoinflammatory syndromes.

DOI: 10.1038/nature04517

PMID: 16407888 [Indexed for MEDLINE]

4161. J Eur Acad Dermatol Venereol. 2006 Jan;20(1):100-1.

Treatment of severe acne in Familial Mediterranean Fever.

Kaptanoglu AF, Karademir A.

DOI: 10.1111/j.1468-3083.2005.01294.x

PMID: 16405620 [Indexed for MEDLINE]

4162. Eksp Klin Farmakol. 2005 Nov-Dec;68(6):36-9.

[The effect of colchicine on the periodicity of the spontaneous and induced respiratory burst of granulocytes and monocytes during familial Mediterranean fever].

[Article in Russian]

Akopian VP, Avetisian SA, Davtian TK.

The influence of colchicine on the spontaneous and chemotaxis-, protein kinase C-, and phagocytosis-induced respiratory burst of neutrophils and monocytes in the peripheral blood of patients with familial Mediterranean fever (FMF) has been studied. The transient activation of neutrophils and monocytes on the level of a single cell has been monitored by means of flow cytofluorimetry. It is shown that colchicine blocks the induction of chemotaxis-, phagocytosis-, and protein kinase C-dependent respiratory burst in vitro, as well as the increased pro-oxidant transient activation of neutrophils and monocytes of FMF patients, both in the period of remission and during the FMF attack. Colchicine stimulates the intensity of the spontaneous respiratory burst of neutrophils and monocytes in patients in the course of remission and during the FMF attack. At the same time, the drug effectively suppresses the periodicity of the multidirectional transient activation of the respiratory burst of effector cells during FMF.

PMID: 16405032 [Indexed for MEDLINE]

4163. Rheumatology (Oxford). 2006 Jun;45(6):746-50. Epub 2006 Jan 10.

Clinical and subclinical inflammation in patients with familial Mediterranean fever and in heterozygous carriers of MEFV mutations.

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**OBJECTIVE:** To prospectively monitor inflammatory activity over a prolonged period in a cohort of Turkish patients with FMF, their healthy relatives and healthy controls and to relate this to their MEFV genotypes.

**METHODS:** 43 patients with FMF and 75 of their asymptomatic relatives underwent fortnightly assessments and venesection for measurement of CRP and SAA over 5 months. 50 unrelated healthy population matched controls were also studied. MEFV genotyping was performed on all participants and comparisons were made between the different groups.

**RESULTS:** Paired MEFV mutations were detected in 84% of FMF patients and single mutations in 12%. Substantial acute phase reactivity was seen among the patients with FMF during attacks (median SAA 693 mg/l, CRP 115 mg/l). Between attacks there was also some inflammatory activity (median SAA 6 mg/l, CRP 4 mg/l). Among healthy controls 16% were heterozygotes for MEFV mutations and 4% had two mutations. As expected there was a substantial carrier rate among healthy relatives with mutations detected in almost 92%. Asymptomatic MEFV heterozygotes had elevated acute phase proteins compared to wild type subjects.

**CONCLUSION:** Substantial sub-clinical inflammation occurs widely and over prolonged periods in patients with FMF, indicating that the relatively infrequent clinically overt attacks represent the 'tip of the iceberg' in this disorder.

Both basal and peak acute phase protein concentrations were greater in MEFV heterozygotes than in wild-type controls, regardless of mutation demonstrating a 'pro-inflammatory' phenotype among FMF carriers. Upregulation of the acute phase response among carriers of FMF may augment their innate host response and contribute to better resistance to infection.

DOI: 10.1093/rheumatology/kei279

PMID: 16403826 [Indexed for MEDLINE]

4164. Gastroenterology. 2006 Jan;130(1):172-8.

Severe TNF receptor-associated periodic syndrome due to 2 TNFRSF1A mutations including a new F60V substitution.

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Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is typically characterized by episodic fever, myalgia, skin rash, conjunctivitis, and abdominal cramps. Recently, mutations in the TNFRSF1A gene on chromosome 12p13 encoding tumor necrosis factor receptor type 1 have been linked to this autoinflammatory syndrome. We report the case of a 29-year-old white woman who experienced periodic inflammatory manifestations with fever up to 40 degrees C, leukocytosis, and elevation of C-reactive protein level (>100 mg/L) in conjunction with acute peritonitis of unknown origin since the age of 19 years. The patient had undergone 2 laparotomies with appendectomy and left hemicolectomy. Familial Mediterranean fever was excluded by sequencing of the MEFV gene. In view of the possibility of TRAPS, sequence analysis of the TNFRSF1A gene was also performed. The patient carried a novel T-->G substitution in exon 3, leading to the replacement of phenylalanine by valine at amino acid position 60 (F60V), as well as the common R92Q low-penetrance mutation, encoded by exon 4. Upon the next flare, the patient started corticosteroid therapy, resulting in complete relief and normalization of elevated C-reactive protein levels. To the best of our knowledge, we report the first case of compound heterozygosity for 2 TNFRSF1A gene mutations, including a novel one that causes a severe form of TRAPS that responds to anti-inflammatory treatment. A history of recurrent sterile peritonitis should prompt genotyping for periodic fever syndromes.

DOI: 10.1053/j.gastro.2005.09.014

PMID: 16401480 [Indexed for MEDLINE]

4165. Rheumatol Int. 2006 Jul;26(9):862-4. Epub 2006 Jan 6.

Plasma interleukin-10 and interleukin-12 levels in patients with familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent attacks of fever, polyserositis and arthritis. A vast array of cytokines were analysed in these patients, however, little is known about the pro-inflammatory cytokine interleukin (IL)-12. Plasma IL-12 and IL-10 were measured in 24 patients with FMF (19 active, 5 inactive) and 18 healthy controls by ELISA. From 15 active patients blood was also drawn in attack-free period. Mean plasma IL-12 levels of the FMF patients (mean  $\pm$  SEM,  $6.84 \pm 3.59$  pg/ml) were higher than the controls ( $0.13 \pm 0.09$  pg/ml,  $P < 0.001$ ). Mean IL-12 levels of active ( $7.02 \pm 5.23$  pg/ml) and inactive patients ( $6.89 \pm 5.61$  pg/ml) were comparable, and they were higher compared to controls ( $P \leq 0.001$ ). Mean plasma IL-10 levels of the total FMF patients ( $3.01 \pm 1.53$  pg/ml) were also higher than the controls ( $P = 0.024$ ). Patients had higher IL-10 levels in attacks ( $3.83 \pm 2.02$  pg/ml) compared to levels when they were in remission ( $1.86 \pm 1.59$  pg/ml,  $P = 0.046$ ). Significantly elevated IL-12 levels in FMF patients regardless of activity may suggest the presence of a pro-inflammatory state also in the inactive period of FMF. Significant increase in IL-10 levels in FMF group may point to the compensatory suppression of inflammation in active periods of the disease.

DOI: 10.1007/s00296-005-0099-7

PMID: 16397779 [Indexed for MEDLINE]

4166. Blood. 2006 Apr 15;107(8):3350-8. Epub 2006 Jan 5.

Mutation of mouse Mayp/Pstpip2 causes a macrophage autoinflammatory disease.

Grosse J(1), Chitu V, Marquardt A, Hanke P, Schmittwolf C, Zeitlmann L, Schropp P, Barth B, Yu P, Paffenholz R, Stumm G, Nehls M, Stanley ER.

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Macrophage actin-associated tyrosine phosphorylated protein (MAYP)/PSTPIP2, a PCH protein, is involved in the regulation of macrophage motility. Mutations in a closely related gene, PSTPIP1/CD2BP1, cause a dominantly inherited autoinflammatory disorder known as PAPA syndrome. A mutant mouse obtained by chemical mutagenesis exhibited an autoinflammatory disorder characterized by macrophage infiltration and inflammation, leading to osteolysis and necrosis in

paws and necrosis of ears. Positional cloning of this recessive mutation, termed Lupo, identified a T to A nucleotide exchange leading to an amino acid substitution (I282N) in the sequence of MAYP. Mayp(Lp/Lp) disease was transferable by bone marrow transplantation and developed in the absence of lymphocytes. Consistent with the involvement of macrophages, lesion development could be prevented by the administration of clodronate liposomes. MAYP is expressed in monocytes/macrophages and in a Mac1<sup>+</sup> subfraction of granulocytes. LPS stimulation increases its expression in macrophages. Because of the instability of the mutant protein, MAYP expression is reduced 3-fold in Mayp(Lp/Lp) macrophages and, on LPS stimulation, does not rise above the level of unstimulated wild-type (WT) cells. Mayp(Lp/Lp) mice expressed elevated circulating levels of several cytokines, including MCP-1; their macrophages exhibited altered cytokine production in vitro. These studies suggest that MAYP plays an anti-inflammatory role in macrophages.

DOI: 10.1182/blood-2005-09-3556

PMCID: PMC1895761

PMID: 16397132 [Indexed for MEDLINE]

4167. J Leukoc Biol. 2006 Mar;79(3):611-5. Epub 2005 Dec 30.

Role of the pyrin M694V (A2080G) allele in acute myocardial infarction and longevity: a study in the Sicilian population.

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A proinflammatory genotype seems to contribute significantly to the risk of developing coronary heart disease (CHD). Conversely, the susceptibility alleles to inflammatory disease should be infrequent in the genetic background favoring longevity. In fact, in a modern environment, attainment of longevity is facilitated by an anti-inflammatory status. To evaluate whether inflammatory alleles of pyrin, the gene responsible for familial Mediterranean fever (FMF) may play an opposite role in CHD and in longevity, we examined three FMF-associated

mutations, M694V (A2080G), M694I (G2082A), and V726A (T2177C), encoded by the FMF gene (MEFV) in 121 patients affected by acute myocardial infarction (AMI), in 68 centenarians, and in 196 age-matched controls from Sicily. None of the Sicilian subjects studied carried the V726A and the M694I FMF-related mutations. The proinflammatory M694V (A2080G) mutation was the only one we found, which was over-represented significantly in CHD patients and under-represented in oldest old, and intermediate values were in healthy, young controls. After adjustment for well-recognized AMI risk factors, the M694V allele still predicted a significant risk to develop AMI. So, according to these results, we suggest that carrying the proinflammatory M694V pyrin allele may increase the risk to develop AMI. Conversely, the wild-type pyrin genotype may predispose to a greater chance to live longer in a modern environment with reduced pathogen load and improved control of severe infections by antibiotics. All these data indicate a strong relationship among inflammation, genetics, CHD, and longevity.

DOI: 10.1189/jlb.0705416

PMID: 16387839 [Indexed for MEDLINE]

4168. J Pediatr Gastroenterol Nutr. 2006 Jan;42(1):9-15.

Combined use of noninvasive tests is useful in the initial diagnostic approach to a child with suspected inflammatory bowel disease.

Canani RB(1), de Horatio LT, Terrin G, Romano MT, Miele E, Staiano A, Rapacciuolo L, Polito G, Bisesti V, Manguso F, Vallone G, Sodano A, Troncone R.

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**OBJECTIVE:** To assess the effectiveness of the combined use of fecal calprotectin (FC), anti-Saccharomyces cerevisiae antibody (ASCA), perinuclear staining antineutrophil antibody (pANCA), small intestinal permeability test (IP), and bowel wall ultrasonography measurement (BWUS) in the diagnostic work-up of children with suspected inflammatory bowel disease (IBD).

**METHODS:** All children referred for initial assessment of possible IBD were eligible. Patients with symptoms or signs (right-lower quadrant mass, perianal disease, or hematochezia) mandating a complete work-up for IBD were excluded. All

enrolled patients underwent a clinical, laboratory, radiographic, and endoscopic evaluation including biopsy examinations. The immunoglobulin (Ig)G and IgA ASCA, IgG pANCA, FC, IP, and BWUS were tested in all patients at the initial assessment.

**RESULTS:** A final diagnosis of IBD was made in 27 patients: 17 Crohn disease and 10 ulcerative colitis. Eighteen children had other gastrointestinal diagnoses (8 functional bowel disorders, 5 food allergy-mediated diseases, 4 infectious enterocolitis, 1 familial Mediterranean fever). In patients with simultaneous abnormal values of FC, BWUS, and ASCA/pANCA, the estimated probability of having IBD was 99.47%. Patients with negative results on all tests had a 0.69% of probability of IBD.

**CONCLUSIONS:** The incorporation of noninvasive diagnostic tests into the initial diagnostic approach may avoid unnecessary invasive procedures and facilitate clinical decision-making when the diagnosis of IBD in children is initially uncertain.

PMID: 16385247 [Indexed for MEDLINE]

4169. Eur J Med Genet. 2005 Oct-Dec;48(4):412-20. Epub 2005 Jun 20.

Familial Mediterranean fever (FMF) in Lebanon and Jordan: a population genetics study and report of three novel mutations.

Medlej-Hashim M(1), Serre JL, Corbani S, Saab O, Jalkh N, Delague V, Chouery E, Salem N, Loiselet J, Lefranc G, Mégarbané A.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease mostly frequent in Mediterranean populations. Over 50 mutations have been identified in the gene responsible for the disease, MEFV. The present study reports the frequencies of MEFV mutations in 558 Lebanese and 55 Jordanian FMF patients and points out the severity of the M694V frequently observed mutation among these patients. Three novel mutations, T177I, S108R and E474K were also identified in the Lebanese group. An excess of homozygotes and a deficit of heterozygotes were

observed in both samples when compared to the expected number of observed genotypes under the Hardy-Weinberg hypothesis. Homozygotes for M694V and M694I were still in excess in the Lebanese group of patients, even after consanguinous homozygotes were removed, or population structure was considered. This excess is therefore neither due to consanguinity nor to subgroups in the Lebanese population, but rather to more remote consanguinity or to a selection bias favoring the census of these genotypes. The fact that FMF female patients were less censused than male patients may be due to the greater resistance of females to pain and to the possibility of confusing abdominal and gynecological pain. The phenotypic heterogeneity of the FMF could then originate both from genetic causes like allelic heterogeneity or modulating genes, and cultural background facing the physiological consequences of genotypes at risk.

DOI: 10.1016/j.ejmg.2005.05.010

PMID: 16378925 [Indexed for MEDLINE]

4170. J Clin Rheumatol. 2005 Dec;11(6):329-30.

Hereditary periodic fever syndrome sans fever or distinct periodicity presenting with psychosis.

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The genetic basis for several hereditary periodic fever syndromes has been identified and consequently, the phenotypic spectrum of these disorders has broadened. We describe a young woman with tumor necrosis factor receptor-associated periodic syndrome (TRAPS), proven by mutational analysis, who presented with psychosis but without fever, symptom periodicity, or similar family medical history. This patient represents the first case of TRAPS-associated psychosis. This case illustrates the importance of mutation analysis for this group of disorders in individuals presenting with unexplained inflammatory symptoms and recurrent psychoses.

PMID: 16371805 [Indexed for MEDLINE]

4171. Clin Rheumatol. 2006 Jul;25(4):606-7. Epub 2005 Dec 20.

Is there a hypothalamic-pituitary-adrenal axis dysfunction in patients with familial Mediterranean fever?

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DOI: 10.1007/s10067-005-0152-7

PMID: 16365686 [Indexed for MEDLINE]

4172. FEBS Lett. 2006 Jan 9;580(1):99-106. Epub 2005 Dec 9.

Structure of the PRYSPRY-domain: implications for autoinflammatory diseases.

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We determined the first structure of PRYSPRY, a domain found in over 500 different proteins, involved in innate immune signaling, cytokine signaling suppression, development, cell growth and retroviral restriction. The fold encompasses a 7-stranded and a 6-stranded antiparallel beta-sheet, arranged in a beta-sandwich. In the crystal, PRYSPRY forms a dimer where the C-terminus of an acceptor molecule binds to the concave surface of a donor molecule, which represents a putative interaction site. Mutations in the PRYSPRY domains of Pyrin, which are responsible for familial Mediterranean fever, map on the putative PRYSPRY interaction site.

DOI: 10.1016/j.febslet.2005.11.076

PMID: 16364311 [Indexed for MEDLINE]



4173. *Pediatr Int.* 2005 Dec;47(6):640-4.

Familial Mediterranean fever in a childhood population in eastern Turkey.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent attacks of inflammation of serosal membranes.

Amyloidosis is the most severe complication of the disease. The aim of this study was to explore the magnitude of the FMF problem and to describe clinical phenotypic and genotypic profile in the childhood population in Eastern Turkey.

**METHODS:** In this study, 52 patients who were diagnosed as FMF between January 2000 and January 2003 in Department of Pediatrics, Ataturk University Hospital, were included. The diagnosis of FMF was based on typical clinical and laboratory features. The 12 FMF mutations were investigated in the patients.

**RESULTS:** Of the 52 patients, 30 (57.7%) were girls, 22 (42.3%) were boys, and the age ranged from 9 months to 15 years (8.5 +/- 3.2 years). A positive family history for FMF was noted in 33 (63.5%) patients. The mean onset age was 6 +/- 3.4 (from 8 months to 14 years). Nineteen children (36.5%) were symptomatic below the age of 5 years. Abdominal pain was observed in 50 (96.2%), fever in 42 (80.8%), arthralgia in 29 (55.8%), arthritis in 18 (34.6%), splenomegaly in 11 (21.2), hepatomegaly in 15 (28.8%), myalgia in 11 (26.2%), erysipelas-like erythema in 10 (19.2%), thoracic pain in four (7.7%), protracted febrile myalgia in three (5.8%), and seizures in two (3.8%). The most frequent mutation was the M694V/M694V. Clinical presentation of the patients was not different in respect with genotypes ( $P > 0.05$ ). Two patients had chronic renal disease suggestive of amyloidosis.

**CONCLUSION:** It was noted that the FMF patients in this study had a broad spectrum of mutation combination, which might reflect the intercultural interactions of ancient ethnic groups that lived in Anatolia, and these mutations were not significantly different in respect to clinical presentations.

DOI: 10.1111/j.1442-200x.2005.02140.x

PMID: 16354216 [Indexed for MEDLINE]

4174. Curr Opin Rheumatol. 2006 Jan;18(1):108-17.

Familial Mediterranean fever and the other autoinflammatory syndromes: evaluation of the patient with recurrent fever.

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**PURPOSE OF REVIEW:** The aim of this article is to summarize recent clinical, genetic and pathophysiologic findings of familial Mediterranean fever and several of the other systemic autoinflammatory diseases, a recently recognized group of disorders characterized by seemingly unprovoked inflammation but lacking high-titer autoantibodies. Genetic and clinical tools are improving the ability of the clinician to better approach patients with periodic fever and inflammation.

**RECENT FINDINGS:** The spectrum of reported genetic mutations and susceptible ethnicities for the hereditary periodic fever subset of the autoinflammatory diseases has continued to expand. At the same time, the pathogeneses of many of these diseases are now understood to involve different aspects of a common pathway, largely affecting inflammatory cascades related to IL-1 or tumor necrosis factor-alpha. Three of these diseases which have been grouped as the cryopyrin-associated periodic syndromes result from defects in the same gene, and all three appear to respond well to anti-IL-1 therapy although controlled trials are still in progress. In addition, cytokine-based therapies are also now under investigation for hyperimmunoglobulinemia D with periodic fever syndrome and pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome.

**SUMMARY:** The identification of the genes and proteins mutated in many of the autoinflammatory diseases has broadened our understanding of the regulation of inflammation and the immune system, and provided the basis for the use of targeted therapies in these syndromes. We propose an algorithm for the evaluation of a patient with periodic fever, taking into account the patient's age, ethnicity, symptoms and signs, and results from laboratory and genetic testing.

PMID: 16344627 [Indexed for MEDLINE]

4175. Clin Rheumatol. 2006 Nov;25(6):914-6. Epub 2005 Dec 3.

Sustained, progressive, nonresolving abdominal pain: a previously undescribed clinical presentation of familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is a genetic disorder characterized by sporadic, acute attacks of fever and serosal inflammation. Typical manifestations are recurrent febrile episodes of acute instauration for brief duration (1 to 4 days) that is associated with severe pain due to serositis at one or more sites. Abdominal crisis occurs in 95% of the patients. Treatment with colchicine is highly effective as preventive treatment, but it is considered to be ineffective for the treatment of established acute attacks. As mentioned, untreated crisis resolves spontaneously in 1 to 4 days. Prolonged, nonresolving crisis of abdominal pain refractory to nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, with fever and elevation of acute phase reactants that resolves after the administration of colchicine, is a clinical presentation undescribed hitherto. The aim of this paper is to report a patient with this distinctively unusual clinical presentation of FMF.

DOI: 10.1007/s10067-005-0093-1

PMID: 16328089 [Indexed for MEDLINE]

4176. Arch Med Res. 2006 Jan;37(1):178-80.

Familial mediterranean fever-related nephrotic syndrome and successful full-term pregnancy.

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Familial Mediterranean fever (FMF) is a systemic disease with an autosomal recessive inheritance. The most serious complication of FMF is renal amyloidosis. Pregnancy may adversely affect renal function in FMF patients with amyloidosis and nephrotic syndrome. A 20-year-old woman with FMF related nephrotic syndrome became pregnant while receiving colchicine therapy. Colchicine treatment was continued during pregnancy with close observation. She gave birth to a 2400 g healthy female newborn at the 38th week of gestation. Pregnancy and neonatal outcome were uneventful. It is advisable to continue colchicine treatment during conception and pregnancy in FMF patients with amyloid related nephrotic syndrome. Colchicine treatment with bed rest, protein reinforcement, acetylsalicylic acid administration and close follow-up may improve the outcome of pregnancy in FMF patients.

DOI: 10.1016/j.arcmed.2005.04.013

PMID: 16314207 [Indexed for MEDLINE]

4177. Clin Neurol Neurosurg. 2005 Dec;108(1):77-9. Epub 2004 Dec 23.

Bilateral carpal tunnel syndrome associated to familial Mediterranean fever.

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A unique case of bilateral severe carpal tunnel syndrome due to familial Mediterranean fever is reported. The syndrome was diagnosed by clinical examination and electrophysiological studies. Bilateral transverse carpal ligaments were released and the biopsy specimens revealed systemic type A amyloidosis. Up to our knowledge, the co-existence of bilateral carpal tunnel syndrome and familial Mediterranean fever has not been reported previously in the literature.

DOI: 10.1016/j.clineuro.2004.11.013  
PMID: 16311153 [Indexed for MEDLINE]

4178. Ann Rheum Dis. 2006 Jul;65(7):958-60. Epub 2005 Nov 24.

"Periodic fever" without fever: two cases of non-febrile TRAPS with mutations in the TNFRSF1A gene presenting with episodes of inflammation or monosymptomatic amyloidosis.

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**BACKGROUND:** Tumour necrosis factor (TNF) receptor associated periodic syndrome (TRAPS) is caused by dominant mutations in the TNFRSF1A gene. In typical cases TRAPS begins early in childhood and is characterised by high and remittent fever over a period of 1-4 weeks or longer, accompanied by systemic and local inflammation.

**CASE REPORTS:** Patient 1 presented with recurrent episodes of weakness, migrating myalgias, arthralgias, exanthema, and chest pain lasting for 1-4 weeks, but without any fever over an initial period of 4 years at least. Diagnosis of TRAPS was confirmed by the heterozygous mutation Y20H in TNFRSF1A. Patient 2, a 23 year old woman never had any symptoms indicative of TRAPS. Genetic evaluation of all members of her family with a TRAPS index patient disclosed the T50M mutation in TNFRSF1A. A medical check up showed proteinuria, and renal biopsy disclosed AA amyloidosis.

**CONCLUSIONS:** TRAPS associated mutations can induce considerable inflammation that is not necessarily accompanied by fever. Even monosymptomatic severe amyloidosis can occur in these patients. Genetic counselling and appropriate management to prevent or mitigate amyloidosis may be necessary.

DOI: 10.1136/ard.2005.043570  
PMCID: PMC1798226  
PMID: 16308343 [Indexed for MEDLINE]

4179. Dtsch Med Wochenschr. 2005 Dec 2;130(48):2774-8.

[Fever of unknown origin in the 21st century. 2. Non-infectious diseases (autoimmune diseases)].

[Article in German]

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DOI: 10.1055/s-2005-922071

PMID: 16307407 [Indexed for MEDLINE]

4180. Rheumatol Int. 2006 Jul;26(9):846-51. Epub 2005 Nov 24.

Familial Mediterranean fever and ankylosing spondylitis in a patient with  
juvenile idiopathic arthritis: A case report and review of the literature.

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The association of familial Mediterranean fever (FMF) with juvenile idiopathic arthritis (JIA) or ankylosing spondylitis (AS), most commonly with negative HLA-B27 antigen, was described in several previous reports, although the pathogenic mechanism of this association still remains unknown. Herein we report an uncommon association of FMF with HLA-B27 positive AS as an occasional coincidence in a patient who had been diagnosed as having JIA 23 years previously.

DOI: 10.1007/s00296-005-0080-5

PMID: 16307274 [Indexed for MEDLINE]

4181. Hematology Am Soc Hematol Educ Program. 2005:74-81.

Hereditary periodic fever syndromes.

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The hereditary periodic fevers are a group of Mendelian disorders characterized by seemingly unprovoked fever and localized inflammation. Recent data indicate that these illnesses represent inborn errors in the regulation of innate immunity. Pyrin, the protein mutated in familial Mediterranean fever, defines an N-terminal domain found in a large family of proteins involved in inflammation and apoptosis. Through this domain pyrin may play a role in the regulation of interleukin (IL)-1beta, nuclear factor (NF)-kappaB, and leukocyte apoptosis. Cryopyrin/NALP3, another protein in this family, is mutated in three other hereditary febrile syndromes and participates in the inflammasome, a newly recognized macromolecular complex crucial to IL-1beta activation. Somewhat unexpectedly, mutations in the 55 kDa receptor for tumor necrosis factor also give rise to a dominantly inherited periodic fever syndrome, rather than immunodeficiency, a finding that has stimulated important investigations into both pathogenesis and treatment. Finally, the discovery of the genetic basis of the hyperimmunoglobulinemia D with periodic fever syndrome suggests an as yet incompletely understood connection between the mevalonate pathway and the regulation of cytokine production. These insights extend our understanding of the regulation of innate immunity in man, while providing the conceptual basis for the rational design of targeted therapies, both for the hereditary periodic fevers themselves and other inflammatory disorders as well.

DOI: 10.1182/asheducation-2005.1.74

PMID: 16304362 [Indexed for MEDLINE]

4182. J Immunol. 2005 Dec 1;175(11):7678-86.

T cell-regulated neutrophilic inflammation in autoinflammatory diseases.

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Previous studies of acute generalized exanthematous pustulosis, a peculiar drug hypersensitivity reaction, suggested that CXCL8-producing T cells regulate sterile, polymorphonuclear neutrophil-rich skin inflammations. In this study, we test the hypothesis of whether CXCL8-producing T cells are present in autoinflammatory diseases like pustular psoriasis and Behçet's disease. Immunohistochemistry of normal skin revealed few CD4+ and CD8+ T cells, few CXCL8+ cells, and no neutrophilic infiltration, whereas in acute exacerbations of atopic dermatitis, numerous CD4+ T cells but few CD8+ T cells, neutrophils, or CXCL8+ cells were detected. In contrast, a pronounced infiltration of neutrophils and of predominantly CD4+ T cells was observed in skin biopsies from pustular psoriasis, Behçet's disease, and acute generalized exanthematous pustulosis, with infiltrating T cells strongly positive for CXCL8 and the chemokine receptor CCR6. Skin-derived T cell clones from pustular skin reactions were positive for CCR6 but negative for CCR8 and secreted high amounts of CXCL8 and GM-CSF, often together with IFN-gamma and TNF-alpha after in vitro stimulation. Moreover, some skin-derived T cell clones from Behçet's disease and from pustular psoriasis predominantly produced CXCL8 and GM-CSF, but failed to secrete IL-5 and IFN-gamma. These cells might represent a particular subset as they differ from both Th1 as well as Th2 T cells and are associated with a unique, neutrophil-rich sterile inflammation. Our findings suggest that CXCL8/GM-CSF-producing T cells may orchestrate neutrophil-rich pathologies of chronic autoinflammatory diseases like pustular psoriasis and Behçet's disease.

PMID: 16301678 [Indexed for MEDLINE]

4183. J Nephrol. 2005 Sep-Oct;18(5):626-9.



Autosomal dominant periodic fever with AA amyloidosis: tumor necrosis factor receptor-associated periodic syndrome (TRAPS) in a Turkish family.

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We investigated the presence of tumor necrosis factor receptor-associated periodic syndrome (TRAPS) in a Turkish family with recurrent fever and systemic reactive (AA) amyloidosis. A missense mutation in exon 3 of the TNFRSF1A gene, resulting in an amino acid substitution Phe60Leu (F60L) was found in the proband and his father. These are the first confirmed TRAPS cases in the Turkish population. This family highlights the importance of considering all the causes of inherited fevers and performing thorough clinical and genetic investigations to secure a diagnosis, even in populations in which familial Mediterranean fever (FMF) is highly prevalent.

PMID: 16299693 [Indexed for MEDLINE]

4184. J Nephrol. 2005 Sep-Oct;18(5):582-4.

Interleukin-6 (IL-6) -174 G/C polymorphism in familial Mediterranean fever patients with and without amyloidosis.

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Familial Mediterranean fever (FMF) is a recessive disorder characterized by attacks of fever and inflammation. A sustained inflammatory reaction is observed in the disease course, and cytokine levels such as interleukin (IL)-1, IL-6 and tumor necrosis factor-alpha (TNF-alfa) are shown to increase during and between

the attacks. In this study, we investigated the role of the functionally important IL-6 -174 G/C polymorphism in the clinical outcome of FMF and amyloidosis. One hundred and fifty-six FMF patients (80 with amyloidosis) and 90 healthy controls were studied. The genotype distributions and allele frequencies of the patients and the controls were found to be similar, and the differences between the groups were not statistically significant. The results show that IL-6 -174 G/C polymorphism is not associated with FMF and amyloidosis. The increase observed in cytokine levels during and between the attacks is more likely due to the inflammatory nature of the disease.

PMID: 16299685 [Indexed for MEDLINE]

4185. J Dermatol Sci. 2006 Jan;41(1):3-10. Epub 2005 Nov 9.

The genetics of generalized vitiligo and associated autoimmune diseases.

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Generalized vitiligo is an acquired disorder in which patches of depigmented skin, overlying hair, and oral mucosa result from progressive autoimmune loss of melanocytes from the involved areas. Although vitiligo is perhaps the most common pigmentary disorder, insufficiently clear clinical definition of the disorder and lack of a good laboratory animal model have inhibited progress in understanding its pathobiology, its environmental triggers, and in developing specific and effective therapeutic approaches. Vitiligo results from a complex interaction of environmental, genetic, and immunologic factors, which ultimately contribute to melanocyte destruction, resulting in the characteristic depigmented lesions. In the past few years, studies of the genetic epidemiology of generalized vitiligo have led to the recognition that vitiligo is part of a broader, genetically-determined, autoimmune/autoinflammatory diathesis. Attempts to identify genes involved in vitiligo susceptibility have involved both allelic association studies of candidate genes and genome-wide linkage analyses to discover new genes, and these studies have begun to shed light on the mechanisms

of vitiligo pathogenesis. It is anticipated that the discovery of biological pathways of vitiligo pathogenesis will provide novel therapeutic and prophylactic targets for future approaches to the treatment and prevention of vitiligo and its associated autoimmune diseases.

DOI: 10.1016/j.jdermsci.2005.10.001

PMID: 16289692 [Indexed for MEDLINE]

4186. Rheumatology (Oxford). 2006 Jan;45(1):31-7. Epub 2005 Nov 15.

Systemic cytokine levels and the effects of etanercept in TNF receptor-associated periodic syndrome (TRAPS) involving a C33Y mutation in TNFRSF1A.

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**OBJECTIVE:** To investigate the levels of the pro-inflammatory cytokines IL-6, TNF-alpha, IL-1beta, IL-8, IL-10 and IL-12p70 in the plasma of patients with TNF receptor-associated periodic syndrome (TRAPS) in relation to CRP levels and treatment with etanercept.

**METHODS:** Cytokine concentrations were measured in sequential plasma samples obtained from eight patients with a C33Y mutation in TNFRSF1A and diagnosed with TRAPS, using cytokine bead array. The TRAPS samples were compared with samples from normal controls and rheumatoid arthritis patients.

**RESULTS:** Levels of IL-6 were significantly elevated in C33Y TRAPS patients and these correlated with CRP levels in some of the patients. IL-8 levels were also significantly elevated in the TRAPS patients. However, neither TNF-alpha nor IL-1beta demonstrated a similar increase. This differed from the patients with rheumatoid arthritis, for whom levels of IL-6, IL-8, TNF-alpha, IL-1beta and IL-10 were significantly elevated. The levels of detectable TNF-alpha in the TRAPS patients' plasma were elevated during etanercept treatment.

**CONCLUSIONS:** The cytokine profile of C33Y TRAPS differs from that of a typical autoimmune inflammatory condition such as rheumatoid arthritis, as only IL-6 and IL-8 were elevated in C33Y TRAPS patients, as distinct from a generalized

elevation of pro-inflammatory cytokines. However, only some of the C33Y patients tested showed a relationship between elevated IL-6 and CRP. This is consistent with clinical observations that there is marked heterogeneity between individuals with TRAPS, including those in the same family cohort. Although etanercept has a therapeutic effect in some TRAPS patients, it induces increased plasma concentrations of TNF-alpha, possibly by increasing TNF-alpha stability.

DOI: 10.1093/rheumatology/kei090

PMID: 16287931 [Indexed for MEDLINE]

4187. Clin Exp Med. 2005 Oct;5(3):87-98.

Hereditary periodic fever and reactive amyloidosis.

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Hereditary periodic fever syndromes (HPF) are a group of diseases characterised by recurrences of fever and inflammation separated by symptom-free intervals. Familial Mediterranean fever (FMF) is the most frequent entity within this group of disorders which further consists of hyperimmunoglobulinaemia D and periodic fever syndrome (HIDS), tumour necrosis factor receptor-associated periodic syndrome (TRAPS) and cryopyrin-associated periodic syndrome (CAPS). In recent years the causative genes have been identified. Reactive amyloidosis is a severe complication of HPFs. This is caused by deposition of fibrils that consist of the proteolytically cleaved acute phase protein serum amyloid A (SAA). Several factors have been identified that modulate the risk for developing amyloidosis, including SAA concentrations, polymorphisms in the SAA gene and ethnic origin. Furthermore, the risk of developing amyloidosis varies widely between the different HPFs. Colchicine is the cornerstone in the management of FMF, as it reduces the severity and frequency of attacks and is also effective in preventing amyloidosis. In the other HPFs, the introduction of anticytokine-based therapies is a promising new option in treating these inflammatory conditions and they potentially can prevent amyloidosis.

DOI: 10.1007/s10238-005-0071-6  
PMID: 16284730 [Indexed for MEDLINE]

4188. Rheumatol Int. 2006 Apr;26(6):489-96. Epub 2005 Nov 10.

Familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is the most frequent hereditary inflammatory disease characterized by self-limited recurrent attacks of fever and serositis. It is transmitted in an autosomal recessive pattern and affects certain ethnic groups mainly Jews, Turks, Arabs, and Armenians. FMF is caused by mutations in MEFV gene, which encodes pyrin. This protein is expressed mainly in myeloid/monocytic cells and modulates IL-1 $\beta$  processing, NF- $\kappa$ B activation, and apoptosis. A mutated pyrin probably results in uncontrolled inflammation. The most devastating complication of FMF is amyloidosis, leading to chronic renal failure. M694V homozygosity, male gender and the  $\alpha/\alpha$  genotype of serum amyloid A1 gene are the currently established risk factors for development of amyloidosis. Daily colchicine is the mainstay of the therapy for the disease, resulting in complete remission or marked reduction in the frequency and duration of attacks in most patients. It is also effective in preventing and arresting renal amyloidosis.

DOI: 10.1007/s00296-005-0074-3  
PMID: 16283319 [Indexed for MEDLINE]

4189. Ann Allergy Asthma Immunol. 2005 Oct;95(4):394-9.

Neutrophil chemotaxis in a patient with neonatal-onset multisystem inflammatory disease and Muckle-Wells syndrome.

Lokuta MA(1), Cooper KM, Aksentijevich I, Kastner DL, Huttenlocher A.

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**BACKGROUND:** Neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic, cutaneous, and articular syndrome is an autoinflammatory disease characterized by urticarial rash, arthropathy, and central nervous system inflammation.

**OBJECTIVE:** To describe a 13-year-old girl with overlapping symptoms of NOMID and Muckle-Wells syndrome who has a mutation in cryopyrin (NALP3).

**METHODS:** We examined neutrophil migration using transwell assay and time-lapse videomicroscopy. We also examined p38 mitogen-activated protein kinase (MAPK) activation in patient and control neutrophils using Western blot analysis.

**RESULTS:** Neutrophil defects in chemotactic migration were found to a variety of chemoattractants, including interleukin 8, N-formyl-methionyl-leucyl-phenylalanine, complement C5a, and leukotriene B4. Her neutrophils exhibited elevated basal and stimulated p38 MAPK activation in response to interleukin 8, N-formyl-methionyl-leucyl-phenylalanine, complement C5a, and leukotriene B4.

**CONCLUSIONS:** This study is the first, to our knowledge, to demonstrate defects in neutrophil chemotaxis and p38 MAPK signaling in a patient with NOMID and Muckle-Wells syndrome and a cryopyrin mutation.

DOI: 10.1016/S1081-1206(10)61159-3

PMID: 16279571 [Indexed for MEDLINE]

4190. Eksp Klin Farmakol. 2005 Sep-Oct;68(5):40-3.

[Pharmacological modulation of phagocytosis of granulocytes and monocytes in patients with familial Mediterranean fever].

[Article in Russian]

Avetisyan SA.

Disturbances in the regulation of phagocytic activity of neutrophils and monocytes (PANM) in whole peripheral blood of patients with Familial Mediterranean Fever (FMF), which had not receive treatment with colchicines, and the effect of drugs from various pharmacological groups on the PANM in the blood of these patients were studied in vitro by quantitative flow cytofluorimetry. A comparative study of the drug action showed that the most effective PANM inhibitors during FMF are colchicine and iodine-lithium-alpha-dextrin (armenicum), while synthetic glucocorticoids and sodium thiosulfate showed low activity and produced no significant effect. It was established that armenicum is capable of modulating the PANM-inhibition effect of colchicine, neutralizing the effect of TNF, and increasing the effect of glucocorticoids. was observed. Sodium thiosulfate produces inhibition of the activity of armenicum.

PMID: 16277210 [Indexed for MEDLINE]

4191. Eksp Klin Farmakol. 2005 Sep-Oct;68(5):36-9.

[The effect of colcichine and iodine-lithium-alpha-dextrin on the phagocytosis of granulocytes and monocytes in patients with familial Mediterranean fever].

[Article in Russian]

Akopian VP, Avetisian SA, Davtian TK.

Disturbances in the regulation of phagocytic activity of neutrophils and monocytes (PANM) in whole peripheral blood of patients with familial Mediterranean Fever (FMF), which had not received treatment with colchicines, were determined by quantitative flow cytofluorimetry. The effect of iodine-lithium-alpha-dextrin (armenicum) and colchicine on the PANM in the blood of FMF patients was studied in vitro. The intensity of phagocytosis in populations of neutrophils and monocytes in FMF patients (n = 6) during the remission period is higher than that during the FMF attack (n = 6) and higher than in healthy donors (n = 9). The PANM in patients during the FMF attack is higher compared to that in healthy donors. Iodine-lithium-alpha-dextrin (armenicum) and colchicine inhibited the phagocytosis of effector cells in FMF patients in a dose-dependent and time-dependent manner. It was shown that the suppressive effect of the drugs increased with decreasing bacteria/effector cells

ratio.

PMID: 16277209 [Indexed for MEDLINE]

4192. Clin Exp Rheumatol. 2005 Jul-Aug;23(4 Suppl 38):S107-8.

Immunosuppressive treatment of AA amyloidosis of familial Mediterranean fever.

Korkmaz C.

PMID: 16273776 [Indexed for MEDLINE]

4193. Clin Exp Rheumatol. 2005 Jul-Aug;23(4 Suppl 38):S81-5.

Oxidative burst response to monosodium urate crystals in patients with Behçet's syndrome.

Gogus F(1), Fresko I, Elbir Y, Eksioglu-Demiralp E, Direskeneli H.

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**OBJECTIVE:** An erythematous response to intradermal injection of monosodium urate crystals (MSU) has been demonstrated in Behçet's syndrome (BS). To further elucidate the pathogenesis of this response, the effects of MSU on in vitro oxidative burst reaction of neutrophils and monocytes were investigated.

**METHODS:** Peripheral blood mononuclear cells from patients with Behçet's syndrome (BS), rheumatoid arthritis (RA), familial Mediterranean fever (FMF) and healthy controls (HC) were incubated with 100 ng/ml phorbol myristate acetate (PMA) and MSU at different dosages (25-500 microg/ml). Oxidative burst reaction was evaluated in neutrophils and monocytes by flow cytometry.

**RESULTS:** In patients with BS, oxidative burst of neutrophils was significantly increased compared to HC at 125 microg/ml and 250 microg/ml dosages of MSU ( $p < 0.001$  and  $0.004$  respectively). In patients with FMF; there was also an



increased oxidative burst reaction at 75 microg/ml, 250 g/ml and 500 microg/ml ( $p \leq 0.007$ ; 0.001 and 0.004 respectively). In patients with BS, oxidative burst of monocytes was increased only at 125 g/ml dosage of MSU ( $p \leq 0.002$ ). However, in patients with FMF monocyte burst response was increased at 25 microg/ml, 75 microg/ml and 125 g/ml ( $p \leq 0.004$ ;  $< 0.0001$ ;  $< 0.0001$  and 0.002 respectively). In RA group, stimulation with PMA resulted in a higher oxidative burst reaction than FMF and BS ( $p \leq 0.000$  and  $p \leq 0.008$ ). No correlation was observed between oxidative burst of neutrophils or monocytes and intradermal responses to MSU crystals.

**CONCLUSION:** Oxidative burst reaction with MSU is augmented in neutrophils and monocytes of BS. However, the response is not specific and is unassociated with skin dermal test which has a high specificity for BS.

PMID: 16273771 [Indexed for MEDLINE]

4194. Clin Exp Rheumatol. 2005 Jul-Aug;23(4 Suppl 38):S77-80.

Serum interleukin 17 and interleukin 18 levels in familial Mediterranean fever.

Haznedaroglu S(1), Oztürk MA, Sancak B, Goker B, Onat AM, Bukan N, Ertenli I, Kiraz S, Calguneri M.

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**OBJECTIVE:** Familial Mediterranean fever (FMF) attacks are characterized by serosal inflammation rich in PMNL leukocytes and activation of a definite cytokine network. Moreover, there is sustained inflammation in attack-free FMF patients. Interleukin (IL)-17 and IL-18 are recently described proinflammatory cytokines, which can modulate certain neutrophil functions. In this study we measured serum levels of IL-17 and IL-18 in FMF patients.

**METHODS:** The study groups comprised of 18 FMF patients in attack-free period (mean age: 30.2  $\pm$  9.5 years; male/female: 10/8), and 18 patients with an acute FMF attack (mean age: 25.4  $\pm$  4.9 years; male/female: 10/8). Twenty age-matched healthy subjects were included as a control group (male/female: 10/10). Levels of IL-17 and IL-18 were determined by commercial ELISA kits (Biosource

International, USA).

**RESULTS:** Serum IL-17 levels were  $42.8 \pm 3.7$ ,  $42.7 \pm 3.2$ , and  $39.9 \pm 2.3$  pg/mL for FMF patients in attack-free period, FMF patients with acute attack, and healthy controls, respectively. Serum IL-18 levels were  $878.8 \pm 315.0$ ,  $854.2 \pm 261.4$ , and  $314.6 \pm 80.8$  pg/mL for FMF patients in an attack-free period, FMF patients with acute attack, and healthy controls, respectively. Levels of both IL-17 and IL-18 were significantly higher in FMF patients with and without acute attack compared to control group ( $p < 0.05$ ). Concentrations of those cytokines were comparable in FMF patients with acute attack and in attack-free period ( $p > 0.05$ ).

**CONCLUSION:** Our data suggest that IL-17 and IL-18 contribute to the cytokine network in the inflammatory cascade of FMF. However, their roles for the initiation of FMF attacks remain to be established.

PMID: 16273770 [Indexed for MEDLINE]

4195. Clin Exp Rheumatol. 2005 Jul-Aug;23(4 Suppl 38):S64-6.

Behçet's disease and hereditary periodic fever syndromes: casual association or causal relationship?

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**OBJECTIVE:** Mutations in the MEFV and the type 1 TNF receptor (TNFRSF 1A) genes have recently been linked to familial Mediterranean fever (FMF) and TNF receptor-associated periodic syndrome (TRAPS), respectively. A higher prevalence of Behçet's disease (BD) among FMF patients has been described compared to the general population. The aim of this study was to evaluate whether FMF TRAPS and BD could be genetically related.

**METHODS:** We screened a cohort of 50 BD patients and 100 healthy subjects for the common MEFV and TNFRSF 1A mutations. An initial screening of exons 10 and 2 of the MEFV gene and exon 4 of the TNFRSF 1A was performed in all chromosomes.

RESULTS: The heterozygous MEFV mutation (K695R) was found in one (2%) BD patient. Analysis for FMF mutations in the control group revealed that 5 (5%) individuals bore MEFV gene mutations (3 were heterozygous for the E148Q and 2 were heterozygous for the A744S). At codon 202, there were no differences in allele frequencies between BD and control population: 73%R 27%Q in the BD patients vs 75%R 25%Q in controls. Concerning mutations in the TNFRSF 1A gene, the R92Q mutation was present in heterozygous state in one (2%) BD patient and in 4 (4%) controls without differences between allele frequencies: 99%R 1%Q in BD patients vs 98%R 2%Q in controls, respectively. There was no association between the clinical manifestations of BD patients and the presence of a particular polymorphism or a mutation.

CONCLUSIONS: Neither FMF nor TRAPS are genetically associated with BD in our cohort of Spanish patients.

PMID: 16273767 [Indexed for MEDLINE]

4196. Clin Exp Rheumatol. 2005 Jul-Aug;23(4 Suppl 38):S3-7.

The rise and fall of FMF research--fifty years of publications.

Ben-Chetrit E, Ben-Chetrit E.

PMID: 16273758 [Indexed for MEDLINE]

4197. Clin Exp Rheumatol. 2005 Jul-Aug;23(4 Suppl 38):S1-2.

Behçet's disease and other autoinflammatory conditions: what's in a name?

Yazici H, Fresko I.

PMID: 16273757 [Indexed for MEDLINE]

4198. Ann Saudi Med. 2005 Sep-Oct;25(5):433, 441-2.

Periodic fever, rash and arthropathy in a child.

Al-Mayouf SM(1).

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PMCID: PMC6089716

PMID: 16270772 [Indexed for MEDLINE]

4199. Clin Rheumatol. 2006 Jul;25(4):458-61. Epub 2005 Nov 3.

Adrenal axis functions in patients with familial Mediterranean fever.

Sav T(1), Ozbakir O, Kelestimur F, Gursoy S, Baskol M, Kula M, Dundar M.

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Erratum in

Clin Rheumatol. 2006 Nov;25(6):937. Tansu, Sav [corrected to Sav, Tansu]; Omer, Ozbakir [corrected to Ozbakir, Omer]; Fahrettin, Kelestimur [corrected to Kelestimur, Fahrettin]; Sebnem, Gursoy [corrected to Gursoy, Sebnem]; Mevlut, Baskol [corrected to Baskol, Mevlut]; Mustafa, Kula [correct.

OBJECTIVE: Familial Mediterranean fever (FMF) is a hereditary disease characterized by recurrent attacks of fever with peritonitis, arthritis, pleuritis or erysipelas-like rash. It is unclear what effects of FMF itself on endocrine system and hormones are. None of the FMF patients without amyloidosis have been reported to have any endocrine disorders, except those who developed colchicine-induced diabetes insipidus. There is a large body of evidence to show that cytokines (IL-1, IL-6 and TNF-alpha) activate the hypothalamic-pituitary-adrenal (HPA) axis. We have designated this study to investigate the HPA axis in FMF patients without amyloidosis.

**METHODS:** Twenty-one patients with FMF were included. ACTH stimulation test was performed on the healthy subjects and during attack period in the patients. In the patient group, same test was repeated during remission period.

**RESULTS:** Peak cortisol levels were significantly higher in the attack period than those in the remission period of patients ( $p<0.05$ ).

**CONCLUSION:** The cytokines play a role on the activation of the HPA axis; we thought the axis would be affected in this disease. The response of cortisol to 250 mug ACTH was significant in attack period when compared with remission period. This result reveals that HPA axis is more activated in an FMF attack. Previous studies suggest that the adrenal hormones increase in acute inflammatory events, and eventually, the changes on these hormones are related to TNF and IL-6 levels. During the FMF attack, HPA axis may be stimulated by cytokines. It seems that HPA axis is regulated normally in FMF patients.

DOI: 10.1007/s10067-005-0083-3

PMID: 16267600 [Indexed for MEDLINE]

4200. J Rheumatol. 2005 Nov;32(11):2278; author reply 2278.

The arthritis of familial Mediterranean fever.

Uthman I.

Comment on

J Rheumatol. 2005 May;32(5):859-62.

PMID: 16265718 [Indexed for MEDLINE]

4201. Arthritis Rheum. 2005 Nov;52(11):3606-10.

Pseudodominant inheritance of the hyperimmunoglobulinemia D with periodic fever syndrome in a mother and her two monozygotic twins.

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Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS) is a recessively inherited recurrent fever syndrome. We describe a family of 2 monozygotic twins and their mother with characteristic symptoms of HIDS, but normal levels of IgD and IgA, and with a dominant inheritance pattern. Mevalonate kinase (MK) activity was deficient in both children, and analysis of the MVK gene revealed compound heterozygosity for 2 new mutations, G25G and R277H. Being positioned adjacent to a donor splice site, the G25G mutation was shown by reverse transcription-polymerase chain reaction analyses to cause aberrant splicing of the MVK messenger RNA, thus being disease-relevant. The mother, who was also symptomatic during her childhood and adolescence, was a compound heterozygote for I268T and R277H. Our findings expand the genetic and ethnic spectrum of HIDS and show that the possible presence of this disease cannot be excluded based solely on inheritance patterns. In each case in which HIDS is clinically suspected, analysis of MK activity and/or the MVK gene (especially exons 9 and 11) should be performed.

DOI: 10.1002/art.21381

PMID: 16255052 [Indexed for MEDLINE]

4202. Arthritis Rheum. 2005 Nov;52(11):3603-5.

MEFV analysis is of particularly weak diagnostic value for recurrent fevers in Western European Caucasian patients.

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**OBJECTIVE:** Familial Mediterranean fever (FMF) is an autosomal-recessive disorder characterized by recurrent attacks of fever, with abdominal, thoracic, or articular pain. FMF is particularly common in Mediterranean populations, while

other populations are rarely affected. MEFV gene analysis provides the only objective diagnostic criterion for FMF. However, the spectrum of MEFV mutations, which was first established in classically affected populations, remains insufficiently studied in other populations. The purpose of this study was to assess involvement of MEFV in the phenotype of western European Caucasian patients with a clinical diagnosis of FMF.

**METHODS:** Mutation analysis was performed in 208 Caucasian patients from western Europe, by screening for the most common MEFV mutations in exons 2, 3, 5, and 10, and by sequencing the promoter region and the whole MEFV coding sequence in 21 of these patients.

**RESULTS:** None of the patients carried 2 mutated alleles. Only 2 patients carried 1 mutated allele.

**CONCLUSION:** FMF-like syndromes in western European Caucasian populations cannot be explained by MEFV mutations. These results should be helpful in avoiding laborious and costly MEFV molecular analyses that, at the population level, seem to be of poor diagnostic value in the case of western European Caucasian patients, and rather should prompt a search for other causes in those patients.

DOI: 10.1002/art.21408

PMID: 16255051 [Indexed for MEDLINE]

4203. *Pediatr Hematol Oncol.* 2005 Dec;22(8):657-65.

The anemia of familial Mediterranean fever disease.

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The aim of this study was to evaluate the incidence of anemia detected in familial Mediterranean fever (FMF) and the effect of disease activity and colchicine therapy along with interleukins to laboratory tests, including serum transferrin receptor (TfR), in the diagnosis of anemia seen in FMF in children. After detecting anemia in 63.4% of 172 FMF patients followed up by our rheumatology outpatient polyclinics, it was decided to study 3 groups of patients: group 1, 17 newly diagnosed FMF patients; group 2, 36 FMF patients on

colchicine therapy; and group 3, 17 healthy children as control for the symptom of anemia. All 3 groups of patients were investigated for their hematological parameters, iron status, including soluble transferrin receptor (sTFR) concentrations and sTFR index, and IL-6 levels. Anemia ratio was 9/17, 53%; 11/36, 31%; and 1/17, 5% in the groups 1, 2 and 3, respectively. There was a significant difference between hemoglobin (Hb) values in the first group and the second (patients who were on colchicine therapy). Furthermore, in the second group there was a significant difference between the Hb concentrations at the time of diagnosis and after colchicine therapy ( $p = .003$ ). There was a positive correlation between Hb and plasma iron and transferrin saturation in group 1 and disease beginning age, iron, transferrin saturation, and erythrocyte sedimentation rate (ESR) in the second group. In the first group the anemic patients' iron and transferrin saturation were significantly lower than normal, while ferritin levels were higher. In the second group, a good correlation was found with ESR and Hb levels; the higher ESR values were detected in patients with lower Hb values. Of the anemic and nonanemic patients of the first and second groups, values for interleukin 6 and iron parameters, including sTFR, were found similar. Anemia detected in FMF patients was found related to iron status more than interleukins. Colchicine therapy had a positive effect on anemia as well as on disease activity. Resolution of symptoms of FMF occurred with correction of the anemia, if the patient ESR values also decreased on colchicine therapy.

DOI: 10.1080/08880010500278681

PMID: 16251171 [Indexed for MEDLINE]

4204. Turk J Gastroenterol. 2005 Sep;16(3):143-6.

Relationship between HLA-DR, HLA-DQ alleles and MEFV gene mutations in familial Mediterranean fever (FMF) patients.

Kinikli G(1), Bektaş M, Misirlioğlu M, Ateş A, Turgay M, Tuncer S, Kinikli S, Tokgöz G.

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**BACKGROUND/AIMS:** Three missense mutations clustered on the carboxyl-terminal portion of the MEFV gene (M680I, M694V, and V726A) have been observed in over 80% of affected alleles in several ethnic groups of familial Mediterranean fever patients. Several immunologic abnormalities were found both in cellular and humoral components in Mediterranean fever patients. Those observations have pointed the way for analysis of the HLA region in Mediterranean fever. We intended to compare HLA DR/DQ alleles with those major mutations in the MEFV gene in Mediterranean fever patients.

**METHODS:** The distribution of MEFV gene mutations and HLA-DR, HLA-DQ alleles were analyzed in 40 index Turkish Mediterranean fever patients, 28 family members and 42 healthy controls. M680I, M694V, and V726A mutations were studied by amplification refractory mutation system-polymerase chain reaction (ARMS-PCR) analysis. HLA-DR and DQ allele subgroups were studied using SSP-PCR technique.

**RESULTS:** A total of 37 (92.5%) patients in 40 Mediterranean fever index patients were found to carry one of the three missense mutations. The HLA-DR4 allele frequency was significantly higher in the Mediterranean fever patient group. When comparisons were made between Mediterranean fever mutations and HLA allele frequencies, M694V mutation with HLA DR3, DR11/5 and DR 13/6 and M680I mutation with DR7 allele subgroups were statistically significant. DQ6/1, DQ7/3, and DQ8/3 allele with M694V, DQ2 allele with M680I, and DQ6/1 with V726A mutations were also statistically significant.

**CONCLUSIONS:** Our results indicate a relationship between some HLA-DR/DQ alleles and MEFV mutations in Mediterranean fever patients. We suggest HLA-DR/DQ alleles and their role in the pathogenesis of Mediterranean fever need further analysis and comparative studies.

PMID: 16245224 [Indexed for MEDLINE]

4205. Rheumatology (Oxford). 2006 Mar;45(3):269-73. Epub 2005 Oct 18.

Approach to genetic analysis in the diagnosis of hereditary autoinflammatory syndromes.

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**OBJECTIVE:** Hereditary autoinflammatory syndromes are characterized by recurrent episodes of fever and inflammation. Seven subtypes have been described, caused by mutations in four different genes. Apart from a common phenotype of lifelong recurrent inflammatory attacks, all subtypes have distinct features and specific therapeutic options, which emphasizes the need for a specific diagnosis in each case. Our aim was to examine whether genetic screening would allow classification of previously unclassified patients, and whether individual patients suffering from an autoinflammatory syndrome carry additional mutations in one of the other autoinflammatory genes.

**METHODS:** We included 60 patients with an unclassified autoinflammatory syndrome, 87 patients diagnosed with either hyper-IgD syndrome, familial Mediterranean fever (FMF) or tumour necrosis factor (TNF)-receptor-associated periodic syndrome and 50 healthy controls. Deoxyribonucleic acid samples were screened for the most prevalent mutations in the MEFV, TNFRSF1A, MVK and CIAS1 genes.

**RESULTS:** We found only one possible diagnosis of FMF in the 60 previously unclassified patients. Two low-penetrance mutations were found in equal numbers in the groups of patients and controls.

**CONCLUSIONS:** Screening of highly prevalent mutations in known genes involved in these disorders does not yield additional relevant information. Differential diagnosis of hereditary autoinflammatory syndromes can be made by thorough clinical examination followed by targeted genetic analysis of the one or two most likely syndromes. High-prevalence low-penetrant mutations from autoinflammatory genes do not occur more frequently in patients with hereditary autoinflammatory syndromes compared with the general population.

DOI: 10.1093/rheumatology/kei138

PMID: 16234278 [Indexed for MEDLINE]

4206. Genet Test. 2005 Fall;9(3):220-5.

Comparison of amplification refractory mutation system and polymerase chain reaction-restriction fragment length polymorphism techniques used for the investigation of MEFV gene exon 10 point mutations in familial Mediterranean fever patients living in Cukurova region (Turkey).

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Familial Mediterranean fever (FMF) is an autosomal recessive inherited disease characterized by recurrent fever, serositis and arthritis. The disease is highly prevalent in Mediterranean basin populations. Recently, the gene responsible for FMF (MEFV) was cloned and at least 40 MEFV gene mutations have been identified. The most frequently observed mutations in the MEFV gene are M694V, M694I, M680I, and V726A. These occur within exon 10 of the gene, and account for 85% of the known MEFV alleles. In this study, the reliability and economical aspects of amplification refractory mutation system (ARMS) and polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) techniques were compared for analyzing the frequencies of the major point mutations of 90 unrelated patients with FMF from the Cukurova region in Turkey. Both techniques yielded similar results: The ratio of independent alleles of 90 patients carrying one of the tested mutations was 81.1%; patients consisted of 12 different genotypes. In 64 of 90 patients (71.1%) mutations were observed in both alleles. Thirty-six patients (40%) were homozygous for the same mutation, 28 (31.1%) were heterozygous for different mutations. Eighteen patients (20%) were heterozygous for one allele with one of the four mutations but the other allele was unknown. In 8 patients (8.8%) no mutation could be detected. The most frequently observed mutation was M694V (51.66%), followed by M680I (17.22%), V726A (10.55%), and M694I (1.66%). In conclusion ARMS and PCR-RFLP techniques were equally reliable to detect the mutations in Turkish FMF patients. However, the ARMS technique was found to be more rapid and economical than the PCR-RFLP techniques.

DOI: 10.1089/gte.2005.9.220

PMID: 16225401 [Indexed for MEDLINE]

4207. Lupus. 2005;14(9):670-4.

Idiopathic recurrent acute pericarditis: familial Mediterranean fever mutations and disease evolution in a large cohort of Caucasian patients.

Brucato A(1), Shinar Y, Brambilla G, Robbiolo L, Ferrioli G, Patrosso MC, Zanni D, Penco S, Boiani E, Ghirardello A, Caforio AL, Bergantin A, Tombini V, Moreo A, Ashtamkar L, Doria A, Shoenfeld Y, Livneh A.

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Idiopathic recurrent acute pericarditis (IRAP) is suspected to be an autoimmune phenomenon. We studied 46 consecutive patients. We looked for: 1) the occurrence of new diagnoses of autoimmune diseases during our follow up; 2) HLA typing; and 3) the presence of the most frequent mutations linked to familial Mediterranean fever (FMF gene or MEFV). HLA typing was done in 21 patients at loci B, DRB1, DQA1 and DQB1. MEFV gene was looked in 23 patients using specific primers. During the follow-up we made a new diagnosis of primary Sjögren's syndrome in four patients (8.7%) and of rheumatoid arthritis in one patient (2.2%). HLA B14, DRB1\*01 and DQB1\*0202 were significantly more prevalent, but we did not find a typical HLA typing. MEFV gene was searched: exon 10 was checked by sequence and the E148Q mutation by restriction site analysis. No mutations were found. In conclusion, the prevalence of definite immunorheumatological diseases and the absence of the mutations linked to FMF reinforce the notion that idiopathic acute recurrent pericarditis is an autoimmune condition.

DOI: 10.1191/0961203305lu2197oa

PMID: 16218464 [Indexed for MEDLINE]

4208. Expert Rev Mol Med. 2005 Oct 10;7(22):1-18.

The tumour necrosis factor receptor-associated periodic syndrome: current concepts.

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The tumour necrosis factor receptor (TNFR)-associated periodic syndrome (TRAPS) is an autosomal dominant, multisystemic, autoinflammatory disorder caused by mutations in the TNFR1 gene ( TNFRSF1A ). Traps seems to be the most common hereditary periodic fever (HPF) syndrome in some western populations, and the second most prevalent HPF worldwide, behind familial mediterranean fever (FMF). The proteins involved in susceptibility to TRAPS (TNFRSF1A) and FMF (pyrin) are both members of the death-domain-fold superfamily. Mutations affecting these proteins might cause dysregulation of innate immune responses, with a propensity to autoinflammation. Most TRAPS patients have reduced blood levels of soluble TNFRSF1A between attacks, with an inappropriately small increase during bouts of fever. The pathogenesis of the 'hyperinflammatory state' in TRAPS has been variously ascribed to a shedding defect of TNFRSF1A from the cell surface resulting in increased TNF inflammatory signalling, or impaired TNF apoptotic signalling. Some low-penetrance TNFRSF1A variants also contribute to the clinical phenotype in individuals carrying other HPF-associated mutations, and have been reported in several disorders such as Behçet's disease and systemic lupus erythematosus. Synthetic anti-TNF agents provide a rational form of therapy for TRAPS, and have been shown to delay or indeed prevent development of systemic amyloidosis (AA type), a life-threatening complication in this condition.

DOI: 10.1017/S1462399405009749

PMID: 16216134 [Indexed for MEDLINE]

4209. Transplant Proc. 2005 Sep;37(7):2967-8.

Effect of amyloidosis on long-term survival in kidney transplantation.

Emiroglu R(1), Başaran O, Pehlivan S, Ozdemir FN, Colak T, Moray G, Noyan T, Haberal M.

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Amyloidosis is characterized by the accumulation of an amorphous material in various organs and tissues secondary to a variety of inflammatory, immune, infectious, and hereditary diseases. Since 1975, our transplantation team has performed 1470 renal transplantations. Between 1985 and July 2004, among 1159

kidney transplantations, 953 (82.3%) were from living donors and 206 (17.7%) from cadaveric donors. There were 32 recipients (28 men, 4 women; mean age, 31.4 +/- 1.7 years; range, 21 to 48 years) with amyloidosis, including, 28 (87.5%) who received grafts from living donors and 4 (12.5%) from cadaveric donors.

Amyloidosis was secondary to familial Mediterranean fever in 22 (68.7%) patients and rheumatoid arthritis in 1 (3.1%). The remaining 9 (28.1%) patients had primary amyloidosis. The mean follow-up time was 51.2 +/- 5.7 months (range, 2-124 months). Mean HLA mismatch rate was 2.2 +/- 1. Twenty-six (81.2%) patients are alive at this time with functioning grafts, and a mean serum creatinine value of 2.1 +/- 1.5 ng/dL. The 1- and 5-year patient and graft survival rates were 90.6% and 84.3%, and 81.2% and 68.7%, respectively. We conclude that patients with amyloidosis may undergo kidney transplantation safely expecting outcomes similar to those patients who receive transplantations for other reasons.

DOI: 10.1016/j.transproceed.2005.07.010

PMID: 16213276 [Indexed for MEDLINE]

4210. Transplant Proc. 2005 Sep;37(7):2933-5.

Simvastatin therapy in lymphocyte cross-match-positive kidney transplantation candidates.

Yakupoglu U(1), Kocak H, Karatas GU, Yakupoglu YK, Dinckan A, Kececioglu N, Gurkan A, Demirbas A, Yegin O, Tuncer M.

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**OBJECTIVES:** Recent identification of several mechanisms by which statins decrease recruitment of monocytes and T cells into the arterial wall and inhibit both T-cell and B-cell activation and proliferation in vitro prompted us to study the immunomodulatory effects of statins. In this study, we examined the effect of simvastatin therapy on lymphocyte cross-match positivity in kidney transplantation candidates.

**METHODS:** Simvastatin therapy (20 mg/d) was administered to 25 patients (18 men, 7 women of mean age 34 +/- 11.7 years who displayed positive lymphocyte cross-matches between July 2002 and October 2004. The etiologies of end-stage

renal disease were vesicoureteral reflux (n = 5), urinary stone disease (n = 4), glomerulonephritis (n = 6), amyloidosis secondary to familial Mediterranean fever (n = 1), and unknown (n = 9).

RESULTS: The lymphocyte cross-match became negative in 10 patients 4-9 months, and successful kidney transplantation was performed in 6 of them. The serum creatinine levels of these patients ranged between 0.8 and 1.4 mg/dL. Two patients required higher doses, but none suffered from adverse effects. The remaining 4 patients are still undergoing pretransplantation evaluation.

CONCLUSION: Simvastatin therapy seems to be a cost-effective and useful method for lymphocyte cross-match-positive kidney transplantation candidates compared with immunoadsorption or intravenous immunoglobulin use.

DOI: 10.1016/j.transproceed.2005.07.034

PMID: 16213265 [Indexed for MEDLINE]

4211. Am J Obstet Gynecol. 2005 Oct;193(4):1513-6.

Chromosomal abnormalities and birth defects among couples with colchicine treated familial Mediterranean fever.

Berkenstadt M(1), Weisz B, Cuckle H, Di-Castro M, Guetta E, Barkai G.

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OBJECTIVE: To determine whether colchicine prescribed for familial Mediterranean fever is teratogenic.

STUDY DESIGN: Reproductive histories were analyzed from 326 couples referred for prenatal diagnosis because 1 partner was affected. Numbers of chromosomal abnormalities and birth defects were compared with numbers expected from published rates.

RESULTS: There were 901 pregnancies, and amniocentesis had been performed in 566, all but 3 conceived while taking colchicine. Seven numerical chromosomal abnormalities were found, not statistically significantly greater than the 4.99 expected from maternal age and gestation of diagnosis ( $P = .24$ ): unbalanced structural abnormalities were 6, compared with 3.22 expected ( $P = .11$ ). There were 7 birth defects, a considerably lower rate than reported in local

malformation registers.

**CONCLUSION:** The current policy of routine amniocentesis in pregnancies of couples taking colchicine should not be changed until sufficient data accumulates to establish whether the higher number of chromosomal anomalies in this group is significant.

DOI: 10.1016/j.ajog.2005.03.043

PMID: 16202748 [Indexed for MEDLINE]

4212. Cell Biochem Funct. 2007 Jul-Aug;25(4):363-7.

A microscopic study of kidney tissue in Familial Mediterranean Fever patients.

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Familial Mediterranean Fever (FMF) is an autosomal recessive hereditary disease leading mostly to renal failure and nephrotic syndrome. The ultrastructure of kidney has not been fully investigated in FMF associated renal disease. The aim of this study is to provide further evidence on the ultrastructure of kidney in patients with FMF who suffer from renal disease. Renal biopsies obtained from two patients who were diagnosed with FMF renal disease complications were examined. Examination of renal tissue by light and electron microscopy identified degenerations both in tubules and the filtration barrier. Foot processes were partly effaced. Amorphous material was found in thickened glomerular basement membranes. Fibrous material deposits in thick Bowman's capsule wall were also seen. Finally, degeneration in the form of folding of plasma membrane and vacuolization as well as fusion in mitochondria cristae, was observed. Accumulation of tissue remnants in the lumen was also found in tubules.

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DOI: 10.1002/cbf.1286

PMID: 16200650 [Indexed for MEDLINE]



4213. Acta Med Port. 2004 Sep-Oct;17(5):391-4. Epub 2004 Dec 20.

[Periodic fever: the first Portuguese case-report of hyper-IgD syndrome (HIDS)].

[Article in Portuguese]

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**BACKGROUND:** Periodic fever can have one of multiple causes. Among the hereditary periodic fever syndromes, hyper-IgD syndrome (HIDS) is a possible diagnosis, although, until now, no cases had been described in Portugal.

**CASE-REPORT:** We report a 25-year-old woman, with periodic fever since she was 8 months old. She had high serum IgD levels, and a molecular study of the mevalonate kinase gene was performed. A compound heterozygote was found for two mutations: V377I and T237S. This last mutation had not been observed before.

**DISCUSSION:** We analyse the clinical features that made us think on HIDS as a possible diagnosis, and we highlight the features that are important for the differential diagnosis between HIDS and other periodic fevers.

**CONCLUSIONS:** HIDS is a possible diagnosis for patients with periodic fever, even in Portugal.

PMID: 16197847 [Indexed for MEDLINE]

4214. Rheumatology (Oxford). 2006 Mar;45(3):274-82. Epub 2005 Sep 27.

Mechanism of the anti-inflammatory effect of colchicine in rheumatic diseases: a possible new outlook through microarray analysis.

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**OBJECTIVE:** Colchicine is an alkaloid that is used to alleviate acute gout and to prevent acute attacks of familial Mediterranean fever (FMF). However, it is not beneficial when given during the occurrence of an acute episode of FMF. It is believed that colchicine exerts its anti-inflammatory effect through direct interaction with microtubules. We aim to study the molecular basis of colchicine action by analysing the effect of this drug on global gene expression of HUVEC (human umbilical vein endothelial cell line) cells.

**METHODS:** HUVEC cells were exposed to various concentrations of colchicine and were harvested at different time points. Ribonucleic acid was extracted, amplified, reverse transcribed and hybridized to complementary deoxyribonucleic acid microarrays containing more than 40,000 probes to human expressed sequence tags. This approach enabled us to have a global look at the transcriptional response induced by colchicine treatment.

**RESULTS:** Colchicine changed the expression of many genes in HUVEC cells following exposure to a concentration of 100 ng/ml or higher. Following short exposure (30 or 120 min), colchicine affected genes known to be involved in the cell cycle and its regulation. However, change in expression of genes involved in neutrophil migration or other inflammatory processes were observed mainly after 12 to 24 h.

**CONCLUSIONS:** The anti-inflammatory effect of colchicine may be mediated not only through direct interaction with microtubules but also through changes at the transcriptional level. This latter effect apparently requires a higher concentration and a longer time to occur. This can explain the observation that colchicine does not have an immediate effect when given during an acute attack of FMF.

DOI: 10.1093/rheumatology/kei140

PMID: 16188942 [Indexed for MEDLINE]

4215. Rheumatol Int. 2006 May;26(7):638-40. Epub 2005 Sep 25.

The phenotype-genotype correlations of FMF patients: a single center study.

Sakallioglu O(1), Gok F, Kalman S, Gul D, Gokcay E.

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4216. Rheumatol Int. 2006 May;26(7):676-9. Epub 2005 Sep 24.

The relations between attacks and menstrual periods and pregnancies of familial Mediterranean fever patients.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by short lived, febrile serosal inflammatory attacks. Although majority of patients have random pattern of attacks, some reports described precipitating factors. There are also contradictory reports relating FMF attacks with menstruation and the natural course of their pregnancies. Seventy-two female patients with FMF with a mean age of  $34.9 \pm 12.4$  were interviewed. A standardized questionnaire was used inquiring any associations of FMF attacks of the patients with their menstruations and pregnancies. Thirty-eight patients (53%) reported that their attacks frequently coincided with their menstrual cycles and 17 patients noticed pleuritic chest pain in addition to their abdominal attacks. One patient experienced only febrile pleural attacks during her menstrual cycles. Unlike dysmenorrhoea, none of these patients' attacks responded to non-steroidal anti-inflammatory drugs. All of the patients could correctly differentiate their FMF attacks from dysmenorrhoea. Forty patients could give detailed information about the frequency and severity of their FMF attacks during 73 pregnancies: 25 patients (62.5%) experienced complete symptomatic remissions; the attacks were aggravated (7 patients), ameliorated (6 patients) or did not change (2 patients) in the rest of the pregnancies. Four patients continued to use colchicine during their pregnancies and delivered healthy babies. One patient gave birth to a child with Down's syndrome although she was not on colchicine therapy. Although FMF attacks and discomforts of menstrual cycles do overlap frequently, patients can easily differentiated them. Patients can be reasonably assured that the period of pregnancy will be comfortable but abstaining from colchicine should not be

recommended. Gynecologists must be aware of FMF in the differential diagnosis of dysmenorrhoea or endometriosis.

DOI: 10.1007/s00296-005-0041-z

PMID: 16184383 [Indexed for MEDLINE]

4217. Rheumatol Int. 2006 Jun;26(8):760-1. Epub 2005 Sep 23.

Regular abdominal pain and fever in each menstruation onset: an unusual menses-associated familial Mediterranean fever attacks and a favor result on colchicine treatment.

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We present a 38-year-old woman suffering from regular abdominal pain and fever only in each menstruation onset for 7 years. The clinical symptoms, along with inflammatory findings during painful attacks, the beneficial effect of colchicine and genetic mutation (M694 V and M680I) supported the diagnosis of familial Mediterranean fever (FMF). A literature review indicated that FMF attacks occurring only during menstruation are rarely seen. This clinical picture may be confused with gynecological disorders especially in the people of Mediterranean origin.

DOI: 10.1007/s00296-005-0055-6

PMID: 16179998 [Indexed for MEDLINE]

4218. J Immunol. 2005 Oct 1;175(7):4458-64.

Loss of IL-4 secretion from human type 1a diabetic pancreatic draining lymph node NKT cells.

Kent SC(1), Chen Y, Clemmings SM, Viglietta V, Kenyon NS, Ricordi C, Hering B, Hafler DA.

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Altered frequency and function of peripheral invariant NKT (iNKT) cells have been implicated in the regulation of murine and human type 1a diabetes. To examine regulatory cells from the site of drainage of autoinflammatory tissue and autoantigenic T cell priming in diabetes, we directly cloned iNKT cells from human pancreatic draining lymph nodes (PLN). From 451 T cell clones from control and diabetic PLN, we derived 55 iNKT cells by two methods and analyzed function by cytokine secretion. iNKT cell clones isolated from control PLN secreted IL-4 and IFN-gamma upon TCR stimulation. For type 1a diabetic subjects, PLN iNKT cell clones from three samples secreted IFN-gamma and no IL-4. In a rare recent onset diabetic sample with islet-infiltrating CD4+ T cells, the phenotype of PLN iNKT cell clones was mixed. From normal and diabetic PLN, one-third of CD1d tetramer+-sorted T cell clones were reactive with CD1d transfectants or proliferated/secreted cytokine in response to alpha-galactosylceramide-pulsed PBMCs; tetramer-staining T cell clones from diabetic PLN did not secrete IL-4. This is the first report directly examining iNKT cells from lymph nodes draining the site of autoimmunological attack in humans; iNKT cells were altered in cytokine secretion as previously reported for circulating iNKT cells in human type 1a diabetes.

PMID: 16177088 [Indexed for MEDLINE]

4219. Clin Rheumatol. 2006 Feb;25(1):83-7. Epub 2005 Sep 20.

Familial Mediterranean fever responds well to infliximab: single case experience.

Ozgocmen S(1), Ozçakar L, Ardicoglu O, Kocakoc E, Kaya A, Kiris A.

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The most common arthritic involvement in familial Mediterranean fever (FMF) is

acute recurrent monoarthritis; however, sometimes spondyloarthropathy-like findings or typical ankylosing spondylitis may also ensue. Reported here is our favorable experience with infliximab in an FMF patient who had been resistant to colchicine and disease-modifying antirheumatic drugs (sulfasalazine and methotrexate) treatments. A 72-week follow-up of the patient yielded complete remission of the febrile abdominal episodes, and spondylitis responded well. The patient's bilateral aseptic necrosis of the femoral head deteriorated and caused hip pain, discomfort, and disability. Overall, we believe that tumor necrosis factor (TNF) alpha has an important role in the disease pathogenesis and also that anti-TNF may represent a promising robust treatment alternative in FMF.

DOI: 10.1007/s10067-005-1122-9

PMID: 16172948 [Indexed for MEDLINE]

4220. Clin Rheumatol. 2006 Mar;25(2):149-52. Epub 2005 Sep 20.

Possible effect of subclinical inflammation on daily life in familial Mediterranean fever.

Ozçakar ZB(1), Yalçinkaya F, Yüksel S, Acar B, Gökmen D, Ekim M.

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(1)Department of Pediatric Nephrology, Ankara University Medical School, Ankara, Turkey. zbozcakar@yahoo.com

This study was performed to investigate the attack-free complaints of patients with familial Mediterranean fever (FMF) and the impact of colchicine on these symptoms and on subclinical inflammation. A questionnaire that includes information about the disease course and symptoms during the attack-free period was administered to the parents of 50 FMF patients. For evaluation of the attack-free period, questions were asked about four items concerning daily activities of the children-weakness, lack of appetite, sleep problems, and decreased activity. The respondents rated the items and the total score was taken as the sum of all of the specific items. The laboratory values were noted from the patients' files. During the attack-free period, patients with mild disease had higher total scores, higher weakness, and decreased activity scores than patients with moderate disease. When we compared the daily activity scores before and after colchicine therapy, a statistically significant increase was observed

in the total scores and in all of the specific item scores. Also a significant decrease was seen in the erythrocyte sedimentation rate and white blood cell counts, and a significant increase was seen in the hemoglobin levels during the attack-free period after colchicine usage. Regression of inflammation together with improvement in daily activities were observed. FMF patients seem to have complaints during the attack-free period that may be related to subclinical inflammation. Moreover, colchicine besides preventing the FMF attacks and the dangerous complication of amyloidosis also seems to hinder the symptoms of the attack-free period in children with FMF.

DOI: 10.1007/s10067-005-1148-z

PMID: 16172947 [Indexed for MEDLINE]

4221. Rheumatology (Oxford). 2005 Dec;44(12):1583-4. Epub 2005 Sep 7.

Periodic fever as a presenting sign of childhood acute lymphoblastic leukaemia.

Koffeman EC, Wulffraat NM, Bruin M, Hogeman PH, Frenkel J.

DOI: 10.1093/rheumatology/kei089

PMID: 16148019 [Indexed for MEDLINE]

4222. Arthritis Rheum. 2005 Sep;52(9):2906-16.

Tumor necrosis factor receptor I from patients with tumor necrosis factor receptor-associated periodic syndrome interacts with wild-type tumor necrosis factor receptor I and induces ligand-independent NF-kappaB activation.

Yousaf N(1), Gould DJ, Aganna E, Hammond L, Mirakian RM, Turner MD, Hitman GA, McDermott MF, Chernajovsky Y.

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OBJECTIVE: To investigate the molecular consequences of expressing mutated forms of tumor necrosis factor receptor I (TNFRI) as found in patients with

TNFR-associated periodic syndrome (TRAPS).

**METHODS:** We cloned and expressed full-length wild-type (WT) and T50K and P46L variants of TNFRI using a new tightly regulated doxycycline-dependent expression system. This system enabled the study of molecular interactions between these receptors at both physiologic and pathophysiologic levels of expression.

**RESULTS:** We used chemical crosslinking on the cell surface to show that WT and mutant forms of TNFRI, derived from TRAPS patients, interact in the absence of TNF ligand. Doxycycline-controlled up-regulation of one TNFRI allele, either WT or mutant, caused down-regulation of the other allele, indicating dynamic control of cell surface assembly. We also demonstrated that increased expression of mutant TNFRI (T50K) was associated with a parallel increase in NF-kappaB p65 (RelA) subunit activation, which did not occur with increased expression of WT TNFRI.

**CONCLUSION:** The T50K TRAPS-related variant is capable of sustaining inappropriate NF-kappaB activation, resulting in persistent auto-inflammation in target organs such as skin, synovial membrane, and the central nervous system. We conclude that some of the inflammatory processes seen in TRAPS do not involve direct interaction of TNF with its receptors, but that other proinflammatory mechanisms capable of up-regulating TNFRI expression may cause cellular activation through the NF-kappaB signaling pathway.

DOI: 10.1002/art.21268

PMID: 16142754 [Indexed for MEDLINE]

4223. Presse Med. 2005 Jul 23;34(13):958-66.

[From familial Mediterranean fever to amyloidosis].

[Article in French]

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The progression of familial Mediterranean fever is marked by the recurrence, at varying intervals, of acute flares that regress spontaneously. Prognosis, which



depends on the occurrence of amyloidosis, has been transformed by colchicine treatment. Incidence of amyloidosis is higher in certain ethnic groups (Jews from North Africa, Turks) and depends on by the specific MEFV mutation. Amyloid is composed of clusters of protein strands identical to the AA protein of secondary amyloidosis and infiltrates the walls of all arterioles except those of the central nervous system. The earliest and most consistent localization is in the kidney, where it develops over several years and in 4 stages--preclinical (latency), proteinuric, nephrotic and uremic--before concluding in end-state renal failure. Before the advent of colchicine, dialysis and transplantation, only renal amyloidosis caused clinical manifestations and lethal complications; any amyloidosis at any other sites remained latent. Prolonged survival with hemodialysis and kidney transplantation now leaves time for manifestation of these other localizations, such as infiltration into the intestines causing malabsorption, or potentially lethal cardiac lesions. Treatment of familial Mediterranean fever is based on the continuous administration of colchicine, which at the average dose of 1 to 2 mg per day can prevent flares or at least reduce their frequency or intensity. Systematic use of colchicine also prevents the onset of amyloidosis, even in the rare cases where it cannot prevent flares. These data fully justify the systematic use of colchicine for continuous prophylactic treatment from diagnosis and even after kidney transplantation, to prevent recurrence of the grafted kidney or extension to other organs. The curative efficacy of colchicine on flares is debatable, although several studies report positive results against progression of early amyloidosis.

PMID: 16142155 [Indexed for MEDLINE]

4224. Presse Med. 2005 Jul 23;34(13):947-57.

[Familial Mediterranean fever among the autoimmune diseases].

[Article in French]

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During the first attacks of familial Mediterranean fever, each of the disease symptoms can suggest a series of disorders. When the disease is older, the recurrence of symptoms may simulate some systemic diseases, but mainly suggests familial Mediterranean fever, one of a group of hereditary autoinflammatory diseases. Before the gene for familial Mediterranean fever was identified, various sets of criteria were used for diagnosis. The presence of MEFV mutations confirms the diagnosis, but the clinical criteria still determine who should undergo this genetic testing. The genotype-phenotype correlations add a prognostic dimension to the mutations identified. Genotyping can also lead to the diagnosis of the other autoinflammatory diseases, which constitute the basis of the differential diagnosis of familial Mediterranean fever. The hyperimmunoglobulinemia D syndrome (HIDS) is very similar to familial Mediterranean fever in its recessive transmission and abdominal and articular symptoms. It can be distinguished by the European origin of the patients, the presence of cervical lymph nodes and the increased IgD levels. Of the diseases with dominant transmission, the TNF receptor-associated periodic syndromes (TRAPS) are suggested by periorbital edema and migrating inflammatory cellulitis. Muckle and Wells syndrome is revealed by episodes of fever with urticaria and arthralgia, complicated by deafness and amyloidosis. Mutations in the same gene are responsible for two disorders, both appearing in childhood: familial cold urticaria syndrome (FCUS) and chronic infantile neurocutaneous articular syndrome (CINCA). The pathogenesis of familial Mediterranean fever is still unclear. Pyrin/marenostrin, the protein produced by the MEFV gene, appears to have a physiological antiinflammatory effect that inhibits proinflammatory cytokines. Mutation of the gene may eliminate this feedback mechanism and expose the patient to flares from any inflammatory stimulus, even minimal. Amyloid is produced by the serum amyloid A protein (SAA), and its occurrence is influenced by the type of MEFV mutation, but also the genotype of the gene producing SAA.

PMID: 16142154 [Indexed for MEDLINE]

4225. Presse Med. 2005 Jul 23;34(13):938-46.

[Familial Mediterranean fever, clinical and laboratory findings].

[Article in French]

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Familial Mediterranean fever is the best known of the recurrent hereditary autoinflammatory diseases. It predominantly affects subjects of Mediterranean origin, Sephardic Jews in particular. Its gene, MEFV, is located on chromosome 16 and has autosomal recessive transmission, with incomplete penetration. It codes for a protein called pyrin or marenostin, which is probably involved in the inflammatory process. In most cases, the first episodes appear before the age of 20 years and very rarely after the age of 40. Episodes usually last a few days, although they may extend over several weeks when localized in joints. Fever, occasionally pseudo-malaria, may accompany various symptoms, the most frequent of which are abdominal, articular, pleural or cutaneous. The abdomen is the classic site of this disease, and acute abdominal flares masquerade as abdominal emergencies. Musculoskeletal involvement is revealed by episodes of inflammation of the joints (more often mono- than oligoarthritis) and muscle pain. The flares are usually brief and totally reversible. Flares of thoracic pain corresponding to pleural inflammation and erysipelas-like skin eruptions have been observed. Acute symptoms disappear between flares, but hepatic splenomegaly, swollen lymph nodes or abnormal fundus of the eye may persist. Laboratory findings are typical of nonspecific inflammation, accompanied by moderate hyperleukocytosis during the flares.

PMID: 16142153 [Indexed for MEDLINE]

4226. Presse Med. 2005 Jul 23;34(13):907.

[Familial Mediterranean fever and other hereditary recurrent inflammatory diseases].

[Article in French]

Grateau G.

PMID: 16142145 [Indexed for MEDLINE]

4227. Ther Umsch. 2005 Aug;62(8):549-55.

[Exanthema as a main symptom in the febrile child].

[Article in German]

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Distinguishing in febrile children between harmless rashes and those, which require specific action, is a common problem in pediatric primary care. Major exanthematous diseases necessitating emergency hospitalization include invasive meningococcal disease and rarely gram-negative septicaemia caused by other pathogens, staphylococcal and streptococcal toxic shock syndrome, endocarditis, fever and rash in travellers returning from tropical countries and drug hypersensitivity syndrome. Therapeutic intervention is also necessary in patients with scarlet fever, rheumatic fever, varicella in postpuberal and immunocompromised individuals, in Kawasaki's disease, in Still's disease and in other non-infectious, inflammatory diseases (e.g., familial mediterranean fever). Finally, various specific measures need to be taken in reportable diseases, erythema infectiosum (parvovirus B19), primary HIV infection and in Henoch-Schölein purpura.

DOI: 10.1024/0040-5930.62.8.549

PMID: 16136820 [Indexed for MEDLINE]

4228. Rheumatol Int. 2005 Aug;25(6):487-8. Epub 2004 Nov 3.

Serum RANTES, MIP-1alpha, and MCP-1 levels in Behçet's disease.

Ozer HT, Erken E, Gunesacar R, Kara O.

DOI: 10.1007/s00296-004-0519-0

PMID: 16133585 [Indexed for MEDLINE]

4229. *Pediatr Nephrol*. 2005 Nov;20(11):1642-4. Epub 2005 Aug 16.

IgA nephropathy in an Italian child with familial Mediterranean fever.

Rigante D(1), Federico G, Ferrara P, Maggiano N, Avallone L, Pugliese AL, Stabile A.

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Familial Mediterranean fever is an autosomal recessive disorder characterized by transient attacks of fever and polyserositis with substantial risk of developing amyloidotic nephropathy over time. We report an Italian child with familial Mediterranean fever presenting with hematuria during attacks in whom kidney biopsy documented the presence of mesangial IgA deposits and the absence of amyloidosis. Kidney biopsy should be performed in patients showing microscopic or gross hematuria during attacks of familial Mediterranean fever in order to gain additional epidemiological data about specific features of renal involvement and to allow adequate treatment.

DOI: 10.1007/s00467-005-2023-5

PMID: 16133043 [Indexed for MEDLINE]

4230. *Bone*. 2006 Jan;38(1):41-7. Epub 2005 Aug 24.

A missense mutation in *pstpip2* is associated with the murine autoinflammatory disorder chronic multifocal osteomyelitis.

Ferguson PJ(1), Bing X, Vasef MA, Ochoa LA, Mahgoub A, Waldschmidt TJ, Tygrett LT, Schlueter AJ, El-Shanti H.

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Chronic recurrent multifocal osteomyelitis (CRMO) is an autoinflammatory disorder that primarily affects bone but is often accompanied by inflammation of the skin and/or gastrointestinal tract. The etiology is unknown but evidence suggests a genetic component to disease susceptibility. Although most cases of CRMO are sporadic, there is an autosomal recessive syndromic form of the disease, called Majeed syndrome, which is due to homozygous mutations in LPIN2. In addition, there is a phenotypically similar mouse, called cmo (chronic multifocal osteomyelitis) in which the disease is inherited as an autosomal recessive disorder. The cmo locus has been mapped to murine chromosome 18. In this report, we describe phenotypic abnormalities in the cmo mouse that include bone, cartilage and skin inflammation. Utilizing a backcross breeding strategy, we refined the cmo locus to a 1.3 Mb region on murine chromosome 18. Within the refined region was the gene pstpip2, which shares significant sequence homology to the PSTPIP1. Mutations in PSTPIP1 have been shown to cause the autoinflammatory disorder PAPA syndrome (pyogenic arthritis, pyoderma gangrenosum and acne). Mutation analysis, utilizing direct sequencing, revealed a single base pair change c.293T --> C in the pstpip2 gene resulting in a highly conserved leucine at amino acid 98 being replaced by a proline (L98P). No other mutations were found in the coding sequence of the remaining genes in the refined interval, although a 50 kb gap remains unexplored. These data suggest that mutations in pstpip2 may be the genetic explanation for the autoinflammatory phenotype seen in the cmo mouse.

DOI: 10.1016/j.bone.2005.07.009

PMCID: PMC3726202

PMID: 16122996 [Indexed for MEDLINE]

4231. Clin Chem. 2005 Sep;51(9):1725-7.

Multiplex molecular diagnosis of MEFV mutations in patients with familial Mediterranean fever by LightCycler real-time PCR.

Rossou E(1), Kouvatsi A, Aslanidis C, Deltas C.

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DOI: 10.1373/clinchem.2005.050344

PMID: 16120953 [Indexed for MEDLINE]

4232. Am J Nephrol. 2005 Sep-Oct;25(5):434-40. Epub 2005 Aug 23.

Genetic risk factors of amyloidogenesis in familial Mediterranean fever.

Delibaş A(1), Oner A, Balci B, Demircin G, Bulbul M, Bek K, Erdoğan O, Baysun S, Yilmaz E.

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**BACKGROUND/AIMS:** Evaluation of the risk factors, and phenotype-genotype correlation of familial Mediterranean fever (FMF) gene (MEFV) and serum amyloid A1 (SAA1) gene polymorphisms in renal amyloidosis.

**METHODS:** We investigated MEFV and SAA1 genotypes (alpha, beta, and gamma isoforms) in 50 FMF patients and 50 healthy children. Tel-Hashomer criteria were used for the diagnosis and severity scoring of FMF.

**RESULTS:** The most common MEFV mutation and SAA1 genotype were M694V/M694V (n = 26/50) and SAA1 alpha/alpha (n = 26/50), respectively. Positive family history for amyloidosis was significantly higher ( $p < 0.001$ ) with more severe clinical course ( $p = 0.006$ ) in the amyloidosis group than the non-amyloid group. In M694V/M694V mutation, erysipelas-like skin erythema ( $p = 0.029$ ), arthritis ( $p = 0.004$ ), arthralgia ( $p < 0.001$ ) were significantly more frequent with higher severity scores ( $p = 0.008$ ) than the patients with other mutations. Comparison of the SAA1 alpha/alpha genotype with other genotypes revealed more frequent arthritis ( $p = 0.003$ ) in the SAA1 alpha/alpha genotype. In amyloidosis group patients having both M694V/M694V and SAA1 alpha/alpha genotypes were the largest subgroup (n = 14,  $p < 0.001$ ). Logistic regression analysis for amyloidosis corrected risk revealed a 1.2 times increase in M694V/M694V, a 2.4 times increase in SAA1 alpha/alpha genotypes and a 2.5 times increase when both are together.

**CONCLUSION:** Positive family history for amyloidosis and presence of SAA1 alpha/alpha genotype in M694V/M694V mutation may predispose to amyloidosis by

increasing the clinical severity. Therefore, in such children early colchicine treatment might be recommended even if they are asymptomatic.

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DOI: 10.1159/000087824

PMID: 16118480 [Indexed for MEDLINE]

4233. Nihon Rinsho. 2005 Jul;63 Suppl 7:15-6.

[Immunologic tests: Immunoglobulin D].

[Article in Japanese]

Kubo N(1), Sakurabayashi I, Kawai T.

Author information:

(1)Brigham and Women's Hospital, Vascular Medicine Research, Harvard Medical School, USA.

PMID: 16111176 [Indexed for MEDLINE]

4234. Adv Exp Med Biol. 2005;568:101-15.

Periodic fever.

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DOI: 10.1007/0-387-25342-4\_7

PMID: 16107068 [Indexed for MEDLINE]



4235. Ann Rheum Dis. 2005 Sep;64(9):1384-5.

Colchicine responsive periodic fever syndrome associated with pyrin I591T.

Fisher BA, Lachmann HJ, Rowczenio D, Goodman HJ, Bhalara S, Hawkins PN.

DOI: 10.1136/ard.2004.030379

PMCID: PMC1755665

PMID: 16100353 [Indexed for MEDLINE]

4236. Curr Opin Rheumatol. 2005 Sep;17(5):586-99.

Familial autoinflammatory diseases: genetics, pathogenesis and treatment.

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**PURPOSE OF REVIEW:** The systemic autoinflammatory diseases are characterized by seemingly unprovoked inflammation, without major involvement of the adaptive immune system. This review focuses mainly on a subset of these illnesses, the hereditary recurrent fevers, which include familial Mediterranean fever, the tumor necrosis factor receptor-associated periodic syndrome, the hyperimmunoglobulinemia D with periodic fever syndrome, and cryopyrin-associated periodic syndromes. This review elucidates how recent advances have impacted diagnosis, pathogenesis, and treatment.

**RECENT FINDINGS:** More than 170 mutations have been identified in the four genes underlying the six hereditary recurrent fevers. Genetic testing has broadened the clinical and geographic boundaries of these illnesses, given rise to the concept of the cryopyrin-associated periodic syndromes as a disease spectrum, and permitted diagnosis of compound heterozygotes for mutations in two different hereditary recurrent fever genes. Genetics has also advanced our understanding of amyloidosis, a complication of the hereditary recurrent fevers, and suggested a possible role for common hereditary recurrent fever variants in other inflammatory conditions. Recent advances in molecular pathophysiology include the

elucidation of the N-terminal PYRIN domain in protein-protein interactions, the description of the NALP3 (cryopyrin) inflammasome as a macromolecular complex for interleukin-1 $\beta$  activation, and the identification of signaling defects other than defective receptor shedding in patients with tumor necrosis factor receptor-associated periodic syndrome. These molecular insights form the conceptual basis for targeted biologic therapies.

SUMMARY: Advances in molecular genetics extend our ability to recognize and treat patients with systemic autoinflammatory diseases and inform our understanding of the regulation of innate immunity in humans.

PMID: 16093838 [Indexed for MEDLINE]

4237. Curr Opin Rheumatol. 2005 Sep;17(5):579-85.

Caspase recruitment domain 15 mutations and rheumatic diseases.

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Comment in

Curr Opin Rheumatol. 2005 Sep;17(5):566-7.

PURPOSE OF REVIEW: The purpose of this article is to review the foundational work and current developments on a group of rheumatic disorders associated with mutations in the caspase recruitment domain 15/nucleotide oligomerization domain 2 gene.

RECENT FINDINGS: To date, there are at least 10 arthritic conditions for which specific genetic mutations have been demonstrated. They include familial Mediterranean fever; tumor necrosis factor receptor associated periodic syndrome; hyper immunoglobulin D syndrome; neonatal onset multisystemic inflammatory disease; pyogenic arthritis pyoderma gangrenosum and acne; Muckle-Wells syndrome; familial cold autoinflammatory syndrome; immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; Crohn's disease; and familial and sporadic sarcoid granulomatous arthritis. This review focuses on recent progress in the

last two diseases and the caspase recruitment domain 15 genetic defects with which they are associated. Up to 50% of patients with familial granulomatous arthritis (Blau's syndrome), 90% of those with sporadic granulomatous arthritis (early-onset sarcoidosis), and 40% of individuals with Crohn's disease have documented mutations in the caspase recruitment domain 15 gene.

SUMMARY: Although histologically, Crohn's disease and familial and sporadic sarcoid granulomatous arthritis are distinct from rheumatoid arthritis because of the defining presence (albeit in not all cases) of non-caseating granulomata in the synovial and intestinal tissues, respectively, they still represent a promising model of both chronic synovitis and uveitis. In addition, once the actual mechanism is discovered by which defects of the caspase recruitment domain 15 gene product lead to chronic arthritis, it may uncover unsuspected biologic targets for therapeutics.

PMID: 16093837 [Indexed for MEDLINE]

4238. Intern Med. 2005 Jul;44(7):765-6.

A Japanese case of familial Mediterranean fever with homozygosity for the pyrin E148Q mutation.

Suzuki T(1), Nakamura A, Yazaki M, Ikeda S.

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(1)Department of Internal Medicine, Omachi City General Hospital, Omachi.

Comment in

Intern Med. 2005 Jul;44(7):694-5.

PMID: 16093605 [Indexed for MEDLINE]

4239. Intern Med. 2005 Jul;44(7):694-5.

Hereditary periodic fever syndromes: autoinflammatory diseases.

Kobayashi S.

Comment on

Intern Med. 2005 Jul;44(7):765-6.

PMID: 16093588 [Indexed for MEDLINE]

4240. Neth J Med. 2005 Jul-Aug;63(7):260-4.

Effect of etanercept and anakinra on inflammatory attacks in the hyper-IgD syndrome: introducing a vaccination provocation model.

Bodar EJ(1), van der Hilst JC, Drenth JP, van der Meer JW, Simon A.

Author information:

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**BACKGROUND:** Hyper-IgD and periodic fever syndrome (HIDS) is an hereditary autoinflammatory syndrome, characterised by recurrent inflammatory attacks. Treatment of HIDS is difficult, although simvastatin is beneficial and etanercept might be effective. Studying the treatment of a rare periodic syndrome is complicated by the varying frequency and severity of symptoms and low prevalence. Our aim was to develop a system of clinical observations to evaluate effectiveness of treatment-on-demand.

**METHODS:** Seven fever episodes in three HIDS patients were monitored, with and without administration of etanercept or anakinra. We developed a clinical score, which includes 12 symptoms. In one patient, inflammatory attacks were provoked by vaccination.

**RESULTS AND CONCLUSIONS:** At the onset of an attack, all patients reported a clinical score between 20 and 25. The score was used to quantify severity and define the end of an attack. Reproducible monitoring of inflammatory episodes was difficult, even in this pilot study. The effect of early administration of etanercept was variable. In one patient, a fever episode could be readily provoked within 12 to 24 hours by vaccination. In this patient, the IL-1ra analogue anakinra was more successful in aborting the inflammatory attack than etanercept. We propose that this vaccination model will allow evaluation of

treatment-on-demand in a controlled setting.

PMID: 16093577 [Indexed for MEDLINE]

4241. Semin Arthritis Rheum. 2005 Aug;35(1):57-64.

Evaluation of disease severity in familial Mediterranean fever.

Mor A(1), Shinar Y, Zaks N, Langevitz P, Chetrit A, Shtrasburg S, Rabinovitz E, Livneh A.

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**OBJECTIVE:** To establish a new, objective, statistically based severity score for familial Mediterranean fever (FMF).

**METHODS:** One hundred consecutive FMF patients were evaluated independently by 2 FMF experts for severity of their disease and were assigned to 1 of 3 severity levels: mild, intermediate, or severe. Nine candidate criteria, reflecting objective suffering and disability, were analyzed to determine their weight for patient placement in the 3 predefined severity groups.

**RESULTS:** Candidate criteria best differentiating between the 3 patient categories were the frequency of attacks, the number of sites affected during an attack and during the course of the disease, and the duration of the attacks. These criteria were applied in a classification-tree model to establish a new FMF-severity score (F-SS). The first set of F-SS (F-SS-1) was highly sensitive and specific.

Integrating F-SS-1 with clinical parameters strongly associated with disease severity resulted in a simplified score, the second set of F-SS (F-SS-2).

**CONCLUSIONS:** New, useful, objective, and valid severity scores were established and found to distinguish between patients with mild, intermediate, and severe diseases with high sensitivity and specificity.

**RELEVANCE:** The F-SS established may be important for treatment decisions, prognosis evaluation, and comparative analysis of patient populations.

DOI: 10.1016/j.semarthrit.2005.02.002

PMID: 16084225 [Indexed for MEDLINE]

4242. J Immunol. 2005 Aug 15;175(4):2630-4.

IL-converting enzyme/caspase-1 inhibitor VX-765 blocks the hypersensitive response to an inflammatory stimulus in monocytes from familial cold autoinflammatory syndrome patients.

Stack JH(1), Beaumont K, Larsen PD, Straley KS, Henkel GW, Randle JC, Hoffman HM.

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Familial cold autoinflammatory syndrome (FCAS) and the related autoinflammatory disorders, Muckle-Wells syndrome and neonatal onset multisystem inflammatory disease, are characterized by mutations in the CIAS1 gene that encodes cryopyrin, an adaptor protein involved in activation of IL-converting enzyme/caspase-1. Mutations in cryopyrin are hypothesized to result in abnormal secretion of caspase-1-dependent proinflammatory cytokines, IL-1beta and IL-18. In this study, we examined cytokine secretion in PBMCs from FCAS patients and found a marked hyperresponsiveness of both IL-1beta and IL-18 secretion to LPS stimulation, but no evidence of increased basal secretion of these cytokines, or alterations in basal or stimulated pro-IL-1beta levels. VX-765, an orally active IL-converting enzyme/caspase-1 inhibitor, blocked IL-1beta secretion with equal potency in LPS-stimulated cells from FCAS and control subjects. These results further link mutations in cryopyrin with abnormal caspase-1 activation, and support the clinical testing of caspase-1 inhibitors such as VX-765 in autoinflammatory disorders.

PMID: 16081838 [Indexed for MEDLINE]

4243. Amyloid. 2005 Mar;12(1):26-32.

Relative transcriptional activities of SAA1 promoters polymorphic at position -13(T/C): potential association between increased transcription and amyloidosis.

Moriguchi M(1), Kaneko H, Terai C, Koseki Y, Kajiyama H, Inada S, Kitamura Y,

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The risk associated with the serum amyloid A (SAA) 1 gene and developing AA-amyloidosis is still controversial. In familial Mediterranean fever or Caucasoid rheumatoid arthritis (RA), the SAA1.1 allele is a risk factor for the development of AA-amyloidosis. However, individuals with the SAA1.3 allele are susceptible to AA-amyloidosis in the Japanese RA population, but those with the SAA1.1 are not. Previous reports have indicated that the -13T/C single nucleotide polymorphism (SNP) at the 5'-flanking region of SAA1 appears to be a better marker of AA-amyloidosis than the exon-3 based haplotype, i.e., SAA1.1 or SAA1.3, in both Japanese and American Caucasian populations. So far, it is unknown why the -13T SNP increases the amyloidogenicity of the patients. In the present study, a luciferase reporter gene assay showed that the transcriptional activity of the SAA1 having the -13T-containing promoter was significantly higher than activities of those with -13C-containing promoters (Fisher's protected least significance difference test). We suggest that having the -13T SNP in the SAA1 promoter correlates with the amyloidogenicity in part as a result of this increased transcriptional activity.

DOI: 10.1080/13506120500032394

PMID: 16076608 [Indexed for MEDLINE]

4244. Hist Sci Med. 2005 Apr-June;39(2):143-54.

[The autumn crocus: two millenniums of actuality].

[Article in French]

Fabre AJ.

Colchicum holds a singular place in the History of Medicine. Many names were given through the ages: "ephemera", "finger of Hermes", "pater noster", "tue-chiens". Modern phytonyms clearly refer to the land of Colchis, a mythical place close to Armenia. Several centuries were needed to understand that, despite

a frightening reputation, colchic was an elective treatment for the gout. In its long story, appears famous personages as Theophraste, Paulus Aeginata, Gilbertus Anglicus, the baron Storck and Benjamin Franklin. In modern times, colchicum has received besides gout, a wide array of new indications, among others: Behcet disease, collagen diseases and malignancies. A scarcely known chapter of genetics is the findings in 1889, by B. Pernice, an obscure physician from Palermo, of the major mitotic changes observed on gastric and intestinal mucosa of two dogs which had received large doses of colchicum. In spite of their scientific value, the works of Pernice remained largely ignored until 1949. Recent advances in colchicotherapy have shown fascinating new fields for research: thus in the familial Mediterranean fever, close to periodic disease, genetic disorder elective for subjects originated from all over Mediterranean and around Black Sea... the mythical country of Colchis. No other medicinal plant than colchic, except poppy, can give such records of perennial use in such a wide range of disorders.

PMID: 16060020 [Indexed for MEDLINE]

4245. Emerg Med J. 2005 Aug;22(8):599-600.

Troponin for prediction of cardiovascular collapse in acute colchicine overdose.

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The use of colchicine, a treatment for acute gout and familial Mediterranean fever, is limited by its toxicity. A relatively low dose of colchicine may be fatal. After a colchicine overdose, monitoring should include 6-12 hourly serum troponin measurements. A rising troponin level predicts cardiovascular collapse and is an indication for more intensive management.

DOI: 10.1136/emj.2002.004036

PMCID: PMC1726901

PMID: 16046775 [Indexed for MEDLINE]



4246. Cell Death Differ. 2006 Feb;13(2):236-49.

Cryopyrin and pyrin activate caspase-1, but not NF-kappaB, via ASC oligomerization.

Yu JW(1), Wu J, Zhang Z, Datta P, Ibrahimi I, Taniguchi S, Sagara J, Fernandes-Alnemri T, Alnemri ES.

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Mutations in cryopyrin and pyrin proteins are responsible for several autoinflammatory disorders in humans, suggesting that these proteins play important roles in regulating inflammation. Using a HEK293 cell-based reconstitution system that stably expresses ASC and procaspase-1 we demonstrated that neither cryopyrin nor pyrin or their corresponding disease-associated mutants could significantly activate NF-kappaB in this system. However, both cryopyrin and two disease-associated cryopyrin mutants induced ASC oligomerization and ASC-dependent caspase-1 activation, with the disease-associated mutants being more potent than the wild-type (WT) cryopyrin, because of increased self-oligomerization. Contrary to the proposed anti-inflammatory activity of WT pyrin, our results demonstrated that pyrin, like cryopyrin, can also assemble an inflammasome complex with ASC and procaspase-1 leading to ASC oligomerization, caspase-1 activation and interleukin-1beta processing. Thus, we propose that pyrin could function as a proinflammatory molecule.

DOI: 10.1038/sj.cdd.4401734

PMID: 16037825 [Indexed for MEDLINE]

4247. J Clin Endocrinol Metab. 2005 Oct;90(10):5884-7. Epub 2005 Jul 19.

Adrenal and gonadal hormone variations during a febrile attack in a woman with tumor necrosis factor receptor-associated periodic syndrome.

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**CONTEXT:** TNF-receptor-associated periodic syndrome (TRAPS) is a hereditary fever syndrome that results from mutations in the TNF-receptor superfamily 1A gene (TNFRSF1A). It is characterized by periodic fever, arthralgia, abdominal pain, myalgia, headache, and skin lesions.

**OBJECTIVE:** Because adrenal and gonadal hormone cascades are modulated by TNF, this study aimed to investigate specific hormones and enzyme steps during an attack phase in a woman with TRAPS.

**DESIGN:** Morning blood samples were taken from a 38-yr-old woman before, during, and after the febrile episode in the late luteal, menstrual, and early follicular phase of the menstrual cycle, respectively.

**RESULTS:** Serum cortisol levels were markedly increased throughout the entire observation period and demonstrated a dip during the attack phase. In contrast, serum levels of dehydroepiandrosterone and 17-hydroxyprogesterone demonstrated a sharp rise during the febrile episode. Dehydroepiandrosterone in relation to androstenedione or cortisol was increased. Indicative of aromatase activation, estrone and 17beta-estradiol demonstrated a marked increase during the attack phase.

**CONCLUSION:** This study suggests that some important steroid hormone-conversion steps are activated (aromatase) and inhibited (second step of the P450c17 and the 3beta-hydroxysteroid dehydrogenase) during the inflammatory attack phase in a TRAPS patient. These changes of enzyme pathways are typical on the basis of increased TNF signaling.

DOI: 10.1210/jc.2005-1016

PMID: 16030167 [Indexed for MEDLINE]

4248. J Orthop Res. 2005 Jul;23(4):877-81. Epub 2005 Feb 19.

Colchicine inhibits fracture union and reduces bone strength--in vivo study.

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**INTRODUCTION:** Recent studies have demonstrated that Colchicine (CO) prevents heterotopic ossification (HO) after total hip replacement in patients suffering from familial Mediterranean fever (FMF). Other investigators have proved that CO is an in vitro inhibitor of proliferation of osteoblasts and osteosarcoma cells, and is a non-selective mitosis inhibitor and selective inhibitor of mineralization.

**METHODS:** A double blind prospective study comprised four groups of adult rats. The left posterior tibia in each rat was fractured except in one of the control groups. The study groups were treated with CO 1 mg/kg/day 1 week before, or on the fracture day. The control groups did not receive CO treatment. Six weeks after fracture induction the groups were compared radiographically mechanically and histologically.

**RESULTS:** Prolonged CO treatment had a significant negative influence on fracture healing according to radiological, clinical, mechanical ( $p<0.02$ ), and pathological parameters ( $p<0.0001$ ).

**CONCLUSIONS:** We were able to demonstrate that prolonged CO treatment reduced bone healing.

DOI: 10.1016/j.orthres.2004.11.014

PMID: 16023003 [Indexed for MEDLINE]

4249. Pathol Biol (Paris). 2006 Apr;54(3):171-8. Epub 2005 Jul 12.

[The "self-inflammatory syndrome"].

[Article in French]

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The "self-inflammatory syndrome" gathers diseases all characterized by a recurrent inflammatory syndrome with fever, in the absence of infection or neoplasia. It is based on a genetic support characterized by mutations in genes implied in the inflammatory response and in the activation of the cytokine network. The diseases associated with this syndrome are familial Mediterranean fever (FMF), TRAPS (tumor necrosis factor receptor super family 1 A-associated periodic syndrome), familial cold urticaria, the Muckle-Wells syndrome, the hyper IgD syndrome and CINCA. The clinical symptoms of all these diseases include in the auto-inflammatory syndrome are quite similar: recurrent attacks, with fever, articular, abdominal, cutaneous symptoms, and an inflammatory syndrome.

DOI: 10.1016/j.patbio.2005.06.001

PMID: 16019157 [Indexed for MEDLINE]

4250. Neurochem Res. 2005 Mar;30(3):297-309.

Hypothalamic proline-rich polypeptide is an oxidative burst regulator.

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The AGAPEPAEPAQPGVY proline-rich polypeptide (PRP) was isolated from neurosecretory granules of the bovine neurohypophysis; it is produced by N. supraopticus and N. paraventricularis. PRP possesses immune-modulating activity, preventing the death of Gram-negative bacteria-infected mice. Here we show that PRP does not affect human peripheral blood neutrophils and monocytes phagocytosis but dramatically enhances spontaneous or fMLP- and PMA-induced, and also phagocytosis-dependent, oxidative burst. We demonstrated the regulatory role of PRP on the oxidative burst induction of normal and relapsing inflammatory disease (Behcet's disease and familial Mediterranean fever) neutrophils and monocytes. Our results suggest a previously undescribed role for the hypothalamic peptide within primary activated neutrophils and monocytes, since we provide evidence

that PRP can differentially regulate both chemotaxis- and phagocytosis-dependent oxidative burst in normal and inflammatory disease effector cells.

PMID: 16018573 [Indexed for MEDLINE]

4251. Amyloid. 2005 Jun;12(2):115-9.

Serum amyloid A serum concentrations and genotype do not explain low incidence of amyloidosis in Hyper-IgD syndrome.

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**BACKGROUND:** Hyper-IgD and periodic fever syndrome (HIDS) is an autosomal recessively inherited disorder characterized by recurrent episodes of fever and inflammation. Unlike other chronic inflammatory conditions, amyloidosis is very rare in HIDS. For deposition of amyloid of the AA type, high concentrations of SAA are a prerequisite, together with certain SAA1 gene polymorphisms. The SAA1.1 genotype predisposes for amyloidosis, while SAA1.5 genotype exerts a protective effect.

**AIM OF THE STUDY:** To determine if SAA concentrations and SAA1 gene polymorphisms could explain the virtual absence of amyloidosis in HIDS patients.

**METHODS:** We measured SAA and CRP concentrations in serum of 20 HIDS patients during an attack and during the asymptomatic phase. Genotype of SAA1 gene was determined in 60 HIDS patients.

**RESULTS:** SAA serum concentrations during attacks were very high (median 205 mg/l; range 75-520 mg/l, normal <3.1 mg/l). During attack-free periods 45% of patients still had elevated SAA concentrations. The distribution of the genotype of SAA1 gene in HIDS was similar to healthy controls (SAA1.1 0.41 vs. 0.50 p=0.32).

**CONCLUSION:** Patients with HIDS have high SAA during attacks and show sub-clinical inflammation when asymptomatic. The low incidence of amyloidosis cannot be explained by a predominance of non amyloidogenic SAA related genotypes.

DOI: 10.1080/13506120500106982  
PMID: 16011988 [Indexed for MEDLINE]

4252. J Surg Oncol. 2005 Jul 1;91(1):17-25.

Malignant peritoneal mesothelioma.

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Comment in

J Surg Oncol. 2006 Apr 1;93(5):434.

**BACKGROUND AND OBJECTIVES:** The incidence of malignant peritoneal mesothelioma (MPM) is rising. Our aim was to present our experience with this entity in order to increase the awareness about this disease to avoid misdiagnosis.

**METHODS:** Records of seven patients with histologically confirmed MPM were retrospectively reviewed. Demographic and clinicopathological findings were studied in detail.

**RESULTS:** There were two females and 5 males; mean age was 50.3 years (range 16-73). Asbestos exposure was recorded in two patients, familial Mediterranean fever in one and previous radiation in one. Main presentations were abdominal pain and distension. None of the patients was diagnosed preoperatively. The average delay in diagnosis was 10 months. Calretinin expression was identified in all tumors. Three patients were treated with cytoreductive surgery combined with systemic chemotherapy. Two patients who remain alive were young female patients who were diagnosed by laparoscopic incidental findings and were treated with cytoreductive surgery combined with hyperthermic intraoperative intraperitoneal chemotherapy (HIIC). Median survival was 19.7 months. The average survival time of the five patients who died of their diseases was 10.2 months.

**CONCLUSIONS:** An awareness of MPM is important to prevent misdiagnosis. Immunohistochemistry has an important role in confirming the diagnosis. MPM remains a difficult therapeutic challenge. Thorough cytoreductive surgery is the cornerstone of current treatment while HIIC is a promising strategy in suitable patients.

DOI: 10.1002/jso.20266

PMID: 15999348 [Indexed for MEDLINE]

4253. Acad Emerg Med. 2005 Jul;12(7):671-4.

Urine leukotriene B4 in familial Mediterranean fever and other forms of right lower abdominal pain.

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**BACKGROUND:** Acute right lower abdominal pain may present a diagnostic dilemma.

Leukotrienes have been found to be elevated in familial Mediterranean fever

(FMF), a disease manifesting with recurrent episodes of "acute abdomen."

**OBJECTIVES:** To determine whether urine leukotriene B4 (LTB4) may differentiate between an FMF attack and some other forms of acute right lower abdominal pain.

**METHODS:** The LTB4 level was determined, using a commercial enzyme-linked immunosorbent assay (ELISA), in urine samples obtained from 36 patients with acute (< 24 hours) right lower abdominal pain presenting to the emergency department, and from 18 healthy volunteers.

**RESULTS:** Compared with the healthy control subjects, LTB4 was significantly higher in those who had FMF (12 patients,  $p < 0.03$ ). In other forms of acute right lower abdominal pain, including appendicitis (eight patients), urologic disorders (eight patients), and nonspecific abdominal pain (eight patients), intermediate levels of LTB4 were observed, not significantly different from those of either FMF patients or healthy control subjects.

**CONCLUSIONS:** In the samples tested, urine LTB4 levels were not instrumental in differentiating FMF from other acute right lower abdominal pain.

DOI: 10.1197/j.aem.2005.02.011

PMID: 15995103 [Indexed for MEDLINE]

4254. J Med Genet. 2005 Jul;42(7):551-7.

Homozygous mutations in LPIN2 are responsible for the syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anaemia (Majeed syndrome).

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**BACKGROUND:** Majeed syndrome is an autosomal recessive, autoinflammatory disorder characterised by chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anaemia. The objectives of this study were to map, identify, and characterise the Majeed syndrome causal gene and to speculate on its function and role in skin and bone inflammation.

**METHODS:** Six individuals with Majeed syndrome from two unrelated families were identified for this study. Homozygosity mapping and parametric linkage analysis were employed for the localisation of the gene responsible for Majeed syndrome. Direct sequencing was utilised for the identification of mutations within the genes contained in the region of linkage. Expression studies and in silico characterisation of the identified causal gene and its protein were carried out.

**RESULTS:** The phenotype of Majeed syndrome includes inflammation of the bone and skin, recurrent fevers, and dyserythropoietic anaemia. The clinical picture of the six affected individuals is briefly reviewed. The gene was mapped to a 5.5 cM interval (1.8 Mb) on chromosome 18p. Examination of genes in this interval led to the identification of homozygous mutations in LPIN2 in affected individuals from the two families. LPIN2 was found to be expressed in almost all tissues. The function of LPIN2 and its role in inflammation remains unknown.

**CONCLUSIONS:** We conclude that homozygous mutations in LPIN2 result in Majeed syndrome. Understanding the aberrant immune response in this condition will shed light on the aetiology of other inflammatory disorders of multifactorial aetiology including isolated chronic recurrent multifocal osteomyelitis, Sweet syndrome, and psoriasis.

DOI: 10.1136/jmg.2005.030759

PMCID: PMC1736104

PMID: 15994876 [Indexed for MEDLINE]



4255. Presse Med. 2005 May 14;34(9):640-6.

[Multisystemic amyloidosis. Clinical study of 39 patients in Lebanon].

[Article in French]

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**OBJECTIVE:** Clinical analysis of multisystem amyloidosis in Lebanon, by histological type.

**METHOD:** Retrospective study of 39 cases of multisystem amyloidosis diagnosed histologically in a university hospital center between 1991 and 2002. It analyzed the following clinical data: age, gender, type of presentation, time from symptom onset to diagnosis, clinical features, concomitant diseases, family history of amyloidosis, biopsy sites, presence of urinary or serum monoclonal gammopathy, immunohistochemical type, prognosis and treatment.

**RESULTS:** Median age at diagnosis was 56+/-18 years. The overall ratio of men to woman was 1.4. AL amyloidosis (amyloid light chain) accounted for 54% (21/39) of the cases, AA (amyloid-associated) amyloidosis 36% (14/39), while 10% (4/39) were not typed. Among the 21 cases of AL amyloidosis, 12 were idiopathic (57%) and 9 (43%) were associated with multiple myeloma; among the 14 cases of AA amyloidosis, 7 were associated with familial Mediterranean fever and 5 with chronic disorders. Proteinuria was often the first symptom. The initial manifestations in AL amyloidosis patients with myeloma were more often related to amyloidosis than to myeloma. Renal involvement was seen in 95% (37/39) of all cases (95% of AL versus 93% of AA), proteinuria in 87% of cases and renal failure in 72%. Cardiac amyloidosis (57% of AL versus 7% of AA;  $p>0.05$ ), infiltration of the tongue (19% of AL versus 0% of AA;  $p>0.05$ ) and neurological manifestations (24% of AL versus 7% of AA;  $p>0.05$ ) were more frequent in AL amyloidosis. The 7 patients who died (18%) had AL amyloidosis (5 of them had myeloma). Heart failure was the most frequent cause of death related to amyloid.

**CONCLUSION:** Multisystem amyloidosis is frequent in Lebanon and familial Mediterranean fever is still frequently associated with the secondary type. Accurate diagnosis and classification are essential for the prognosis and

treatment of the disease. Poor prognosis was associated with the AL type, especially when accompanied by myeloma, and with cardiac amyloidosis.

PMID: 15988337 [Indexed for MEDLINE]

4256. Nephrol Dial Transplant. 2005 Aug;20(8):1721-5. Epub 2005 Jun 21.

Clinicopathological and epidemiological analysis of amyloidosis in Turkish patients.

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**BACKGROUND:** The aim of the present study was to assess the correlation of immunohistochemical subtyping with clinical diagnosis in order to achieve useful epidemiological data regarding amyloidosis in Turkish patients.

**METHOD:** We carried out immunohistochemical studies on 128 biopsies from various sites of 111 patients with biopsy-proven amyloidosis and, based on the results, classified the patients. We assessed the correlation of immunohistochemical subtype with clinical diagnosis and gathered epidemiological data.

**RESULTS:** The sites most biopsied were kidney and rectum, followed by the testicle, liver, small intestine and bladder. Amyloid deposits showed positive staining with a single antibody in 120 biopsies. Pure amyloid A (AA) positivity was seen in 113 biopsies; six biopsies were positive for amyloid lambda (AL) and one for beta2-microglobulin (beta2MG). The clinical diagnoses of 81 patients (98 biopsies all AA positive) were suggestive of familial Mediterranean fever (FMF). Also AA positive were eight patients with tuberculosis, seven patients with rheumatoid arthritis, four patients with bronchiectasis and one patient with Crohn's disease. The biopsies from seven patients clinically suspected to have plasma cell dyscrasias were AL positive. One patient undergoing haemodialysis was beta2MG positive. Two patients without definite diagnoses showed double or triple positivity, which could not be interpreted and classified immunohistochemically.

**CONCLUSIONS:** This study demonstrates that the predominant association of AA amyloidosis is with FMF. It also suggests that the routine immunohistochemical

study of patients with amyloidosis who are of certain ethnic backgrounds suffices for classifying the subtype of amyloid fibril protein and the related disease.

DOI: 10.1093/ndt/gfh890

PMID: 15972323 [Indexed for MEDLINE]

4257. Clin Exp Rheumatol. 2005 May-Jun;23(3):357-63.

Diagnosis delay in familial Mediterranean fever (FMF): social and gender gaps disclosed.

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**OBJECTIVE:** To characterize the factors contributing to a greater than 10 year delay in the diagnosis of familial Mediterranean fever (FMF).

**METHODS:** 50 patients, in whom diagnosis of FMF was delayed by more than 10 years, comprised the study population. The clinical, demographic and molecular genetic characteristics were compared to a control group of 50 FMF patients, in whom the diagnosis was made within a reasonable time period (less than 5 years from onset). Additional factors contributing to a delayed diagnosis in the study group, including physician-related factors, patient-related factors, disease-factors and other factors, were studied as well.

**RESULTS:** Overall, attack sites, duration and severity were comparable among study and control groups. No differences in ethnic origin or family history of FMF were noted between the groups. There were significantly more females ( $p = 0.009$ ), newly-arrived immigrants ( $p = 0.005$ ) and carriers of unidentified MEFV mutations ( $p = 0.04$ ) in the study group. Delayed diagnosis of FMF stemmed from misdiagnosis and physician negligence (70%), as well as from patient negligence (70%). The diagnosis was ultimately made mainly due to a change in disease pattern and other causes, such as diagnosis of FMF in a relative.

**CONCLUSION:** The study unveils unexpected causes behind a prolonged delay in the diagnosis of FMF such as social status (immigrant), female gender, physician negligence and lack of patient awareness. The possibility that the delay stems from a milder disease pattern was dismissed.

PMID: 15971424 [Indexed for MEDLINE]

4258. *Pediatr Nephrol*. 2005 Sep;20(9):1352-4. Epub 2005 Jun 22.

Familial Mediterranean fever and mesangial proliferative glomerulonephritis: report of a case and review of the literature.

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In familial Mediterranean fever (FMF), a genetically inherited disease characterized by fever and serositis, renal involvement is mainly AA amyloidosis. We report a patient with FMF who developed mesangial proliferative glomerulonephritis; presumably in response to colchicine treatment, the activity of the disease decreased and renal function tests and urinary findings normalized. This report emphasizes the concurrent existence of mesangial proliferative glomerulonephritis with FMF in the absence of renal amyloidosis. Due to increased inflammatory response observed in FMF, immunologic glomerular injury, a common cause of glomerulonephritis, may occur more frequently in patients with FMF.

DOI: 10.1007/s00467-005-1991-9

PMID: 15971069 [Indexed for MEDLINE]

4259. *Rheumatol Int*. 2005 Jun;25(5):398-400. Epub 2004 Dec 10.

Familial Mediterranean fever protracted febrile myalgia in children: report of two cases.

Ertekin V, Selimoğlu MA, Alp H, Yilmaz N.

DOI: 10.1007/s00296-004-0535-0

4260. Ann Rheum Dis. 2005 Jul;64(7):1009-14.

Severe disease in patients with rheumatoid arthritis carrying a mutation in the Mediterranean fever gene.

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**BACKGROUND:** Pyrin is a newly recognised intracellular regulator of inflammation, and mutations in MEFV, the gene encoding pyrin, are the cause of familial Mediterranean fever.

**OBJECTIVE:** To determine if known mutations of MEFV are associated with rheumatoid arthritis (RA) morbidity or can modify RA severity.

**METHODS:** The frequency of the three most common MEFV mutations: M694V, V726A, and E148Q, was determined in 98 Israeli patients with RA (74 women, 24 men) and compared with that in 100 healthy subjects matched for origin. RA severity was determined using a new clinical score of 126 grades. The median severity score of mutation carrier and non-carrier groups was compared after confounding measures were eliminated by logistic regression.

**RESULTS:** 17/98 (17%) patients with RA (all women) were heterozygous for common MEFV mutations, predominantly E148Q (12 patients), and one patient was homozygous for the V726A mutation. The overall mutation rate was comparable between patients with RA and healthy subjects. Patients carrying a mutation had a higher median severity score than the non-carrier group (42 v 29,  $p = 0.0005$ ). The logistic regression model assigned a 15-fold odds ratio for severe RA in carriers, after adjusting for sex, presence of rheumatoid factor, age at onset, and disease duration ( $n = 97$ ,  $p = 0.01$ , 95% CI 1.74 to 128).

**CONCLUSION:** MEFV, and particularly the E148Q mutation, is an independent modifier of the clinical manifestations of RA. This is the second Th1-type autoimmune disease in which MEFV mutations have been shown to aggravate the clinical status.

PMID: 15958759 [Indexed for MEDLINE]

4261. Saudi Med J. 2005 May;26(5):732-7.

Genetic screening of familial Mediterranean fever mutations in the Palestinian population.

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**OBJECTIVE:** To investigate the spectrum of mutations and genotypes in the pyrin gene in familial Mediterranean fever (FMF) patients.

**METHODS:** Blood samples of 511 suspected FMF patients, received from the Molecular Genetics Laboratory, Makassed Islamic Charitable Hospital, Mount Olives, Jerusalem during the period from June 1999 to August 2004, were investigated by genotyping 24 different MEFV mutations.

**RESULTS:** Our work revealed the presence of 14 different mutations from the identified 24 mutations in the gene which are assembled in 6 homozygous, 9 heterozygous and 16 compound heterozygous genotypes. The homozygous genotypes represent the predominant format among our patients representing approximately 38% of the revealed genotypes. Interestingly, in 94 (31.4%) of the tested subjects, only one mutation in the pyrin gene could be identified while the other mutant allele remains unidentified. Moreover, the genotype of 3 (1%) patients revealed the presence of triplet mutations in the pyrin gene.

**CONCLUSION:** The results of our study clearly suggest that the origin of FMF among the Palestinian population is mostly homozygous. The identification of a significant number of patients with one known mutation indicates potentially the presence of new mutations in the gene which will be investigated in the future.

PMID: 15951859 [Indexed for MEDLINE]

4262. Semin Arthritis Rheum. 2005 Jun;34(6):813-8.

The spectrum of familial Mediterranean fever gene mutations in Arabs: report of a large series.

Majeed HA(1), El-Khateeb M, El-Shanti H, Rabaiha ZA, Tayeh M, Najib D.

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**OBJECTIVES:** To identify the frequency and distribution of familial Mediterranean fever (FMF) gene (MEFV) mutations in Arab patients.

**PATIENTS AND METHODS:** The study was performed in the pediatric FMF clinic of Jordan University Hospital over a period of 4 years. Patients were referred by their physicians for diagnosis, management, genetic study, and counseling. A diagnosis of FMF was made according to published criteria. Screening for 5 mutations, namely M694V, V726A, M694I, M680I, and E148Q, was performed by amplification refractory mutation system (ARMS) for the first 4 and by restriction endonuclease testing for E148Q.

**RESULTS:** Of the 407 unrelated patients investigated, 239 (59%) had 1 or 2 mutations and 168 (41%) had none of the studied mutations detected. Of those with mutations, 92 were homozygous, 53 were compound heterozygotes, 3 had complex alleles, and 91 patients had only 1 identifiable mutation. Of the mutations, M694V, V726A, M694I, M680I, and E148Q accounted for 38, 26, 14, 10 and 13%, respectively. Twelve of our patients developed the protracted febrile myalgia syndrome (PFMS) of whom 5 (42%) were homozygous for M694V. Only 2 developed chronic renal failure, both of whom were homozygous for M694V and were not on colchicine prophylaxis. However, 43 patients had a family history of chronic renal failure, and 15 (35%) were homozygous for M694V.

**CONCLUSIONS:** Our data indicate that the 5 MEFV mutations are well distributed in Arabs. They also show that M694V is the most common mutation in Arab patients with FMF and seems to have an association with the development of amyloidosis and the PFMS. The high frequency of V726A, and the unique high frequency of M694I in Arabs compared with 3 other ethnic groups, are confirmed.

DOI: 10.1016/j.semarthrit.2005.01.010

PMID: 15942916 [Indexed for MEDLINE]

Interaction of pyrin with 14.3.3 in an isoform-specific and phosphorylation-dependent manner regulates its translocation to the nucleus.

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**OBJECTIVE:** Pyrin, the familial Mediterranean fever gene product, exists in several isoforms of unknown functions. The recombinant full-length isoform (pyrin.fl) is cytoplasmic, whereas an alternatively spliced isoform lacking exon 2 (pyrin.DeltaEx2) concentrates in the nucleus. Native pyrin, mainly consisting of pyrin.fl, is also cytoplasmic in monocytes but is predominantly nuclear in other cell types. To understand pyrin-dependent biologic pathways and to decipher the mechanisms accounting for such different patterns of subcellular compartmentalization, binding partners and posttranslational modifications of pyrin were assessed.

**METHODS:** A yeast 2-hybrid screen was performed with pyrin.fl as the bait. The interaction identified between pyrin.fl and 14.3.3 proteins was confirmed by immunoprecipitation of (35)S-radiolabeled protein complexes; similar experiments were performed with pyrin.DeltaEx2, pyrin.fl after alkaline phosphatase treatment, and pyrin.fl mutants in which several exon 2-encoded serine residues were replaced by nonphosphorylatable alanines. The subcellular localization of the different wild-type and mutated pyrin proteins was assessed by immunofluorescence.

**RESULTS:** Two members of the 14.3.3 protein family were identified as pyrin partners. Whereas pyrin.fl interacted with 14.3.3tau and 14.3.3epsilon, these interactions did not occur with pyrin.DeltaEx2. Pyrin.fl was phosphorylated, and this modification mediated 14.3.3 binding. Serines 208, 209, and 242, within exon 2, acted as critical residues in the interaction between pyrin.fl and 14.3.3. When an S208-S209-S242A pyrin.fl triple mutant or wild-type pyrin.fl in the presence of an inhibitor of 14.3.3-ligand interactions was used, promotion of nuclear translocation of pyrin was observed.

**CONCLUSION:** These results disclose the role played by 14.3.3 in the regulation of the subcellular compartmentalization of pyrin in a phosphorylation- and isoform-dependent manner. They also reconcile the observations made in vitro with those made in vivo, while providing a direct link between 14.3.3-dependent pathways and pyrin.



DOI: 10.1002/art.21050

PMID: 15934090 [Indexed for MEDLINE]

4264. *Pediatr Infect Dis J*. 2005 Jun;24(6):573-4.

Periodic fever in children with hyperimmunoglobulinemia D and mevalonate kinase mutations.

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Hyperimmunoglobulinemia D syndrome (HIDS) is one cause of periodic fevers in children. HIDS is associated with mutations in the mevalonate kinases gene on chromosome 12. Most cases of HIDS have been reported from the Netherlands and surrounding European countries. It is likely that HIDS is underdiagnosed in the United States.

PMID: 15933578 [Indexed for MEDLINE]

4265. *Pediatr Clin North Am*. 2005 Jun;52(3):811-35, vii.

Distinguishing among prolonged, recurrent, and periodic fever syndromes: approach of a pediatric infectious diseases subspecialist.

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Most children with prolonged, recurrent, or periodic fever are healthy and have self-limited, common illnesses, and the primary care practitioner usually can reassure families and continue to reassess the patient as circumstances dictate.

For a child with true fever of unknown origin, a pediatric infectious diseases subspecialist should be consulted. This article discusses three objectives for the clinician: (1) to categorize patterns of fever illnesses and prioritize differential diagnoses; (2) to diagnose and manage the most frequently encountered prolonged fever syndrome, deconditioning; and (3) to expand knowledge and approach to diagnosing periodic fever syndromes. The approach described in this article represents the honed, 30-year experience of a pediatric infectious diseases subspecialist.

DOI: 10.1016/j.pcl.2005.02.007

PMID: 15925664 [Indexed for MEDLINE]

4266. *Pediatr Dermatol*. 2005 May-Jun;22(3):262-5.

Dramatic improvement of pyoderma gangrenosum with infliximab in a patient with PAPA syndrome.

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Infliximab, a chimeric antitumor necrosis factor alpha monoclonal antibody (anti-TNF alpha), has been recently shown to have a beneficial effect on pyoderma gangrenosum associated with inflammatory bowel disease. Patients with the syndromic triad of pyogenic sterile arthritis, pyoderma gangrenosum, and acne, an autoinflammatory process caused by mutations in the CD2 binding protein-1 (CD2BP1) gene, can have severe pyoderma gangrenosum. We describe a 14-year-old patient with this syndrome who was unresponsive to multiple therapies. A dramatic improvement in his pyoderma gangrenosum was observed after one infusion of infliximab, and a second infusion led to its resolution. Our observation extends the therapeutic use of infliximab to this component of PAPA syndrome.

DOI: 10.1111/j.1525-1470.2005.22320.x

PMID: 15916580 [Indexed for MEDLINE]

4267. Clin Chim Acta. 2005 Sep;359(1-2):207-9.

Composition of urinary glycosaminoglycans in a patient with pseudoxanthoma elasticum and familial Mediterranean fever.

Volpi N, Maccari F.

DOI: 10.1016/j.cccn.2005.04.008

PMID: 15913588 [Indexed for MEDLINE]

4268. Scand J Rheumatol. 2005;34(1):56-8.

MEFV gene is a probable susceptibility gene for Behçet's disease.

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**OBJECTIVE:** Behçet's disease (BD) is a rare, chronic, multisystem inflammatory disorder. The prevalence of BD is higher in the Middle Eastern and Mediterranean populations. Another chronic inflammatory disease, familial Mediterranean fever (FMF), is also known to be highly prevalent in these populations. The prevalence of BD is higher in the FMF patient population than in populations known to be rich in BD. Both BD and FMF have some pathophysiological features in common and they result from inappropriate activation of neutrophils. Clinical manifestations of both diseases can mimic each other and the coexistence of both diseases in the same patient has been reported. Given that BD and FMF have similar pathophysiological, epidemiological, and clinical features, we hypothesized that the gene responsible for FMF, MEFV, may also play a role in the pathogenesis of BD.

**METHODS:** Forty-two BD patients who had no symptoms and family history for FMF and 66 healthy controls were screened for common MEFV gene mutations (E148Q, M680I, M694V, and V726A).

**RESULTS:** Fifteen patients (36%) displayed MEFV mutations (nine M694V, five E148Q, and one M680I) and mutation rates were significantly elevated compared to 66 (11%) healthy controls ( $p = 0.0034$ ).

**CONCLUSION:** The occurrence of frequent MEFV mutations in BD patients suggests

that the MEFV gene is involved in the pathogenesis of Behçet's disease.

PMID: 15903027 [Indexed for MEDLINE]

4269. J Dermatolog Treat. 2005 Feb;16(1):58-61.

Treatment of hidradenitis suppurativa with infliximab in a patient with Crohn's disease.

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**BACKGROUND:** Hidradenitis suppurativa is a chronic, inflammatory, scarring disease characterized by recurrent flares. Recently, a group of 'autoinflammatory disorders' has been described. These disorders are characterized by recurrent inflammatory episodes not mediated by autoantibodies or antigen-specific T-cells. Some of these autoinflammatory disorders have been successfully treated with anti-tumor necrosis factor antibodies.

**OBSERVATIONS:** We describe a patient with hidradenitis suppurativa and a history of inactive Crohn's disease who was treated with infliximab, with subsequent improvement in her skin disease.

**CONCLUSIONS:** This case suggests that infliximab may be effective in the treatment of hidradenitis suppurativa in association with Crohn's disease. We also suggest that hidradenitis suppurativa may be closely linked with this new group of autoinflammatory disorders.

DOI: 10.1080/09546630410024547

PMID: 15897171 [Indexed for MEDLINE]

4270. Clin Exp Rheumatol. 2005 Mar-Apr;23(2):133-6.

Inherited autoinflammatory syndromes: an expanding new group of chronic inflammatory diseases.

Gattorno M, Martini A.

PMID: 15895880 [Indexed for MEDLINE]

4271. Pharmacol Ther. 2005 Jul;107(1):44-58.

The clinical potential of chemokine receptor antagonists.

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Chemokines belong to a family of chemotactic cytokines that direct the migration of immune cells towards sites of inflammation. They mediate their biological effects by binding to cell surface receptors, which belong to the G protein-coupled receptor superfamily. Since chemokines and their receptors have been implicated in the pathophysiology of a number of autoinflammatory diseases, chemokine receptor antagonists could prove to be useful therapeutics to target these diseases. Here, we review the role of chemokines in autoimmunity, concentrating mainly on the chemokine receptors CCR1 and CCR5, and discuss the potential utility of antagonists that target these 2 receptors as they progress through the clinic.

DOI: 10.1016/j.pharmthera.2005.01.004

PMID: 15894378 [Indexed for MEDLINE]

4272. Rheumatol Int. 2005 May;25(4):314-6. Epub 2004 Nov 10.

Clinical quiz: a pediatric case presenting with fever and diffuse myalgia.

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Izmir, Turkey.

Familial Mediterranean fever (FMF) is a multisystem disease characterized by recurrent polyserositis episodes seen in certain ethnic groups. In recent years the clinical picture of FMF has been expanded and severe myalgia is a frequently recognized component of the syndrome. Protracted febrile myalgia syndrome (PFMS), characterized by severe paralyzing myalgia, high fever, abdominal pain, diarrhea, arthritis/arthralgia, and transient vasculitic rashes mimicking Henoch-Schonlein purpura, was first described in patients with FMF in 1994. We describe an 11-year-old Turkish girl with a second attack of PFMS before being diagnosed as having FMF, emphasizing the importance of myalgia for the diagnosis of FMF even in the absence of other symptoms.

DOI: 10.1007/s00296-004-0530-5

PMID: 15889305 [Indexed for MEDLINE]

4273. Nature. 2005 May 12;435(7039):224-8.

Expanded T cells from pancreatic lymph nodes of type 1 diabetic subjects recognize an insulin epitope.

Kent SC(1), Chen Y, Bregoli L, Clemmings SM, Kenyon NS, Ricordi C, Hering BJ, Hafler DA.

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Comment in

Nature. 2005 May 12;435(7039):151-2.

Nature. 2005 Nov 24;438(7067):E5; discussion E5-6.

In autoimmune type 1 diabetes, pathogenic T lymphocytes are associated with the specific destruction of insulin-producing beta-islet cells. Identification of the autoantigens involved in triggering this process is a central question. Here we examined T cells from pancreatic draining lymph nodes, the site of islet-cell-specific self-antigen presentation. We cloned single T cells in a non-biased manner from pancreatic draining lymph nodes of subjects with type 1

diabetes and from non-diabetic controls. A high degree of T-cell clonal expansion was observed in pancreatic lymph nodes from long-term diabetic patients but not from control subjects. The oligoclonally expanded T cells from diabetic subjects with DR4, a susceptibility allele for type 1 diabetes, recognized the insulin A 1-15 epitope restricted by DR4. These results identify insulin-reactive, clonally expanded T cells from the site of autoinflammatory drainage in long-term type 1 diabetics, indicating that insulin may indeed be the target antigen causing autoimmune diabetes.

DOI: 10.1038/nature03625

PMID: 15889096 [Indexed for MEDLINE]

4274. Dig Liver Dis. 2005 Mar;37(3):153-8. Epub 2004 Dec 9.

Co-existence of *Helicobacter pylori* infection in patients with Familial Mediterranean Fever (FMF) and the effect of *Helicobacter pylori* on the frequency and severity of FMF attacks.

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**BACKGROUND:** The inflammatory reactions both in Familial Mediterranean Fever and in *Helicobacter pylori* infection have similarities. Whether there is interactions in case of co-existence of both diseases has not been evaluated. **AIM.:** To evaluate, if there is a significant relation between *H. pylori* infection and Familial Mediterranean Fever; if *H. pylori* has an effect on the frequency and severity of Familial Mediterranean Fever attacks; and if eradication treatment has any affects.

**METHODS:** Thirty-two Familial Mediterranean Fever patients were tested for *H. pylori* infection. Acute phase responses were evaluated and attack frequency and severity were determined in both *H. pylori*-positive and *H. pylori*-negative groups. Same determinations were done after the eradication treatment in *H. pylori*-positive patients. Levels of acute phase determinants as well as frequency and severity of attacks were compared in *H. pylori*-positive and -negative groups.

**RESULTS:** C-reactive protein, erythrocyte sedimentation rate, white blood count

and fibrinogen levels were significantly ( $p<0.01$ ) higher during the attacks than before the attacks in all patients. However, there was no difference between the groups. *H. pylori*-positive patients have a higher frequency and a longer duration of attacks when compared to *H. pylori*-negative patients before treatment ( $p<0.05$ ). The frequency was also significantly lower and duration was shorter in patients whose infections were eradicated ( $p<0.05$ ).

CONCLUSION: *H. pylori* infection was not significantly frequent in our group of Familial Mediterranean Fever patients. *H. pylori* can decrease both the frequency and the duration of the attacks. Studies that will evaluate the relationship of *H. pylori* and MEFV gene along with the roles of yet unknown cytokines, which can presumably play a role in the pathogenesis of both diseases, are needed to reach better conclusions.

DOI: 10.1016/j.dld.2004.09.027

PMID: 15888278 [Indexed for MEDLINE]

4275. World J Gastroenterol. 2005 May 14;11(18):2844-6.

Encapsulating peritonitis and familial Mediterranean fever.

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AIM: To investigate the relationship between encapsulating peritonitis and familial Mediterranean fever (FMF).

METHODS: The patient had a history of type 2 diabetes and laparoscopic cholecystectomy was performed one year ago for cholelithiasis. Eleven months after the operation she developed massive ascites. Biochemical evaluation revealed hyperglycemia, mild Fe deficiency anemia, hypoalbuminemia and a CA-125 level of 2 700 IU. Ascitic evaluation showed characteristics of exudation with a cell count of 580/mm<sup>3</sup>. Abdominal CT showed omental thickening and massive ascites. At exploratory laparotomy there was generalized thickening of the peritoneum and a laparoscopic clip encapsulated by fibrous tissue was found adherent to the uterus. Biopsies were negative for malignancy and a prophylactic total abdominal hysterectomy and bilateral salpingoophorectomy were performed.



RESULTS: The histopathological evaluation was compatible with chronic nonspecific findings and mild mesothelial proliferation and chronic inflammation at the uterine serosa and liver biopsy showed inactive cirrhosis.

CONCLUSION: The patient was evaluated as sclerosing encapsulating peritonitis induced by the laparoscopic clip acting as a foreign body. Due to the fact that the patient had FMF the immune response was probably exaggerated.

PMCID: PMC4305931

PMID: 15884137 [Indexed for MEDLINE]

4276. Int J Clin Pract Suppl. 2005 Apr;(147):60-1.

Meningitis associated with familial Mediterranean fever.

Karachaliou I(1), Karachalios G, Charalabopoulos A, Charalabopoulos K.

Author information:

(1)Second Department of Medicine, Red Cross Hospital, Athens, Greece.

Neurologic involvement in patients with familial Mediterranean fever is relatively uncommon, and rarely described in the literature. Although headache occurs frequently, meningitis and convulsions are rare. We describe the case of a 30-year-old man with attacks of meningitis. After colchicine therapy, no further recurrence of fever and meningitis were observed. These findings suggest that meningitis should be considered as an unusual manifestation of familial Mediterranean fever.

PMID: 15875625 [Indexed for MEDLINE]

4277. J Rheumatol. 2005 May;32(5):859-62.

Arthritis as the sole episodic manifestation of familial Mediterranean fever.

Lidar M(1), Kedem R, Mor A, Levartovsky D, Langevitz P, Livneh A.

Author information:

(1)Heller Institute of Medical Research, Sheba Medical Center, Tel-Hashomer, Israel.

Comment in

J Rheumatol. 2005 Nov;32(11):2278; author reply 2278.

**OBJECTIVE:** To clinically and genetically characterize patients with familial Mediterranean fever (FMF) in whom arthritis constitutes the only manifestation, and to establish the most important features distinguishing FMF arthritis in such a setting from other forms of mono/oligo arthritides.

**METHODS:** The study population comprised 14 patients with episodes of arthritis as the only manifestation of FMF who nevertheless fulfilled the diagnostic criteria for FMF. The control group consisted of 28 patients with episodic mono/oligo arthritis of different disease entities (palindromic, reactive, inflammatory bowel disease, Reiter's, seronegative spondyloarthropathy, chronic juvenile, Behcet's, and gouty arthritis) who presented to the rheumatology clinic during the study period. Patients in both groups underwent clinical evaluation and donated blood for FMF gene analysis.

**RESULTS:** The study and control groups shared similar age and sex distribution and experienced the monoarthritic attacks at similar sites, usually the knee and ankle joint. The 2 groups differed significantly in features of arthritis (which were febrile and of short duration in FMF), family history of FMF, mutation analysis, and response to colchicine. These differences allowed the defining of a rule, which readily distinguishes FMF arthritis from other forms of episodic mono/oligo arthritis.

**CONCLUSION:** The clinical, ethnic, and genetic features of recurrent monoarthritis of FMF are specific and may separate FMF from other entities with mono/oligo arthritis.

PMID: 15868622 [Indexed for MEDLINE]

4278. Ann Ital Med Int. 2005 Jan-Mar;20(1):54-7.

[TRAPS syndrome, a rare cause of fever of unknown origin: case report and review of the literature].

[Article in Italian]

Benucci M(1), Nenci G, Taccetti G, Rosso A, Cappelletti C.

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Tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is an autosomal dominant inherited condition of periodic fever and pain. TRAPS is caused by mutations of the TNFRSF1A gene localized at 12p13. The gene encodes extracellular region of the p55 TNF-alpha receptor, resulting in impaired cleavage and down-regulation of the membrane expressed form of the receptor, a diminished shedding of potentially antagonistic soluble form of the receptor and, as a consequence, an unbalanced TNF-alpha action. Most affected patients are from northern Europe. Fever, sterile peritonitis, pleural pain, arthralgia, myalgia, skin rash, and/or conjunctivitis occur during the syndrome episodes; some patients also develop systemic amyloidosis, with some differences among patients. An acute-phase response occurs during the episodes. We describe a case of a 23-year-old Moldavian woman, living in Italy presenting recurrent fever episodes with abdominal pain and skin rash. A biopsy showed small vessel vasculitis. The genetic analysis showed a TNFRSF1A gene (R92Q) mutation. In this paper we report also a literature review on this rare disease.

PMID: 15859396 [Indexed for MEDLINE]

4279. Int J Clin Pract. 2005 Feb;59(2):202-5.

Characteristics of patients with adult-onset familial Mediterranean fever in Turkey: analysis of 401 cases.

Sayarlioglu M(1), Cefle A, Inanc M, Kamali S, Dalkilic E, Gul A, Ocal L, Aral O, Konice M.

Author information:

(1)Division of Rheumatology, Department of Internal Medicine, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey. sayarli@hotmail.com

It has been generally accepted that the clinical onset of familial Mediterranean fever (FMF) begins before 20 years of age in most patients. In this study, we aimed to investigate the demographic and clinical characteristics of our FMF patients with an age of onset  $\geq 20$ . Records of 401 patients (female/male: 204/197) that followed up between 1990 and 1999 were reviewed according to a pre-defined protocol. All patients fulfilled the diagnostic criteria of Livneh et al. The demographic and clinical features of adult-onset FMF patients were compared to those of patients with a disease onset before 20 years of age. There were 57 patients (14%) who experienced symptoms of FMF at  $\geq 20$  years of age; 34 of them (8.5%) reported their first attack between 20 and 29 years of age; 18 of them (4.5%) between 30 and 39 years of age and five patients (1.25%) had their first attack after 40 years of age. Arthritis (42 vs. 65%,  $p = 0.001$ ) and erysipelas-like erythema (7 vs. 17%,  $p = 0.047$ ) were significantly less frequent in patients with adult-onset FMF compared to patients with disease onset before 20 years of age. Arthritis and erysipelas-like erythema were less frequent in adult-onset patients compared to those with an earlier disease onset. Adult-onset FMF may be a form of disease with distinct clinical, demographic and molecular characteristics. Prospective clinical studies and investigation of genotypic features are needed to identify the characteristics of this phenotypic variant.

DOI: 10.1111/j.1742-1241.2004.00294.x

PMID: 15854197 [Indexed for MEDLINE]

4280. Rheumatology (Oxford). 2005 Aug;44(8):1072-3. Epub 2005 Apr 19.

Positive clinical and biochemical responses to anakinra in a 3-yr-old patient with cryopyrin-associated periodic syndrome (CAPS).

Ramos E, Aróstegui JI, Campuzano S, Rius J, Bousoño C, Yagüe J.

DOI: 10.1093/rheumatology/keh652

PMID: 15840596 [Indexed for MEDLINE]

4281. Nervenarzt. 2005 Oct;76(10):1263-6.

[Tumour necrosis factor receptor-associated periodic syndrome. A rare

differential diagnosis of multiple sclerosis].

[Article in German]

Günther P(1), Minden K, Hermann W, Schneider JP, Wagner A.

Author information:

(1)Klinik und Poliklinik für Neurologie, Universität Leipzig.

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Tumour necrosis factor receptor-associated periodic syndrome (TRAPS), a rare autosomal dominant disorder, is characterised by recurrent attacks of fever, myalgias, and abdominal pain. However, manifestations in the central nervous system are hardly known. We describe a family in which one of three affected members developed central nervous system symptoms. First diagnosed as multiple sclerosis (MS), the demyelination seems to be a feature of TRAPS rather than MS. The syndrome is discussed as a rare differential diagnosis of MS.

DOI: 10.1007/s00115-005-1906-9

PMID: 15834693 [Indexed for MEDLINE]

4282. Ann Rheum Dis. 2005 May;64(5):786-7.

C reactive protein: protecting from lupus in familial Mediterranean fever.

Ozen S, Bakkaloglu A.

DOI: 10.1136/ard.2004.027037

PMCID: PMC1755480

PMID: 15834062 [Indexed for MEDLINE]

4283. Best Pract Res Clin Gastroenterol. 2005 Apr;19(2):199-213.

Familial Mediterranean fever--a not so unusual cause of abdominal pain.

Simon A(1), van der Meer JW, Drenth JP.

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Familial Mediterranean fever is a hereditary syndrome characterised by recurrent episodes of fever and serositis, resulting in pain in the abdomen, chest, joints and muscles. It is primarily diagnosed in people of Jewish, Arabic, Turkish or Armenian ancestry and is caused by mutations in the gene encoding for pyrin. Abdominal FMF attacks resemble the clinical presentation of 'acute abdomen', with severe abdominal pain and rigidity, but in FMF symptoms always resolve spontaneously. It is important to distinguish these regular pain episodes from small bowel obstruction due to adhesions to prevent life-threatening bowel strangulation. In most cases, colchicine will prevent new painful attacks. This seminar also discusses other causes of abdominal pain in FMF patients.

DOI: 10.1016/j.bpg.2004.11.009

PMID: 15833688 [Indexed for MEDLINE]

4284. Rev Prat. 2005 Feb 28;55(4):353-9.

[Auto-inflammatory syndromes].

[Article in French]

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Auto-inflammatory syndromes are a group of hereditary diseases characterised by intermittent bouts of clinical inflammation with focal organ involvement mainly: abdomen, musculoskeletal system and skin. The most frequent is familial Mediterranean fever, which affects patients of Mediterranean descent all over the world. Three other types have been recently clinically as well as genetically characterised. A thorough diagnosis is warranted, as clinical and therapeutic management is specific for each of these diseases, as underlied by a specific

inflammatory pathway. This new group of diseases has already opened new avenues in our understanding of the inflammatory response.

PMID: 15828611 [Indexed for MEDLINE]

4285. *Pediatr Clin North Am.* 2005 Apr;52(2):577-609, vii.

Periodic fever syndromes.

Padeh S(1).

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(1)Pediatric Rheumatology, Edmond & Lily Safra Children Hospital, The Chaim Sheba Medical Center, Tel Hashomer 52621, Israel. padeh@012.net.il

Republished in

*Rheum Dis Clin North Am.* 2007 Aug;33(3):585-623.

Human autoinflammatory diseases (except for the periodic fever, adenopathy, pharyngitis, aphthae syndrom) are a heterogeneous group of genetically determined diseases characterized by seemingly unprovoked inflammation, in the absence of autoimmune or infective causes. Tremendous advances in the understanding of these disorders have been seen in the last decade. This article discusses hereditary autoinflammatory syndromes that are associated with recurrent fevers.

DOI: 10.1016/j.pcl.2005.01.005

PMID: 15820380 [Indexed for MEDLINE]

4286. *Arthritis Rheum.* 2005 Apr;52(4):1287-92.

Reduced tumor necrosis factor signaling in primary human fibroblasts containing a tumor necrosis factor receptor superfamily 1A mutant.

Siebert S(1), Amos N, Fielding CA, Wang EC, Aksentijevich I, Williams BD, Brennan P.

Author information:

(1)Section of Infection and Immunity, Wales College of Medicine, Cardiff University, Cardiff, UK. sieberts@cardiff.ac.uk

Comment in

Arthritis Rheum. 2005 Sep;52(9):2952; author reply 2952-3.

**OBJECTIVE:** Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is an autoinflammatory syndrome associated with mutations in the gene that encodes tumor necrosis factor receptor superfamily 1A (TNFRSF1A). The purpose of this study was to describe a novel TNFRSF1A mutation (C43S) in a patient with TRAPS and to examine the effects of this TNFRSF1A mutation on tumor necrosis factor alpha (TNFalpha)-induced signaling in a patient-derived primary dermal fibroblast line.

**METHODS:** TNFRSF1A shedding from neutrophils was measured by flow cytometry and enzyme-linked immunosorbent assay (ELISA). Primary dermal fibroblast lines were established from the patient with the C43S TRAPS mutation and from healthy volunteers. Activation of NF-kappaB and activator protein 1 (AP-1) was evaluated by electrophoretic mobility shift assays. Cytokine production was measured by ELISA. Cell viability was measured by alamar blue assay. Apoptosis was measured by caspase 3 assay in the fibroblasts and by annexin V assay in peripheral blood mononuclear cells.

**RESULTS:** Activation-induced shedding of the TNFRSF1A from neutrophils was not altered by the C43S TRAPS mutation. TNFalpha-induced activation of NF-kappaB and AP-1 was decreased in the primary dermal fibroblasts with the C43S TNFRSF1A mutation. Nevertheless, the C43S TRAPS fibroblasts were capable of producing interleukin-6 (IL-6) and IL-8 in response to TNFalpha. However, TNFalpha-induced cell death and apoptosis were significantly decreased in the samples from the patient with the C43S TRAPS mutation.

**CONCLUSION:** The C43S TNFRSF1A mutation results in decreased TNFalpha-induced nuclear signaling and apoptosis. Our data suggest a new hypothesis, in that the C43S TRAPS mutation may cause the inflammatory phenotype by increasing resistance to TNFalpha-induced apoptosis.

DOI: 10.1002/art.20955

PMCID: PMC2842000

PMID: 15818692 [Indexed for MEDLINE]



4287. Eur J Hum Genet. 2005 Jun;13(6):742-7.

A new CARD15 mutation in Blau syndrome.

van Duist MM(1), Albrecht M, Podswiadek M, Giachino D, Lengauer T, Punzi L, De Marchi M.

Author information:

(1)Department of Clinical and Biological Sciences, Division of Medical Genetics, University of Torino, Orbassano, Italy.

The caspase recruitment domain gene CARD15/NOD2, encoding a cellular receptor involved in an NF-kappaB-mediated pathway of innate immunity, was first identified as a major susceptibility gene for Crohn's disease (CD), and more recently, as responsible for Blau syndrome (BS), a rare autosomal-dominant trait characterized by arthritis, uveitis, skin rash and granulomatous inflammation. While CARD15 variants associated with CD are located within or near the C-terminal leucine-rich repeat domain and cause decreased NF-kappaB activation, BS mutations affect the central nucleotide-binding NACHT domain and result in increased NF-kappaB activation. In an Italian family with BS, we detected a novel mutation E383K, whose pathogenicity is strongly supported by cosegregation with the disease in the family and absence in controls, and by the evolutionary conservation and structural role of the affected glutamate close to the Walker B motif of the nucleotide-binding site in the NACHT domain. Interestingly, substitutions at corresponding positions in another NACHT family member cause similar autoinflammatory phenotypes.

DOI: 10.1038/sj.ejhg.5201404

PMID: 15812565 [Indexed for MEDLINE]

4288. Intern Med. 2005 Mar;44(3):261-5.

A Japanese patient with familial Mediterranean fever associated with compound heterozygosity for pyrin variant E148Q/M694I.

Nakamura A(1), Yazaki M, Tokuda T, Hattori T, Ikeda S.

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Comment in

Intern Med. 2005 Mar;44(3):177-8.

Familial Mediterranean fever (FMF) is an inherited inflammatory disease occurring mainly in Mediterranean and Middle Eastern populations. FMF is caused by mutations in the MEFV gene that encodes pyrin/marenostrin. Here, we report a Japanese female FMF patient with heterozygosity for the compound pyrin E148Q/M694I showing recurrent fever, serositis or delay in skin wound healing. Her father and elder sister were heterozygous for pyrin variant M694I alone and sometimes suffered from mild fever or delay in wound healing, but her mother was heterozygous for pyrin variant E148Q alone and had no symptoms. This suggested that the inheritance of FMF occurred not only in an autosomal recessive manner but also in an autosomal dominant manner in this Japanese family, and the severity of the disease differed among the family members in relation to the mutation. In the treatment of FMF, colchicine, reserpine or prazosin hydrochloride have been reported to prevent the attacks, but, in our patient such drugs were ineffective or caused side effects, and only the anti-allergic drug azelastine was of benefit in relieving the attacks.

PMID: 15805719 [Indexed for MEDLINE]

4289. Intern Med. 2005 Mar;44(3):177-8.

Hereditary periodic Fever syndromes in Japan.

Ida H, Eguchi K.

Comment on

Intern Med. 2005 Mar;44(3):261-5.

PMID: 15805703 [Indexed for MEDLINE]

4290. *Pediatr Dermatol*. 2005 Mar-Apr;22(2):138-41.

Henoch-Schönlein purpura in a child with hyperimmunoglobulinemia D and periodic fever syndrome.

Wickiser JE(1), Saulsbury FT.

Author information:

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This report describes a 3-year-old girl with a long history of periodic fever who presented with Henoch-Schönlein purpura. She was diagnosed with hyperimmunoglobulinemia D and periodic fever syndrome by means of mutation analysis of the mevalonate kinase gene. The serum IgA concentration was markedly elevated, but the serum IgD concentration was normal. This report emphasizes that Henoch-Schönlein purpura may be an important clinical feature of hyperimmunoglobulinemia D and periodic fever syndrome. In addition, this syndrome should be considered in patients with Henoch-Schönlein purpura in whom there is a history of recurrent fevers, even when the serum IgD concentration is normal.

DOI: 10.1111/j.1525-1470.2005.22210.x

PMID: 15804303 [Indexed for MEDLINE]

4291. *Clin Rheumatol*. 2004 Dec;23(6):559-61.

A case of recurrent pancreatitis due to hyperlipidemia misdiagnosed as familial Mediterranean fever.

Birlik M, Demir T, Zeybel M, Akar S, Onen F, Comlekci A, Tunca M, Akkoc N.

Familial Mediterranean fever (FMF) is prevalent among Arabic, Turkish, Armenian, and Jewish people and it must always be considered in the differential diagnosis of patients from these ethnic groups presenting with recurrent abdominal pain with fever. In cases of fever and recurrent abdominal pain, acute pancreatitis is an important clinical condition, which should be considered in the differential diagnosis. Serum amylase concentration in acute pancreatitis is usually more than three times the upper limit of normal. However, in recurrent pancreatitis

secondary to hypertriglyceridemia, serum amylase levels, for reasons that are not well understood, may be normal or mildly elevated. Recurrent pancreatitis secondary to hypertriglyceridemia may thus pose a problem in the differential diagnosis and may lead to an erroneous diagnosis of FMF. Measurement of serum triglyceride along with amylase levels should be required for a suspected diagnosis. Computerized examination of the abdomen may need to be undertaken to exclude acute pancreatitis in the presence of hypertriglyceridemia since serum amylase levels may be normal or slightly elevated.

PMID: 15801080 [Indexed for MEDLINE]

4292. Eur J Pediatr. 2005 Jun;164(6):391-4. Epub 2005 Mar 16.

Tendonitis in variant hyperimmunoglobulinaemia D and periodic fever syndrome--a rare disease with a new symptom.

Armbrust S(1), Drenth JP, Schröder C, Domning E, Poeschl E, Wiersbitzky SK.

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Hyperimmunoglobulinaemia D syndrome (HIDS) is defined as recurrent fever, generalised lymphadenitis, abdominal pain, arthritis and raised polyclonal serum IgD >100 IU/ml. The cause is a mutation in the mevalonate kinase gene. Other periodic fever syndromes are known. We report a new patient and describe orbital tendonitis as a hitherto unreported symptom. CONCLUSION: Without any underlying cause, the tendonitis must be seen as new symptom of variant hyperimmunoglobulinaemia D syndrome. We speculate that the inflammation of the Tenon spatium is similar to the process of inflammation of the connective tissue in the joint in hyperimmunoglobulinaemia D syndrome where deposits of C3 and IgM are present. Variant hyperimmunoglobulinaemia D syndrome can be present in one family.

DOI: 10.1007/s00431-005-1652-9

PMID: 15770507 [Indexed for MEDLINE]

4293. Rheumatol Int. 2005 Aug;25(6):475-7. Epub 2005 Mar 12.

Spontaneous renal laceration as the presenting feature of polyarteritis nodosa in a patient with familial Mediterranean fever after hepatitis A infection.

Candan F(1), Ayan S, Tas F, Gökce G, Elagoz S.

Author information:

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We report a life-threatening spontaneous renal laceration with no history of bleeding diathesis or any trauma in a patient with FMF after acute hepatitis A virus (HAV) infection. Right nephrectomy was inevitable and histological investigation of the removed right kidney revealed a polyarteritis nodosa (PAN). This case underlines the possibility that simultaneous PAN and immunosuppressive treatment besides colchicine should be considered for patients with FMF. Also, patients with FMF who are not immune may be vaccinated for HAV which could be a predisposing mechanism for vasculitic hemorrhage.

DOI: 10.1007/s00296-005-0597-7

PMID: 15765217 [Indexed for MEDLINE]

4294. Vestn Khir Im I I Grek. 2004;163(6):17-20.

[Surgical aspects of periodic disease abdominal paroxysms].

[Article in Russian]

Grigorian SKh.

Thorough investigation of abdominalgia symptoms in 220 patients allowed to reveal a number of peculiarities of the periodic disease (PD) promoting the correct diagnosis. The case history data, pain localization, fever and great potentialities of diagnostic laparoscopy carried on during the acute paroxysm of the abdominal form of PD are of great significance. The differential diagnosis of PD acute paroxysm and urgent pathology of the organs of the abdominal cavity are

considered by the author to be possible when using diagnostic laparoscopy in difficult situations.

PMID: 15757299 [Indexed for MEDLINE]

4295. J Immunol. 2005 Mar 15;174(6):3773-80.

CD1a and CD1c activate intrathyroidal T cells during Graves' disease and Hashimoto's thyroiditis.

Roura-Mir C(1), Catálfamo M, Cheng TY, Marqusee E, Besra GS, Jaraquemada D, Moody DB.

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Molecular studies have shown that CD1 proteins present self and foreign lipid Ags to T cells, but the possible roles of CD1 in human autoimmune diseases in vivo are not known, especially for the group 1 CD1 isoforms (CD1a, CD1b, and CD1c). To investigate the hypothesis that CD1-restricted T cells might be activated and home to target tissues involved in Hashimoto's thyroiditis and Graves' disease, we performed ex vivo analysis of lymphocytes from peripheral blood and autoimmune lesions of thyroid tissue. Immunofluorescence analysis identified two types of CD1-expressing APCs in inflamed thyroid tissues. CD1a, CD1b, and CD1c were expressed on CD83+ dendritic cells, and CD1c was expressed on an abundant population of CD20+ IgD+ CD23- CD38- B cells that selectively localized to the mantle zone of lymphoid follicles within the thyroid gland. CD1c-restricted, glycolipid-specific T cells could not be detected in the peripheral blood, but were present in polyclonal lymphocyte populations isolated from affected thyroid glands. In addition, polyclonal thyroid-derived lymphocytes and short-term T cell lines were found to recognize and lyse targets in a CD1a- or CD1c-dependent manner. The targeting of CD1-restricted T cells and large numbers of CD1-expressing APCs to the thyroid gland during the early stages of autoimmune thyroiditis suggests a possible effector function of CD1-restricted T cells in tissue destruction and point to a new model of organ-specific autoimmune disease involving lipid Ag presentation.

PMID: 15749918 [Indexed for MEDLINE]

4296. Sante. 2004 Oct-Dec;14(4):261-6.

[Familial Mediterranean Fever (FMF): from diagnosis to treatment].

[Article in French]

Medlej-Hashim M(1), Loiselet J, Lefranc G, Mégarbané A.

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Familial Mediterranean Fever (FMF), also known as paroxysmal polyserositis, is an autosomal recessive disease affecting mainly Mediterranean populations (Jews, Armenians, Arabs, Turks). It is characterised by recurrent crises of fever and serosal inflammation, leading to abdominal, thoracic or articular pain.

Erysipela-like erythema affecting mainly feet and legs and effort-induced myalgia are less frequently encountered symptoms. The major complication of FMF is the development of renal amyloidosis. Standard laboratory tests of FMF patients are non-informative, except for the high sedimentation rate and white blood cell count, but during and immediately after crises, diminished albumin concentrations and elevated fibrinogen, C-reactive protein, beta2 and alpha2 M globulins, haptoglobin and lipoprotein concentrations are noted. Studies have measured immunoglobulin (Ig) levels in the sera of FMF patients and found elevated levels of IgA, IgM, IgG, and IgD in 23%, 13%, 17% and 13%, respectively. FMF crises are characterised by a massive influx of polymorphonuclear leukocytes into the inflamed regions. Moreover, the peritoneal fluid of FMF patients contains abnormally low levels of the inhibitor of complement fragment C5a and interleukin 8. Failure to suppress inflammatory response to C5a may explain the typical inflammatory FMF crises. The MEFV (for MEiterranean FeVer) gene responsible for the disease has been identified on 16p13.3. It is composed of 10 exons and spans approximately 14 Kb of genomic DNA. More than 35 mutations have so far been identified. The most frequent are M694V, M694I, M680I, V726A and E148Q. The M694V mutation is the most frequent mutation in the various ethnic groups considered,

although its frequency varies from group to group. The V726A mutation is observed mainly among Ashkenazi and Iraqi Jews, Druzes and Armenians, and the M680I among Armenians and Turks. M694I and A744S seem specific to Arab populations, and R761H is frequently found in Lebanese FMF patients. The M694V mutation is often correlated with severe phenotypes, mainly in the homozygous state. It has been specifically correlated with arthritis, pleuritis and especially amyloidosis. Patients with other mutations in the 694 and 680 codons can also have severe phenotypes. The V726A mutation, although identified in FMF patients with a relatively mild phenotype, has also been detected in patients with renal amyloidosis. E148Q is often associated with a mild phenotype, and whether it is even a polymorphism has been questioned. The MEFV gene codes for a protein that was respectively called pyrin and marenostrin by the French and international consortia that simultaneously identified the gene. Its function is still not determined, but it was recently colocalised with microtubules and actin filaments in the cytoplasm. It contains a death domain called PYD (Pyrin Domain), usually associated with proteins involved in apoptosis. Some genes have been tested to assess their possible modifying effects on clinical features of FMF. The alpha/alpha genotype of the serum amyloid A or SAA1 gene is associated with an increased risk of amyloidosis in FMF patients, especially in patients homozygous for M694V, whereas the MICA (Major Histocompatibility Complex, MHC class-I-chain-related type A) gene seems to have an effect on disease course but not its clinical manifestations. The most effective treatment for FMF patients is colchicine, which should be taken regularly on a life-long basis. It decreases the frequency and severity of crises and prevents renal amyloidosis.

PMID: 15745878 [Indexed for MEDLINE]

4297. Egypt J Immunol. 2004;11(1):103-10.

Application of refractory fragment amplification system for detection of Egyptian variant of Familial Mediterranean Fever.

Zekri AR(1), el-Bassuoni MA, Hammad OM, Sakr MA, Ibrahim AA.

Author information:

(1)Department of Cancer Biology, Virology and Immunology Unit, National Cancer Institute, Cairo University, Egypt.



Until recently, the diagnosis of familial Mediterranean fever (FMF) was, based on clinical manifestations, ethnicity, family history and response to colchicines. The aim of this study is to evaluate the use of polymerase chain reaction (PCR) for diagnosis of FMF and to detect the prevalence of the most common MEFV gene (FMF gene) mutations, M694V and V726A in FMF Egyptian patients. From January 2002 to December 2002, twenty patients with FMF as well as 10 healthy subjects with no symptoms suggestive of FMF were enrolled in this study. All patients were subjected to PCR for MEEV gene mutations detection. Fifteen patients (75%) have age of onset of FMF less than 20 years. Five patients (25%) had past history of appendicectomy or laparotomy. The clinical features of patients during attacks were fever (100%), abdominal pain (95%), arthritis (55%), pleurisy (40%) and no skin rash or pericarditis. The M694V mutation was detected in 20 patients (100%) and V726A mutation in 17 patients (85%). No false positive or false negative results were obtained by using the three sets of primers for each sample, indicating a sensitivity and specificity of 100% of this assay.

PMID: 15724392 [Indexed for MEDLINE]

4298. Arch Dermatol. 2005 Feb;141(2):248-53.

Neonatal-onset multisystem inflammatory disorder: the emerging role of pyrin genes in autoinflammatory diseases.

Kilcline C(1), Shinkai K, Bree A, Modica R, Von Scheven E, Frieden IJ.

Author information:

(1)Department of Dermatology, University of California, San Francisco 94143-0316, USA.

Comment in

Arch Dermatol. 2005 Feb;141(2):242-7.

Neonatal-onset multisystem inflammatory disorder (NOMID) is a rare congenital disorder characterized by a neonatal-onset urticarial rash, arthropathy, recurrent fevers, and central nervous system disease. We report 3 cases in which patients presented with neonatal-onset urticarial eruption and other organ

involvement of varying severity. Genetic testing of 2 of these patients revealed previously unreported genetic mutations in exon 3 of the CIAS1 gene, a recently discovered member of the pyrin gene family. The third patient did not demonstrate a CIAS1 mutation. These cases illustrate the genetic basis of NOMID, an autoinflammatory disorder, and highlight the emerging role of the pyrin gene family in the regulation of nuclear factor kappaB signaling and other pathways involved in inflammation and apoptosis.

DOI: 10.1001/archderm.141.2.248

PMID: 15724022 [Indexed for MEDLINE]

4299. Arch Dermatol. 2005 Feb;141(2):242-7.

The pyrin family of fever genes: unmasking genetic determinants of autoinflammatory disease.

Shinkai K(1), Kilcline C, Connolly MK, Frieden IJ.

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Comment on

Arch Dermatol. 2005 Feb;141(2):248-53.

DOI: 10.1001/archderm.141.2.242

PMID: 15724021 [Indexed for MEDLINE]

4300. Curr Drug Targets Inflamm Allergy. 2005 Feb;4(1):117-24.

Pharmacological and clinical basis of treatment of Familial Mediterranean Fever (FMF) with colchicine or analogues: an update.

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Familial Mediterranean Fever (FMF), an autosomal recessive disorder, is characterised by recurrent attacks of fever and serositis, lasting 24-72 hours. Since 1972 colchicine has become the drug of choice for prophylaxis against FMF attacks and amyloidosis FMF-associated. Colchicine, an alkaloid neutral, is absorbed in the jejunum and ileum. It is metabolised by liver and only small amounts are recovered unchanged in the urine. Really plasma half-life is prolonged in patients with liver or renal failure. Colchicine is able to prevent activation of neutrophils, binding beta-tubulin and making beta-tubulin-colchicine complexes; this way inhibits assembly of microtubules and mitotic spindle formation; moreover its mode of action includes modulation of chemokines, prostanoids production, inhibition of neutrophil and endothelial cell adhesion molecules. The minimal daily dose in adults is 1.0 mg/die, but in children there is not a definite dose. Since in vitro high dosages of colchicine stop mitosis, this drug might interfere with male and female fertility and with children growth, but, according to current guidelines and because of rare side effects of the drug, FMF patients are recommended to take colchicine. Since colchicine treatment is often complicated by frequent gastrointestinal side effects, by our experience, in order to improve colchicine tolerance we recommend: lactose-free diet and treatment of intestinal bacterial overgrowth and/or Hp-infection, assessed by breath tests. Since our data showed that 10-15% of FMF patients seem are non-responders or intolerant to colchicine, today we are working in the design of colchicine analogues which may have lesser toxicities and a larger therapeutic window.

PMID: 15720245 [Indexed for MEDLINE]

4301. Curr Drug Targets Inflamm Allergy. 2005 Feb;4(1):113-6.

Molecular study of FMF patients in Armenia.

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Familial Mediterranean Fever (FMF, MIM 249100), or Periodic disease, is a recessively transmitted and ethnically restricted condition prevalent in population from the Mediterranean decent. FMF notoriously has been hard to diagnose until mutations in the MEFV gene have been identified and as a tremendous help are used for the diagnosis of difficult cases. Since FMF can be controlled by medication, it is extremely desirable to have a firm diagnosis. The aim of this study was to establish the frequency of the most common mutations and genotypes in Armenian population. Molecular analysis of MEFV gene mutations in 3000 Armenian patients has demonstrated direct correlation between the clinical severity and the molecular diagnostic criteria of the disease, including the development of renal amyloidosis with MEFV genotypes. MEFV genotyping performed in the framework of a genetic counseling may reveal and identify affected individuals in presymptomatic phase, providing the possibility of a precocious start of the therapy.

PMID: 15720244 [Indexed for MEDLINE]

4302. Curr Drug Targets Inflamm Allergy. 2005 Feb;4(1):105-12.

MEFV mutation carriers and diseases other than familial Mediterranean fever: proved and non-proved associations; putative biological advantage.

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Vasculitis is definitely associated with familial Mediterranean fever. This familial Mediterranean fever-associated vasculitis takes one of three forms: polyarteritis nodosa, with or without microscopic polyangiitis, and Henoch-Schonlein purpura. Behcet disease and inflammatory bowel diseases may also be associated with familial Mediterranean fever, though this is yet to be formally proven. The selective biological advantage, if any, for carriers of simple heterozygotic mutations in the gene responsible for familial Mediterranean fever, MEFV, is not known. Indirect arguments are given for a better defense

against certain groups of bacterial pathogens and amongst intra-cellular bacteria, *Mycobacterium tuberculosis*.

PMID: 15720243 [Indexed for MEDLINE]

4303. Curr Drug Targets Inflamm Allergy. 2005 Feb;4(1):85-98.

Oxidative stress in the molecular mechanism of pathogenesis at different diseased states of organism in clinics and experiment.

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According to modern images and results of our observations the oxidative stress (OS) is a non-specific though certain component of pathogenesis at numerous diseased states of organism having in the basis the thoroughness of pathogenic disturbances of phospholipids (PL) metabolism and processes of their free radical oxidation (FRO), which takes place in the membrane formations of as the whole cell, as well as the mitochondrial and microsomal fractions (MCF and MSF) of the white rat brain, liver mitochondria, lung shadows, at the same time erythrocyte and lymphocyte shadows at brain acute edema, ischemia, reperfusion and desympathization, infarction of myocardium, tuberculosis of lungs, diabetes, Familial Mediterranean Fever (FMF), intoxications under halothane anaesthesia (HA) and with micotoxin zearalenon. The regularities observed promote to understand from the point of view of modern approaches the molecular mechanisms of initiation, development and generalization of factors for OS formation under pathologic conditions. It is more obvious at zearalenon intoxication with intensification of lipids FRO processes and failures in PL-PL ratio phenomena. The lymphocytes membranes of the white rats spleen subjected OS induced by zearalenon intoxication permit us conclude that the general immune status of the organism decreases. It is generally peculiar to the states under conditions of generalized intoxication. The observed increase of phospholipase A(2) activity induces the release of high concentrations of lysophosphatidylcholines (LPC) and

non-etherified fatty acids (NEFA) of polyenic range with prevail of arachidonic acid as a pathogenic factor, namely, at modelling brain acute edema by tetraethylolovo to white rats. Formation of the above mentioned disturbances to some extent depends on hydrophobic properties of toxins, particularly, zearalenon. The latter gives certain tropism to dopamine-beta-monooxygenase (DBM), and ability to stimulate functional activity of the enzyme. Striking haemolytic properties of phospholipase A(2) induced by existence of LPC and NEFA high concentrations, and products of their peroxidation, promote elimination of separate protein fractions of erythrocyte membranes (EM) responsible for OS formation and decrease of erythrocytes resistance to peroxide hemolysis. Increase of DBM activity under the effect of relatively moderate doses of zearalenon (1-15 microg/ml) is accompanied with extra intensification of catecholamine synthesizing function of the organism with lethal result. Data of publications represented testify exceptional efficiency of sodium thiosulfate (STS) as a powerful synergist for endogenous factors of antioxidant effect, particularly alpha-tocopherol (alpha-T), which is the main component for the system of cell antiradical defence. Detoxicating effect of STS can be demonstrated indeed on the example of zearalenon intoxication during the first two hours with the reduction of metabolism disturbances of PL and products of its peroxidation. Comparative evaluation of molecular mechanisms of STS normalizing effect as a supplier for hydrogen and sulphur ions, as well as an effective synergist for alpha-T on the level of various formations of the live cell in compare with the effects of alpha-T and ubiquinone, allowed to make a special accent on the role of STS in interaction with energy-dependent enzymatic systems of cell antiradical defence, as well as accumulation and transformation of energy on the level of mitochondrial membranes. The results obtained by us confirm a number of clinical experimental observations, which demonstrate treatment and prophylactic role of STS at different pathologic states of the organism. STS protectory role at toxic injuries of the organism is higher at its preliminary introduction to the organism before modelling of the studied diseased states, especially at zearalenon and halothane (H) intoxication (in the last case before HA). These data serve a sound affirmation for protectory function of STS, detailed revelation of molecular properties of pathogenesis of the studied intoxication to which a part of our clinical and experimental studies at present is devoted.

4304. Curr Drug Targets Inflamm Allergy. 2005 Feb;4(1):81-3.

Behçet's disease as an autoinflammatory disorder.

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Autoinflammatory diseases are a group of heritable disorders that are characterized by seemingly unprovoked episodes of inflammation at certain locations and relative lack of high-titer autoantibodies or antigen-specific T cells. Behçet's disease is an inflammatory disorder of unknown aetiology, and many of its characteristic recurrent manifestations overlap with those of autoinflammatory diseases. Behçet's disease has a complex genetic aetiology, and it is more prevalent in certain geographic regions and/or in particular ethnic groups. Enhanced inflammatory response and over-expression of proinflammatory cytokines are the prominent features of Behçet's disease, and they are compatible with the findings in other autoinflammatory disorders. There are also evidences of antigen-driven immune response in Behçet's disease, but it possibly develops on the background of enhanced innate immune reactivity. Delineation of the similarities of Behçet's disease to other hereditary autoinflammatory diseases may help to clarify its pathogenesis and also to identify the missing links in the shared inflammatory pathways.

PMID: 15720240 [Indexed for MEDLINE]

4305. Curr Drug Targets Inflamm Allergy. 2005 Feb;4(1):77-80.

Molecular and genetic characteristics of hereditary autoinflammatory diseases.

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Autoinflammatory diseases are defined as recurrent "unprovoked" inflammatory events which do not produce high-titer autoantibodies or antigen-specific T cells. There are currently eight hereditary forms of these diseases: Familial Mediterranean fever (FMF), hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS), chronic infantile neurologic cutaneous articular (CINCA) syndrome or neonatal-onset multisystem inflammatory disease (NOMID), pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) and Blau syndrome. Apart from FMF (which has a prevalence of about 0.1 percent among non-Ashkenazi Jews, Armenians, Turks and Arabs), they are very rare disorders. FMF and HIDS are autosomal recessive diseases, all the other members of the family are autosomal and dominantly transmitted. Their common clinical features are recurrent and usually short attacks of synovitis and various skin eruptions; abdominal pain and fever are also frequently observed. The genes of all of these diseases have been discovered and, with the exception of HIDS, it was found that the proteins they encode share certain domains taking part in innate immunity and apoptosis. Thus it was evident that hereditary autoinflammatory diseases may help us understand better a number of important and prevalent pathologic events. We have reviewed the recent and rapidly accumulating knowledge on the molecular aspects of these disorders.

PMID: 15720239 [Indexed for MEDLINE]

4306. Curr Drug Targets Inflamm Allergy. 2005 Feb;4(1):67-76.

Familial Mediterranean fever in the post-genomic era: how an ancient disease is providing new insights into inflammatory pathways.

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Familial Mediterranean fever (FMF, MIM24900), described as a clinical entity only



slightly over a half-century ago, has ancient roots among populations surrounding the Mediterranean basin. It is the most prevalent of the hereditary periodic fever syndromes, a group of disorders characterized by episodic attacks of fever and inflammation. Seven years ago, it was discovered that FMF is caused by mutations in MEFV, a gene that encodes a protein variously called pyrin or marenostin. As exciting as that discovery was, physicians and patients alike were disappointed that the protein sequence of pyrin/marenostin did not immediately suggest clues as to the molecular etiology of FMF. Though we are still far from a complete understanding of the function of pyrin/marenostin at the cellular level, continued study of this intriguing protein is revealing new molecular details about inflammatory processes; the emerging information is relevant not only to FMF, but to innate immunity in general. Data from several laboratories demonstrate that pyrin/marenostin is intimately connected to three important cellular pathways: apoptosis, cytoskeletal signaling and cytokine secretion. These connections occur, at least in part, through the direct interaction of the pyrin/marenostin protein with two cytosolic protein adaptors: ASC (also called PyCARD or Tms1) and PSTPIP (also called CD2BP1). Here, we review the more recent literature regarding the molecular and cellular biology of pyrin/marenostin and pinpoint open questions for future study.

PMID: 15720238 [Indexed for MEDLINE]

4307. Curr Drug Targets Inflamm Allergy. 2005 Feb;4(1):57-65.

Amyloidosis and auto-inflammatory syndromes.

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Amyloidosis remains currently a severe potential complication of many chronic inflammatory disorders. It is not exactly known why some patients develop a progressive amyloidosis, whereas others do not although latent deposits may be present. A permanent acute phase response, ideally evaluated with serial

measurement of serum protein SAA, the precursor of the AA protein deposited in tissues, seems to be a prerequisite to the development of inflammatory (AA) amyloidosis. Genetic factors have however been recently emphasized. Among persistent or emerging causes of AA amyloidosis, hereditary periodic fever syndromes also known as auto-inflammatory syndromes are a group of diseases characterised by intermittent bouts of clinical inflammation with focal organ involvement mainly: abdomen, musculoskeletal system and skin. The most frequent is familial Mediterranean fever which affects patients of Mediterranean descent all over the world. Three other types have been recently clinically as well as genetically characterised. A thorough diagnosis is warranted, as clinical and therapeutic management is specific for each of these diseases.

PMID: 15720237 [Indexed for MEDLINE]

4308. Int J Hematol. 2005 Jan;81(1):26-8.

Familial Mediterranean fever and E148Q pyrin gene mutation in Greece.

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Familial Mediterranean fever (FMF) is an inherited disease characterized by recurrent inflammatory polyserositis. Although FMF is classically expected only in Middle East populations, it is becoming evident that the disease affects more groups than initially thought. The disease is associated with a number of mutations of the MEFV gene, which codes for a protein named pyrin. The role of E148Q pyrin gene mutation in the development of FMF remains inconclusive. Some authors believe it causes the disease, whereas others favor the concept of a noncausative role. To understand better the role of this mutation, gathering data from different populations may be of value. We studied 60 Greek cases fulfilling the criteria for FMF diagnosis, 30 cases being a definite FMF diagnosis and 30 a probable diagnosis. Twenty-one of the patients, carried mutation E148Q. One was a homozygote (E148Q/E148Q), and 20 carried mutation E148Q in combination with other mutations (compound heterozygotes). In 6 of the 60 cases studied, no mutations

were found. Compared with the results for healthy controls, E148Q mutation is significantly frequent. Because different populations may exhibit different patterns of pyrin mutations, association of the E148Q mutation with FMF should be considered in connection with origin data.

PMID: 15717684 [Indexed for MEDLINE]

4309. Rheumatol Int. 2005 Oct;25(8):641-4. Epub 2005 Feb 12.

Sacroiliitis in familial Mediterranean fever and seronegative spondyloarthropathy: importance of differential diagnosis.

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Familial Mediterranean fever (FMF) is a multisystemic autosomal recessive disease, occasionally accompanied by sacroiliitis. Transient and non-erosive arthritis of the large joints is the most frequent articular involvement. Amyloidosis is also the most significant complication of FMF, leading to end stage renal disease. Here we present three cases of FMF with sacroiliitis and review the literature for spinal arthritic involvement of FMF. All cases were referred to our clinic with a diagnosis of seronegative spondyloarthropathy and with low back pain sourced by sacroiliitis. They also had homozygous M694V gene mutations and negative HLA B27 antigens. Molecular analysis of the gene mutation is recommended during the evaluation of uncertain cases in order to clarify diagnostic discrimination. We suggest that FMF with sacroiliitis, which is rare in rheumatological practice, should be considered in the differential diagnosis of seronegative spondyloarthropathy or other rheumatologic diseases causing spinal involvement.

DOI: 10.1007/s00296-004-0578-2

PMID: 15711787 [Indexed for MEDLINE]

4310. Rheumatol Int. 2005 Oct;25(8):633-4. Epub 2005 Feb 8.

Familial Mediterranean fever mimicking septic arthritis.

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We report the case of a young Lebanese female who presented with recurrent episodes of left knee and calf swelling and a synovial fluid leucocyte count suggestive of septic arthritis, however bacteriologic cultures were negative. Familial Mediterranean fever (FMF) was suspected in view of a positive family history and genetic analysis for the mutations in the pyrin/marenostrin (MEFV) gene revealing a homozygote mutation at methionine-694-valine. The arthritis was controlled with prophylactic colchicine therapy. FMF should be considered in the differential diagnosis of acute monoarticular arthritis with elevated synovial fluid white blood cells counts in regions with high incidence of FMF.

DOI: 10.1007/s00296-004-0576-4

PMID: 15700115 [Indexed for MEDLINE]

4311. Ugeskr Laeger. 2005 Jan 10;167(2):183-4.

[Colchicine treatment of a pregnant woman with familial Mediterranean fever].

[Article in Danish]

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PMID: 15697133 [Indexed for MEDLINE]

4312. Arthritis Rheum. 2005 Feb 15;53(1):146-7.

Infliximab therapy in a patient with familial Mediterranean fever and chronic hip arthritis.

Daysal S, Akcil G, Goker B, Haznedaroglu S, Ercan N, Ozturk MA.

DOI: 10.1002/art.20920

PMID: 15696552 [Indexed for MEDLINE]

4313. Rheumatol Int. 2006 Jan;26(3):220-3. Epub 2005 Feb 3.

Evaluation of joints using Tc 99m-MDP bone scintigraphy in patients with familial Mediterranean fever: should bone scans be used for diagnosis and follow-up?

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Familial Mediterranean fever (FMF) is an autosomal recessively-inherited disorder typically manifested by recurrent attacks of fever and polyserositis. The articular disease occurs in 50-70% of patients. Bone scintigraphy is more sensitive in the diagnosis of arthritis than clinical examination or conventional radiological imaging, allowing earlier diagnosis through the visualization of disease in multiple sites. To assess joint involvements in FMF patients with or without joint symptoms, bone scintigraphy was performed in 36 patients with FMF and in 25 controls. There was arthritis in 72% of patients. Of these, 65% knee, 42% ankle, 50% sacroiliac, 8% elbow, 8% wrist, 4% sternoclavicular and 4% hip involvements were found. The sacroiliac joints with sacroiliac index higher than 1.34 were diagnosed as sacroiliitis, which was higher than 2 SD of normal. FMF is frequently associated with joint disease such as knee and ankle arthritis and sacroiliitis. This high incidence of sacroiliitis in our study has not been previously reported. This difference could be explained by the different methodology used for the screening of the joints. Thus, we recommend that bone scintigraphy can be used in patients with FMF to determine the presence of

arthritis, especially in sacroiliac joints, even asymptomatic.

DOI: 10.1007/s00296-004-0555-9

PMID: 15690143 [Indexed for MEDLINE]

4314. J Gastroenterol Hepatol. 2005 Feb;20(2):325-6.

Peritoneal amyloidosis caused by Familial Mediterranean Fever.

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DOI: 10.1111/j.1440-1746.2005.03718.x

PMID: 15683444 [Indexed for MEDLINE]

4315. Joint Bone Spine. 2005 Jan;72(1):38-40.

Interferon-gamma levels in familial Mediterranean fever.

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AIMS: To evaluate the levels of endogenous interferon-gamma (IFN-gamma) in patients with familial Mediterranean fever (FMF).

METHODS: Plasma levels of IFN-gamma were assayed in 29 FMF patients in attack-free period (mean age: 32, min-max: 17-48; male/female: 10/19), 18 FMF patients with acute FMF attack (mean age: 32, min-max: 19-50; male/female: 8/10), and 19 healthy controls (mean age: 31.94 +/- 1.50, min-max: 23-42; male/female: 11/8). IFN-gamma levels were also compared among colchicine treated and untreated groups.

RESULTS: Median plasma IFN-gamma levels were significantly higher in patients both with and without FMF attack than the control group ( $P < 0.05$ ). Moreover, plasma IFN-gamma levels were higher in patients with acute FMF attack compared to patients in attack-free periods ( $P < 0.05$ ). Plasma levels of IFN-gamma were

comparable in colchicine treated and untreated groups.

CONCLUSION: Our results suggest that IFN-gamma may contribute to the inflammatory cascade of FMF.

DOI: 10.1016/j.jbspin.2004.03.011

PMID: 15681246 [Indexed for MEDLINE]

4316. Clin Rheumatol. 2005 Feb;24(1):92-4. Epub 2004 Jul 8.

Hyperimmunoglobulinemia D syndrome in an Arab child.

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Hyperimmunoglobulinemia D syndrome (HIDS) is newly recognized and resembles familial Mediterranean fever (FMF). It is inherited as an autosomal recessive trait. Mutation of the gene coding for mevalonate kinase is responsible for the disease. The gene is located at chromosome 12q24. The patients initially described were of Dutch ancestry. Other cases from Turkey and Armenia were reported. The case we present is the first from Arab countries to be registered in the International HIDS Registry and to our knowledge the first to be reported.

DOI: 10.1007/s10067-004-0953-0

PMID: 15674660 [Indexed for MEDLINE]

4317. Genes Immun. 2005 Mar;6(2):134-9.

Prevalence and significance of mutations in the familial Mediterranean fever gene in patients with Crohn's disease.

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The concurrence of Crohn's disease (CD) and familial Mediterranean fever was repeatedly reported. In this study we determined the distribution and

contribution of MEFV gene mutations to CD susceptibility and clinical heterogeneity. An Israeli cohort of 209 CD patients (120 men and 89 women) was investigated for mutations in the MEFV gene. A detailed chart review, interview and physical examination were used to determine sociodemographic and clinical characteristics. MEFV and NOD2/CARD15 genotypes were analyzed in all patients and a genotype-phenotype correlation analysis was undertaken. The results of this study do not implicate MEFV mutations as major modifiers in CD. However, the E148Q MEFV variant was associated with susceptibility to perianal disease. More specifically, 19% (9/47) of CD patients with perianal disease carried the E148Q mutation compared to 6.7% (11/162) of CD patients without perianal involvement (OR 3.26, 95% CI 1.2-8.8, P=0.02). Although, for all mutations taken together, the prevalence of MEFV gene mutations among CD patients and controls was similar, the hypothesis that E148Q mutation modulates the phenotypic expression of CD is corroborated by the results of this study and needs to be further evaluated.

DOI: 10.1038/sj.gene.6364156

PMID: 15674370 [Indexed for MEDLINE]

4318. Rheumatol Int. 2005 Dec;26(2):162-7. Epub 2004 Nov 3.

Different ELR (+) angiogenic CXC chemokine profiles in synovial fluid of patients with Behçet's disease, familial Mediterranean fever, rheumatoid arthritis, and osteoarthritis.

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The aim of the present study was to determine synovial levels of ELR (+) CXC chemokines, known to attract mainly neutrophils to inflamed tissues by binding the neutrophil chemokine receptors CXCR1 and CXCR2 and promoting neovascularization in patients with various inflammatory disorders. The study group consisted of 14 patients with Behçet's disease and nine with familial Mediterranean fever. Fourteen patients with rheumatoid arthritis and 16 with osteoarthritis served as controls. Synovial chemokine levels were measured by two-step sandwich enzyme-linked immunosorbent assay, and significant differences



were found in the various chemokines studied. In addition to its angiogenic properties, increased synovial levels of interleukin-8 by attraction of more neutrophils to synovial fluids might also be responsible for the acute synovitis in patients with Behçet's disease. However, the absence of chronic changes with the eventual development of pannus and erosions might result from relatively lower expression of interleukin-8 and the transient, short-lived nature of the arthritis observed in these patients.

DOI: 10.1007/s00296-004-0524-3

PMID: 15672235 [Indexed for MEDLINE]

4319. Am J Gastroenterol. 2005 Feb;100(2):338-43.

The familial Mediterranean fever (MEVF) gene as a modifier of Crohn's disease.

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**OBJECTIVES:** Crohn's disease (CD) has been reported to be more frequent among non-Ashkenazi Jewish patients suffering from familial Mediterranean fever (FMF). Interestingly, functional similarities between the CD susceptibility gene (NOD2/CARD15) and the FMF gene (MEFV) have been described: both belong to the death domain containing protein family, important in the regulation of apoptosis, cytokine processing and inflammation.

**AIMS:** To investigate the prevalence of MEFV mutations in Jewish non-Ashkenazi CD patients and its putative effect on CD presentation.

**METHODS:** Germline DNA of 105 Israeli CD patients of non-Ashkenazi and mixed Ashkenazi-non-Ashkenazi ethnic background was analyzed for three most common MEFV mutations: M694V, V726A, and E148Q. Five patients (4.7%) with a clinical diagnosis of FMF were included. Data obtained from each patient included: age of onset, disease location, and behavior, the presence of extraintestinal manifestations of CD and therapeutic regimens.

**RESULTS:** The overall prevalence of mutation carriers among non-FMF-CD patients was 13% (13/100). A stricturing disease pattern was observed in 56% (10/18) of

all carriers, FMF-CD, and non-FMF-CD patients, and in 25% (22/87) of noncarriers (OR: 3.7, 95% CI: 1.3-10.5,  $p=0.015$ ). The prevalence of fistulas was comparable in both groups. Extraintestinal manifestations were significantly more frequent among carriers than noncarriers (65% vs 32%, OR 3.9, 95% CI = 1.3-11.5,  $p=0.015$ ). No differences were observed in disease location and disease severity.

CONCLUSIONS: MEFV mutations are not associated with CD susceptibility, yet the presence of these mutations appears to be associated with a stricturing disease pattern and extraintestinal disease manifestations of CD.

DOI: 10.1111/j.1572-0241.2005.40810.x

PMID: 15667491 [Indexed for MEDLINE]

4320. Eur J Hum Genet. 2005 Apr;13(4):510-2.

Identification of a novel mevalonate kinase gene mutation in combination with the common MVK V377I substitution and the low-penetrance TNFRSF1A R92Q mutation.

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The hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) is an autosomal recessively inherited autoinflammatory disease caused by mutations in the mevalonate kinase (MVK) gene on chromosome 12q24, which lead to a depressed enzymatic activity of mevalonate kinase (MK). TNF-receptor associated periodic syndrome (TRAPS), on the other hand, is the most frequent autosomal dominantly inherited periodic fever syndrome due to mutations in exons 2-4 and 6 of the TNFRSF1A gene on chromosome 12p13.2. We describe a girl with heterozygosity for the common MVK V377I mutation and for a novel T(1132) --> C transition, leading to the exchange of serine (TCC) by proline (CCC) at amino-acid position 378. Interestingly, our patient presented only with mild clinical features typical of HIDS and slightly increased immunoglobulin D levels, but a distinctly diminished MK activity. The girl was also heterozygous for the TNFRSF1A R92Q low-penetrance mutation, which may have significant proinflammatory effects. However, at the time of presentation, the patient had no TRAPS-associated symptoms.

DOI: 10.1038/sj.ejhg.5201352

PMID: 15657603 [Indexed for MEDLINE]

4321. Medicine (Baltimore). 2005 Jan;84(1):1-11.

Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study.

Tunca M(1), Akar S, Onen F, Ozdogan H, Kasapcopur O, Yalcinkaya F, Tutar E, Ozen S, Topaloglu R, Yilmaz E, Arici M, Bakkaloglu A, Besbas N, Akpolat T, Dinc A, Erken E; Turkish FMF Study Group.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease that is prevalent among eastern Mediterranean populations, mainly non-Ashkenazi Jews, Armenians, Turks, and Arabs. Since a large proportion of all the FMF patients in the world live in Turkey, the Turkish FMF Study Group (FMF-TR) was founded to develop a patient registry database and analyze demographic, clinical, and genetic features. The cohort was composed of 2838 patients (mean age, 23.0 +/- 13.33 yr; range, 2-87 yr), with a male:female ratio of 1.2:1. There was a mean period of 6.9 +/- 7.65 years from disease onset to diagnosis; the period was about 2 years shorter for each decade since 1981. Ninety-four percent of patients were living in the central-western parts of the country; however, their familial origins (70% from the central-eastern and Black Sea regions) reflected not only the ongoing east to west migration, but also the historical roots of FMF in Turkey. Patients' clinical features included peritonitis (93.7%), fever (92.5%), arthritis (47.4%), pleuritis (31.2%), myalgia (39.6%), and erysipelas-like erythema (20.9%). Arthritis, arthralgia, myalgia, and erysipelas-like erythema were significantly more frequent ( $p < 0.001$ ) among patients with disease onset before the age of 18 years. Genetic analysis of 1090 patients revealed that M694V was the most frequent mutation (51.4%), followed by M680I (14.4%) and V726A (8.6%). Patients with the M694V/M694V genotype were found to have an earlier age of onset and higher frequencies of arthritis and arthralgia compared with the other groups (both  $p < 0.001$ ). In contrast to other reported studies, there was

no correlation between amyloidosis and M694V homozygosity in this cohort. However, amyloidosis was still remarkably frequent in our patients (12.9%), and it was prevalent (27.8%) even among the 18 patients with a disease onset after age 40 years. Twenty-two patients (0.8%) had nonamyloid glomerular diseases. The high prevalence of vasculitides (0.9% for polyarteritis nodosa and 2.7% for Henoch-Schonlein purpura) and high frequency of pericarditis (1.4%) were striking findings in the cohort. Phenotype II cases (those patients with amyloidosis as the presenting or only manifestation of disease) were rare (0.3% or less). There was a high rate of a past diagnosis of acute rheumatic fever, which suggested a possible misdiagnosis in children with FMF presenting with recurrent arthritis. To our knowledge, this is the largest series of patients with FMF reported from 1 country. We describe the features of the disease in the Turkish population and show that amyloidosis is still a substantial problem.

PMID: 15643295 [Indexed for MEDLINE]

4322. Clin Exp Rheumatol. 2004 Nov-Dec;22(6):791-2.

Inefficacy of etanercept in a child with hyper-IgD syndrome and periodic fever.

Marchetti F, Barbi E, Tommasini A, Oretti C, Ventura A.

PMID: 15638064 [Indexed for MEDLINE]

4323. Nephrol Dial Transplant. 2005 Jan;20(1):238.

Massive renal and adrenal calcifications in a young dialysis patient with familial Mediterranean fever.

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DOI: 10.1093/ndt/gfh481

PMID: 15632359 [Indexed for MEDLINE]

4324. J Rheumatol. 2005 Jan;32(1):175-7.

Myocarditis and sacroiliitis: 2 previously unrecognized manifestations of tumor necrosis factor receptor associated periodic syndrome.

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Tumor necrosis factor receptor associated periodic syndrome (TRAPS) is an autosomic-dominant periodic syndrome associated with mutations in the extracellular domain of the 55 kDa TNF receptor. Clinically, episodes of severe myalgia, arthralgia/arthritis, sterile peritonitis, scrotal inflammation, serositis, migratory rash, conjunctivitis, and recurrent fever are characteristic. We describe a 9-year-old African American boy with the P46L mutation of the TNF receptor who presented with 2 previously unrecognized manifestations: sacroiliitis and myocardiopathy, both showing a reversible course.

PMID: 15630744 [Indexed for MEDLINE]

4325. Ann Intern Med. 2005 Jan 4;142(1):47-55.

Narrative review: diseases that masquerade as infectious cellulitis.

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Comment in

Ann Intern Med. 2005 Jun 7;142(11):949.

Ann Intern Med. 2005 Oct 18;143(8):614.

For cellulitis that does not respond to conventional antimicrobial treatment, clinicians should consider, among other explanations, several noninfectious disorders that might masquerade as infectious cellulitis. Diseases that commonly masquerade as this condition include thrombophlebitis, contact dermatitis, insect stings, drug reactions, eosinophilic cellulitis (the Wells syndrome), gouty arthritis, carcinoma erysipelatoides, familial Mediterranean fever, and foreign-body reactions. Diseases that uncommonly masquerade as infectious cellulitis include urticaria, lymphedema, lupus erythematosus, sarcoidosis, lymphoma, leukemia, Paget disease, and panniculitis. Clinicians should do an initial diagnostic work-up directed by the findings from a detailed history and complete physical examination. In many cases, skin biopsy is the only tool that helps identify the correct diagnosis. Special tests may also be needed.

PMID: 15630108 [Indexed for MEDLINE]

4326. An Med Interna. 2004 Dec;21(12):590-2.

[Fever and abdominal pain. A case of familial mediterranean fever].

[Article in Spanish]

Perelló Carbonell R(1), Smithson Amat A, Supervía Caparrós A, Arenillas Rocha L, Torrente Segarra V, Skaf Peters E.

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Familial mediterranean fever (FMF) is an hereditary disease transmitted in an autosomal recessive way and characterized by recurrent and brief episodes of fever and pain secondary to serositis. The pain is usually located in abdomen simulating an acute abdomen, and in thorax in the form of pleuritic pain. The most severe complication of the FMF is the development of amyloidosis being the main cause of death. This illness affects an specific ethnic group of the mediterranean area, but the prevalence in our area is low. We present the case of

a 30 years old man with recurrent thoracic and abdominal pain, whose final diagnostic was FMF. Insisting on the difficulty that it was recognize this proper illness.

PMID: 15628954 [Indexed for MEDLINE]

4327. Nephron Clin Pract. 2004;98(4):c119-23.

Continuous ambulatory peritoneal dialysis in familial Mediterranean fever amyloidosis patients with end-stage renal failure: a single-centre experience from Turkey.

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**BACKGROUND/AIMS:** Familial Mediterranean fever (FMF) is an autosomal recessive disease characterised by recurrent fever attacks and polyserositis which may lead to the development of AA amyloidosis and end-stage renal disease (ESRD). In this study, we aimed to evaluate the efficacy of continuous ambulatory peritoneal dialysis (CAPD) in FMF-amyloidosis patients with ESRD.

**METHODS:** Forty age- and sex-matched patients undergoing CAPD at our centre between 1996 and 2002 were included in the study. Of these, 10 had FMF-amyloidosis, 10 had diabetes mellitus (DM), 10 had chronic glomerulonephritis (CGN) and 10 had chronic interstitial nephritis (CIN). Efficiency of CAPD, development of complications, presence of other diseases and survival were compared.

**RESULTS:** With the onset of ESRD, the frequency of FMF peritonitis attacks decreased, with less attacks occurring during CAPD in FMF-amyloidosis patients ( $p < 0.05$ ). There was no significant difference between the FMF-amyloidosis group and other groups in terms of efficiency of CAPD, peritoneal function, complications and survival. DM patients had a shorter survival period compared with CGN and CIN patients ( $p < 0.05$ ), but there was no survival difference between FMF-amyloidosis patients and other groups ( $p > 0.05$ ).

**CONCLUSIONS:** We conclude that CAPD is an effective and safe renal replacement

therapy for FMF-amyloidosis patients with ESRD.

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DOI: 10.1159/000081553

PMID: 15627789 [Indexed for MEDLINE]

4328. Transplant Proc. 2004 Nov;36(9):2632-4.

Long-term outcome of renal transplantation in patients with familial Mediterranean fever amyloidosis: a single-center experience.

Keven K(1), Sengul S, Kutlay S, Ekmekci Y, Anadol E, Nergizoglu G, Ates K, Erturk S, Erbay B.

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Although recurrence of amyloid A deposition in the allograft can be seen in patients with secondary amyloidosis due to familial Mediterranean fever (FMF), renal transplantation remains to be a choice of treatment for end-stage renal disease. The aim of this study was to determine short- and long-term results of renal transplantation in patients with FMF amyloidosis. We compared the outcomes of 17 patients with FMF amyloidosis among 431 (3.9%) transplants with 209 control patients. We observed 93% and 94% graft and patient survivals at 1 year, and 89% and 90% at 5 years. Also, the mean serum creatinine levels at 1 and 5 years posttransplant were similar. Recurrence of amyloidosis was documented in two allograft recipients presenting with nephrotic range proteinuria (12%), one of whom lost the allograft due to recurrence. Eleven patients had FMF gene analysis. The results of MEFV mutation analyses were: M694V/M694V homozygote in six patients, M694V/EQ148 in one patient, M694V/V726A in one patient, 680M-I/E148Q in one patient. FMF gene analysis was negative in two patients. Recurrence was noticed in one patient with M694V/M694V, while the other did not have an FMF gene analysis. Colchicine was reduced in nine patients due to side effects. In conclusion, the long-term outcomes of transplantation in patients with amyloidosis secondary to FMF is similar to that in the general transplant population and maintenance colchicine, even at low dose, appears to effectively



prevent recurrence of amyloidosis in the allograft.

DOI: 10.1016/j.transproceed.2004.09.065

PMID: 15621109 [Indexed for MEDLINE]

4329. Free Radic Biol Med. 2005 Jan 15;38(2):271-5.

Oxidative stress status in familial Mediterranean fever with or without proteinuria.

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Although several studies have indicated oxidative system abnormalities in patients with familial Mediterranean fever, it is still obscure whether proteinuria seen in this disease has an effect on the oxidative system. In the present study, oxidative system changes were investigated in familial Mediterranean fever with or without proteinuria. Plasma malondialdehyde levels in proteinuric and nonproteinuric patients were higher than those of the controls and they were also significantly higher in the patients with proteinuria compared to patients without proteinuria. The patients had significantly lower plasma glutathione peroxidase activities than the controls. Glutathione peroxidase activities did not show statistically significant differences between the patients with and those without proteinuria. A significant difference was not established for erythrocyte superoxide dismutase activities. These data suggest that there is an increase in lipid peroxidation in familial Mediterranean fever. Decreased plasma glutathione peroxidase activities seem to be responsible for increased plasma malondialdehyde levels in both patient groups. However, the fact that higher plasma malondialdehyde levels in proteinuric patients were observed compared to nonproteinuric patients in the presence of the unchanged plasma glutathione peroxidase activities in these groups suggests that the nephrotic state may have a contribution to this situation.

DOI: 10.1016/j.freeradbiomed.2004.10.026

PMID: 15607910 [Indexed for MEDLINE]

4330. Arthritis Rheum. 2004 Dec;50(12):4045-50.

Clinical and genetic heterogeneity among Spanish patients with recurrent autoinflammatory syndromes associated with the CIAS1/PYPAF1/NALP3 gene.

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**OBJECTIVE:** To investigate the involvement of the CIAS1/PYPAF1/NALP3 gene in 7 unrelated Spanish families with recurrent autoinflammatory diseases characterized by early onset, recurrent fever, and a chronic urticarial rash, in whom a clinical diagnosis of cryopyrin-associated periodic syndromes (CAPS) is suspected.

**METHODS:** Clinical symptoms, results of laboratory analyses, and data on previous treatments in members of the 7 families were recorded on a questionnaire specific for hereditary autoinflammatory diseases. All coding regions and intronic flanking boundaries of the CIAS1/PYPAF1/NALP3 gene were amplified by polymerase chain reaction and sequenced.

**RESULTS:** Five different missense mutations, including 2 de novo and 1 previously unreported mutation (R488K), were identified in exon 3 of the CIAS1/PYPAF1/NALP3 gene in 5 of the 7 affected families. Expanded genetic analysis among the healthy individuals identified incomplete penetrance in 2 families. No mutations were found in 2 of the 3 patients with chronic infantile neurologic, cutaneous, articular (CINCA) syndrome/neonatal-onset multisystem inflammatory disease (NOMID).

**CONCLUSION:** The clinical data suggested a diagnosis of familial cold-induced autoinflammatory syndrome in 3 families, CINCA/NOMID syndrome in 3 others, and a possible Muckle-Wells syndrome, whereas mutational analysis showed different CIAS1/PYPAF1/NALP3 missense mutations in 5 families. These data are consistent with a common molecular basis of these diseases and highlights the phenotypic heterogeneity among CIAS1/PYPAF1/NALP3 gene-associated syndromes. The previously unreported mutation and the incomplete penetrance found in 2 families expand the genetic basis underlying these autoinflammatory syndromes. These findings should alert clinicians to the possible genetic basis of these conditions, even in the

absence of a family history, in their attempts to establish an accurate diagnosis and the optimal therapeutic approach.

DOI: 10.1002/art.20633

PMID: 15593220 [Indexed for MEDLINE]

4331. J Rheumatol. 2004 Dec;31(12):2519-22.

Two familial cases with tumor necrosis factor receptor-associated periodic syndrome caused by a non-cysteine mutation (T50M) in the TNFRSF1A gene associated with severe multiorgan amyloidosis.

Kallinich T(1), Briese S, Roesler J, Rudolph B, Sarioglu N, Blankenstein O, Keitzer R, Querfeld U, Haffner D.

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An adolescent boy had had recurrent episodes of fever, abdominal pain, and arthralgias since the age of 7 years. Progressive renal failure due to renal amyloidosis developed, leading to renal transplant at the age of 14.5 years. Five years later, he developed AA amyloidosis in the transplant as well as the thyroid gland. His father had had similar symptoms including systemic amyloidosis since the age of 6 years. DNA sequence analysis revealed a heterozygous mutation in the TNFRSF1A (TNF $\alpha$ -receptor 1) gene (T50M) in both father and son causing tumor necrosis factor receptor-associated periodic syndrome (TRAPS). Previous phenotype/genotype analyses have proposed that this mutation is usually not associated with the occurrence of amyloidosis. This difference in the clinical course in different families may indicate a strong influence of modifier genes. Treatment with a TNFRSF1B fusion protein TNF antagonist (etanercept) favorably influenced the disease course.

PMID: 15570662 [Indexed for MEDLINE]

4332. Am J Nephrol. 2004 Nov-Dec;24(6):582-6. Epub 2004 Nov 19.

Long-term evaluation of neuromyopathy in live donor FMF amyloidotic kidney transplant recipients.

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**BACKGROUND:** Neuromyopathy was reported to be a problem among live donor familial Mediterranean fever (FMF) amyloid kidney transplant recipients. We aimed to address this issue on a long-term basis.

**METHODS:** 14 FMF amyloid live donor kidney transplant recipients with a mean post-transplant follow-up period of 82.43 +/- 50.1 months in comparison to a control group of 19 non-amyloid renal transplant patients were subjected to thorough neurological examination, laboratory and electrophysiologic studies.

**RESULTS:** Both groups were comparable with regard to mean serum creatinine levels cyclosporine doses ( $p > 0.05$ ), however trough cyclosporine levels were significantly lower in the amyloidotics than the controls ( $p = 0.04$ ). Serum creatine phosphokinase was comparable in both groups ( $p = 0.59$ ). The amyloid patients showed significantly increased polyphasic motor unit potentials and abnormal interference patterns in the biceps brachii muscle ( $p = 0.03$ ) and the abductor polices brevis muscle ( $p = 0.05$ ). Multivariate analysis showed a significant level for biceps myopathy in amyloidotics ( $p = 0.001$ ). Both groups attained no difference with regard to median nerve conduction velocity.

**CONCLUSION:** Electrophysiologically evidenced neuromyopathy is more liable to occur in long-term live donor FMF amyloidotic kidney transplant recipients than in the other non-amyloidotic kidney transplant recipients even with no clinical manifestations or high creatine phosphokinase levels.

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DOI: 10.1159/000082251

PMID: 15557771 [Indexed for MEDLINE]

Etanercept plus colchicine treatment in a child with tumour necrosis factor receptor-associated periodic syndrome abolishes auto-inflammatory episodes without normalising the subclinical acute phase response.

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We investigated the cause of hereditary periodic fever syndrome in a Spanish child with recurrent long episodes of fever, migratory skin rash, myalgia, arthralgia, conjunctivitis and abdominal pain. Infectious and autoimmune causes were ruled out. No familial history was reported. Analysis of the tumour necrosis factor receptor superfamily 1A (TNFRSF1A) gene identified a missense mutation (G36E) on exon 3. The absence of this variant in the patient's parents and in controls identified it as a de novo disease-associated mutation. Clinical symptoms disappeared with administration of etanercept; however, levels of acute-phase reactants remained increased and could not be stabilised by the addition of colchicine. We believe that this patient gained some symptomatic relief with etanercept therapy, although not enough to completely avoid the risk of amyloidosis. Thus it is debatable whether etanercept alone or combined with other drugs, is the treatment of choice for patients with tumour necrosis factor receptor-associated periodic syndrome. CONCLUSION: Since there is variability in treatment responses among different patients with tumour necrosis factor receptor-associated periodic syndrome, we suggest that a systematic evaluation of acute-phase reactants, especially SAA-1, could be useful in maintaining or modifying a given therapeutic approach in these patients.

DOI: 10.1007/s00431-004-1563-1

PMID: 15549379 [Indexed for MEDLINE]

4334. J Pediatr Surg. 2004 Nov;39(11):1724-5.

A very rare consequence of steroid therapy: ileal perforation in a patient with familial mediterranean fever.

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Intestinal perforation rarely occurs in children with familial Mediterranean fever (FMF). When this does happen, it is the result of untreated intestinal obstruction caused by compression from peritoneal adhesions. Intestinal perforation is a well-known complication of steroid therapy in all ages. The duodenum is affected most frequently, but perforation may also occur in other parts of the small intestine and, very rarely, the colon. Intestinal wall changes that occur in chronic FMF may promote the harmful effects of steroids. Here we present an unexpected complication, ileal perforation, in an 8-year-old boy who was taking prednisolone for FMF-related arthritis.

PMID: 15547842 [Indexed for MEDLINE]

4335. Clin Exp Immunol. 2004 Dec;138(3):526-33.

Does immune activation continue during an attack-free period in familial Mediterranean fever?

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Although some information is available regarding immune activation in familial Mediterranean fever (FMF), little is known about either peripheral blood T cell activation marker expression or the T cell proliferative response to phytohaemagglutinin (PHA). In the present study, we aimed to investigate the percentages of peripheral blood lymphocyte subsets, T cell expression of cellular activation markers (CD25, CD69, HLA-DR), the T cell response to PHA and serum levels of soluble interleukin-2 receptor (sIL-2R) and interleukin (IL)-10 in patients with FMF. Forty patients with FMF were enrolled into the study. Control

groups were sex- and age-matched and consisted of 20 healthy blood donors and 15 patients with inactive Behcet's disease. The patients with FMF in an attack period had higher levels of sIL-2R than those in an attack-free period, and also in comparison with both control groups. The levels of sIL-2R were also found to be higher in patients with FMF in an attack-free period than those in both control groups. The mean levels of IL-10 were found to be lower in patients with FMF in an attack-free period than those in an attack period and were also lower than those in the healthy controls. In an acute attack period, the absolute counts of CD3+HLA-DR+, CD4+CD69+, CD8+CD25+ and CD8+CD69+ T cells in peripheral blood samples were also higher than those in both control groups. Both the percentages and absolute counts of CD4+CD69+ T cells in peripheral blood samples of patients with FMF in an attack-free period were slightly but significantly higher than those in the healthy controls. In conclusion, our study indicates that the T cell system is abnormally activated in patients with FMF in both the attack and attack-free period and that decreased IL-10 levels may create a tendency to perpetuate subclinical immune activation in the attack-free period.

DOI: 10.1111/j.1365-2249.2004.02632.x

PMCID: PMC1809227

PMID: 15544632 [Indexed for MEDLINE]

4336. Lancet. 2004 Nov 13-19;364(9447):1779-85.

Prevention of cold-associated acute inflammation in familial cold autoinflammatory syndrome by interleukin-1 receptor antagonist.

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**BACKGROUND:** Familial cold autoinflammatory syndrome (FCAS) is an autosomal dominant disorder characterised by recurrent episodes of rash, arthralgia, and fever after cold exposure. The genetic basis of this disease has been elucidated. Cryopyrin, the protein that is altered in FCAS, is one of the adaptor proteins that activate caspase 1, resulting in release of interleukin 1.

**METHODS:** An experimental cold challenge protocol was developed to study the acute inflammatory mechanisms occurring after a general cold exposure in FCAS patients and to investigate the effects of pretreatment with an antagonist of interleukin 1 receptor (IL-1Ra). ELISA, real-time PCR, and immunohistochemistry were used to measure cytokine responses.

**FINDINGS:** After cold challenge, untreated patients with FCAS developed rash, fever, and arthralgias within 1-4 h. Significant increases in serum concentrations of interleukin 6 and white-blood-cell counts were seen 4-8 h after cold challenge. Serum concentrations of interleukin 1 and cytokine mRNA in peripheral-blood leucocytes were not raised, but amounts of interleukin 1 protein and mRNA were high in affected skin. IL-1Ra administered before cold challenge blocked symptoms and increases in white-blood-cell counts and serum interleukin 6.

**INTERPRETATION:** The ability of IL-1Ra to prevent the clinical features and haematological and biochemical changes in patients with FCAS indicates a central role for interleukin 1beta in this disorder. Involvement of cryopyrin in activation of caspase 1 and NF-kappaB signalling suggests that it might have a role in many chronic inflammatory diseases.

**RELEVANCE TO PRACTICE:** These findings support a new therapy for a disorder with no previously known acceptable treatment. They also offer insights into the role of interleukin 1beta in more common inflammatory diseases.

DOI: 10.1016/S0140-6736(04)17401-1

PMCID: PMC4321997

PMID: 15541451 [Indexed for MEDLINE]

4337. Eur J Hum Genet. 2005 Mar;13(3):314-20.

MVK mutations and associated clinical features in Italian patients affected with autoinflammatory disorders and recurrent fever.

D'Osualdo A(1), Picco P, Caroli F, Gattorno M, Giacchino R, Fortini P, Corona F, Tommasini A, Salvi G, Specchia F, Obici L, Meini A, Ricci A, Seri M, Ravazzolo R, Martini A, Ceccherini I.

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Autosomal recessive autoinflammatory disorder caused by mutations of the mevalonate kinase gene (MVK), leading to mild, incomplete MK enzyme deficiency (MKD), has been known so far as Hyper-IgD and periodic fever syndrome (HIDS) and regarded as mostly occurring in Northern Europe. Here we report the results of the molecular characterization of the first Italian series of patients affected with autoinflammatory disorders and periodic fever. A total of 13 different mutations, scattered throughout the MVK coding region, were identified in either homozygous or compound heterozygous state in 15 patients. The mutation leading to the V377I amino-acid change, already described also in other series, resulted the most common with a frequency of 50% of all MKD alleles. Among the other mutations, eight had never been described before, including an interstitial deletion of 19 nucleotides in exon 2. In addition to these nucleotide changes, private and polymorphic MVK variants have been detected in the patients under analysis and checked also in a set of control individuals. Clinical features are reported for each of the 15 MKD patients, and life-threatening infections and systemic amyloidosis presented as unexpected MKD-related complications. Our study demonstrates that MKD is a common cause of recurrent fever also in the Italian population, where it is associated with both a wide spectrum of previously unreported MVK mutations and peculiar phenotypic features.

DOI: 10.1038/sj.ejhg.5201323

PMID: 15536479 [Indexed for MEDLINE]

4338. Curr Biol. 2004 Nov 9;14(21):1929-34.

Identification of bacterial muramyl dipeptide as activator of the NALP3/cryopyrin inflammasome.

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Activation of caspase-1 and subsequent processing and secretion of the pro-inflammatory cytokine IL-1 $\beta$  is triggered upon assembly of the inflammasome complex. It is generally believed that bacterial lipopolysaccharides (LPS) are activators of the inflammasome through stimulation of Toll-like receptor 4

(TLR4). Like TLRs, NALP3/Cryopyrin, which is a key component of the inflammasome, contains Leucine-Rich-Repeats (LRRs). LRRs are frequently used to sense bacterial components, thus raising the possibility that bacteria directly activate the inflammasome. Here, we show that bacterial peptidoglycans (PGN), but surprisingly not LPS, induce NALP3-mediated activation of caspase-1 and maturation of proIL-1 $\beta$ . Activation is independent of TLRs because the PGN degradation product muramyl dipeptide (MDP), which is not sensed by TLRs, is the minimal-activating structure. Macrophages from a patient with Muckle-Wells syndrome, an autoinflammatory disease associated with mutations in the NALP3/Cryopyrin gene, show increased IL-1 $\beta$  secretion in the presence of MDP. The activation of the NALP3-inflammasome by MDP may be the basis of the potent adjuvant activity of MDP.

DOI: 10.1016/j.cub.2004.10.027

PMID: 15530394 [Indexed for MEDLINE]

4339. Arthritis Rheum. 2004 Nov;50(11):3679-89.

Lipopolysaccharide-induced expression of multiple alternatively spliced MEFV transcripts in human synovial fibroblasts: a prominent splice isoform lacks the C-terminal domain that is highly mutated in familial Mediterranean fever.

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**OBJECTIVE:** To investigate the expression of the familial Mediterranean fever (FMF) gene (MEFV) in human synovial fibroblasts.

**METHODS:** MEFV messenger RNA in synovial fibroblasts, chondrocytes, and peripheral blood leukocytes (PBLs) was analyzed by semiquantitative and real-time polymerase chain reaction and ribonuclease protection assay. The subcellular localization of pyrin, the MEFV product, was determined in transfected synovial fibroblasts and HeLa cells with plasmids encoding pyrin isoforms. Native pyrin was detected with an antipyrin antibody.

**RESULTS:** MEFV was expressed in synovial fibroblasts, but not in chondrocytes. Four alternatively spliced transcripts were identified: an extension of exon 8

(exon 8ext) resulting in a frameshift that predicts a truncated protein lacking exons 9 and 10, the addition of an exon (exon 4a) predicting a truncated protein at exon 5, the in-frame substitution of exon 2a for exon 2, and the previously described removal of exon 2 (exon 2Delta). Exon 8ext transcripts represented 27% of the total message population in synovial fibroblasts. All other alternatively spliced transcripts were rare. Consensus and alternatively spliced transcripts were induced by lipopolysaccharide in synovial fibroblasts and PBLs. In transfected cells, the proteins encoded by all highly expressed splice forms were cytoplasmic. In contrast, native pyrin was predominantly nuclear in synovial fibroblasts, neutrophils, and dendritic cells, but was cytoplasmic in monocytes. CONCLUSION: Several MEFV transcripts are expressed and inducible in synovial fibroblasts. A prominent isoform lacks the C-terminal domain that contains the majority of mutations found in patients with FMF. While recombinant forms of all major pyrin isoforms are cytoplasmic, native pyrin is nuclear in several cell types. Thus, mechanisms in addition to splicing patterns must control pyrin's subcellular distribution.

DOI: 10.1002/art.20600

PMID: 15529356 [Indexed for MEDLINE]

4340. Presse Med. 2004 Oct 9;33(17):1195-206.

[Hereditary intermittent fever].

[Article in French]

Grateau G(1), Granel B, Hentgen V, Dodé C, Cuisset L, Delpech M.

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Other than familial mediterranean fever: Four hereditary diseases presenting in the form of intermittent inflammatory flares are now recognized and have been characterised clinically and genetically. At the head of this group is Familial Mediterranean Fever (FMF), which affects thousands of patients originating from the Mediterranean area. However the familial Mediterranean Fever is no longer the only recurrent hereditary inflammatory disease. Three other entities have now

been clearly defined: intermittent fever secondary to mutations in the type 1A Tumour Necrosis Factor receptor (TNF), of dominant autosomic genetic transmission, the hyperimmunoglobulinemia D syndrome and an entity regrouping the Muckle Wells syndrome, familial cold-induced urticaria, and the Chronic Infantile Neurological Cutaneous and Articular (CINCA) syndrome. IN PRACTICE: Because they require specific management and treatment, precise diagnosis of these entities is crucial.

PMID: 15523291 [Indexed for MEDLINE]

4341. Clin Exp Rheumatol. 2004 Jul-Aug;22(4 Suppl 34):82.

Familial Mediterranean fever and Celiac sprue--are they related?

Mor A, Mekori YA, Livneh A.

PMID: 15515796 [Indexed for MEDLINE]

4342. Clin Exp Rheumatol. 2004 Jul-Aug;22(4 Suppl 34):80.

Necrotizing crescentic glomerulonephritis with granulomatous vasculitis in a patient with familial Mediterranean fever and renal amyloidosis.

Cefle A, Kilicaslan I, Gul A, Kamali S, Inanc M, Konice M.

PMID: 15515794 [Indexed for MEDLINE]

4343. Clin Exp Rheumatol. 2004 Jul-Aug;22(4 Suppl 34):79.

Hypermobility and fibromyalgia frequency in childhood familial Mediterranean fever.

Kasapçopur O, Tengirsek M, Ercan G, Yologlu N, Caliskan S, Sever L, Arisoy N.

PMID: 15515793 [Indexed for MEDLINE]

4344. Clin Exp Rheumatol. 2004 Jul-Aug;22(4 Suppl 34):S75-8.

Severe outcome of juvenile idiopathic arthritis (JIA) associated with familial Mediterranean fever (FMF).

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Author information:

(1)Department of Rheumatology, Bnai Zion Medical Center, Haifa, Israel.  
mrozenb@netvision.net.il

Juvenile Idiopathic Arthritis (JIA) and Familial Mediterranean Fever (FMF) may involve the same population of children and be confused at times. In a cohort of 350 consecutive FMF patients followed by us, 98 had onset before 10 years of age and, of those, JIA was present in 3. All three had the M694 V mutation of the MEFV gene and were of North African ancestry. The prognosis of these 3 was extremely poor: one developed bilateral knee osteonecrosis with total joint replacement, repeated ileal obstruction with small bowel resection, renal failure and sterility due to amyloidosis and osteoporotic fractures and died at 42 years of age; a second developed deforming erosive arthropathy and underwent bilateral total hip replacement; the third developed severe erosive polyarthritis and also underwent bilateral hip replacements. Aggressive treatment is indicated when JIA and FMF coexist.

PMID: 15515792 [Indexed for MEDLINE]

4345. Clin Exp Rheumatol. 2004 Jul-Aug;22(4 Suppl 34):S69-70.

Protracted febrile myalgia of familial Mediterranean fever.

Kotevoglu N(1), Sahin F, Ozkiris SO, Bankaoglu M, Sakiz D, Kuran B.

Author information:

(1)Physical Therapy and Rehabilitation Department, Sisli Etfal Teaching Hospital, Istanbul, Turkey. nurdankotevoglu@hotmail.com

Protracted febrile myalgia (PFM) includes severe myalgia of the upper and lower extremities accompanied by fever lasting up to 6 weeks, an elevated erythrocyte sedimentation rate and leucocytosis. We report a 13-year-old girl with PFM, and discuss the magnetic resonance imaging findings of the involved calf muscles. To our knowledge these are the only images of the pathology in the literature.

PMID: 15515790 [Indexed for MEDLINE]

4346. Clin Exp Rheumatol. 2004 Jul-Aug;22(4 Suppl 34):S56-8.

Urine leukotriene B4 in familial Mediterranean fever.

Bentancur AG(1), Naveh N, Lancri J, Selah BA, Livneh A.

Author information:

(1)Emergency Medicine Department, Sheba Medical Center, Tel Hashomer, Israel.

**OBJECTIVE:** To determine urinary leukotriene B4 (LTB4) levels and their role in FMF:

**METHODS:** Urinary LTB4 levels were studied using a commercial ELISA kit in 12 FMF patients during abdominal attacks, and 20 FMF patients during remission.

**RESULTS:** Urinary LTB4 levels in FMF patients during attacks were comparable to those during remission, but higher than normal levels ( $p = 0.03$ ).

**CONCLUSIONS:** These findings suggest a persistent activation of the leukotriene pathway in FMF. Whether elevated LTB4 levels are the cause or the effect of inflammation is yet to be determined.

PMID: 15515787 [Indexed for MEDLINE]

4347. Clin Exp Rheumatol. 2004 Jul-Aug;22(4 Suppl 34):S41-4.

The efficacy of continuous interferon alpha administration as an adjunctive agent to colchicine-resistant familial Mediterranean fever patients.

Calguneri M(1), Apras S, Ozbalkan Z, Ozturk MA, Ertenli I, Kiraz S.

Author information:

(1)Section of Rheumatology, Department of Internal Medicine, Hacettepe University Faculty of Medicine, Ankara, Turkey.

**OBJECTIVE:** About 10-20% of familial Mediterranean fever (FMF) patients are resistant to regular colchicine treatment and have painful recurrent attacks due to polyserositis. In clinical practice there is no alternative drug for such patients. In a previous pilot study on a small number of colchicine-resistant patients, interferon-alpha (IFN-alpha) was administered when painful attacks were about to occur.

**METHODS:** In this study we gave IFN-alpha continuously to 8 colchicine-resistant FMF patients in a schedule while the colchicine therapy had been continued. All those patients were complicated with vasculitis or arthritis or together during the FMF course. Those complications were treated with the other immunosuppressive drugs. While they were under intense immunosuppressive therapy, the abdominal and the other serosal attacks remained to continue.

**RESULTS:** After the administration of IFN-alpha therapy only one out of eight patients had abdominal painful attacks in twice, and one patient had arthritis in knees and ankles, the others responded well. Observed side effects were generally mild and acceptable.

**CONCLUSION:** Continuous IFN administration in addition to the regular colchicine treatment may be useful for the colchicine-resistant attacks in FMF patients.

PMID: 15515783 [Indexed for MEDLINE]

4348. Clin Exp Rheumatol. 2004 Jul-Aug;22(4 Suppl 34):S37-40.

The effect of interferon alpha administration on acute attacks of familial Mediterranean fever: A double-blind, placebo-controlled trial.

Tunca M(1), Akar S, Soytürk M, Kirkali G, Resmi H, Akhunlar H, Gönen O, Gallimore JR, Hawkins PN, Tankurt E.

Author information:

(1)Dokuz Eylül University School of Medicine, Department of Internal Medicine, Izmir, Turkey. tunca@superonline.com

**BACKGROUND:** About a quarter of familial Mediterranean fever (FMF) patients are partially or totally resistant to colchicine. A previous observation reported that acute attacks may be shortened by administration of interferon alpha (IFN).

**OBJECTIVE:** We designed a double-blind, placebo-controlled trial to test our initial observations of a beneficial response with IFN in FMF attacks.

**METHODS:** We treated 34 acute abdominal attacks with IFN 5 million IU or placebo sc in the early phase of the attack. Leucocytes, thrombocytes, the erythrocyte sedimentation rate, fibrinogen, C-reactive protein (CRP), serum amyloid A protein (SAA), haptoglobin, transferrin, IL-1beta and TNF-alpha were measured at hours 0, 6, 12, 24 and 48.

**RESULTS:** The median time to recovery in those treated with IFN and placebo was not significantly different, while the leucocytosis and high levels of fibrinogen were significantly more prolonged in placebo-treated patients. CRP and SAA were extremely elevated and peaked at 24h, remaining less marked in the IFN-treated patients but the difference was not statistically significant. Observations regarding the other parameters were unremarkable.

**CONCLUSIONS:** Although there were some clues indicating a depressed inflammatory response with IFN, we could not demonstrate a definitive effect of this agent in this double-blind trial. The drug may suppress the acute inflammation of FMF only if administered at the earliest phase. CRP and SAA may be more sensitive indicators of an attack than ESR or fibrinogen.

PMID: 15515782 [Indexed for MEDLINE]

4349. Clin Exp Rheumatol. 2004 Jul-Aug;22(4 Suppl 34):S34-6.

Levels of interleukin-6 (IL-6) and its soluble receptor (sIL-6R) in familial Mediterranean fever (FMF) patients and their first degree relatives.

Oktem S(1), Yavuzsen TU, Sengül B, Akhunlar H, Akar S, Tunca M.

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**OBJECTIVE:** Familial Mediterranean Fever (FMF) is a hereditary disease characterized by recurrent inflammatory attacks. A subclinical inflammation may persist in periods between the attacks and heterozygotes may have higher than normal levels of acute phase proteins. We investigated the levels of interleukin-6 (IL-6) and its soluble receptor (sIL-6R) in FMF patients and their obligatory carrier relatives.

**METHODS:** Serum levels of IL-6 and sIL-6R were measured during acute attacks (n = 18) and in attack-free FMF patients (n = 26), obligatory carriers of FMF (n = 17) and normal controls (n = 11).

**RESULTS:** The median levels of IL-6 were significantly higher (45.71 pg/ mL, p = 0.001) during acute attacks of FMF only, and were normal (0.01 pg/ mL) in the other groups studied. There was no statistically significant difference in the median sIL-6R values between any of the groups (p = 0.22).

**CONCLUSION:** IL-6 was extremely elevated during FMF attacks but could not detect hypothetical "subclinical" inflammation during attack-free intervals or in the heterozygote relatives of patients. Serum levels of sIL-6R were comparable in all four groups.

PMID: 15515781 [Indexed for MEDLINE]

4350. Clin Exp Rheumatol. 2004 Jul-Aug;22(4 Suppl 34):S31-3.

Increased frequency of familial Mediterranean fever in Central Anatolia, Turkey.

Onen F(1), Sumer H, Turkay S, Akyurek O, Tunca M, Ozdogan H.

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**OBJECTIVE:** It has been observed that familial Mediterranean fever is more prevalent among people coming from central Anatolia in Turkey. To test this observation the frequency of FMF was investigated by a field survey in Sivas, a

city located in central of Turkey.

**METHODS:** The survey was conducted in a cohort of 4809 persons selected by systematic sampling from 2 districts of Sivas, with a total population of 83,274. Face to face interviewing was done with registered households using a standard questionnaire developed to screen FMF. A second interview was conducted by a rheumatologist and an internist of those individuals who were regarded to have possible FMF.

**RESULTS:** The suspicion of FMF emerged in the cases of 46 individuals during the survey and 36 were interviewed for a second time. FMF was diagnosed in 10 cases. Only one had a previous diagnosis of FMF. The overall frequency of FMF among a cohort of 3,948 inhabitants of Sivas was 1/395 (0.25%).

**CONCLUSION:** This study indicates that the prevalence of FMF in Sivas may be higher than that in general Turkish population, which has been reported to be 0.1%.

PMID: 15515780 [Indexed for MEDLINE]

4351. Clin Exp Rheumatol. 2004 Jul-Aug;22(4 Suppl 34):S27-30.

The prevalence of familial Mediterranean fever in the Turkish province of Denizli: a field study with a zero patient design.

Cobankara V(1), Fidan G, Türk T, Zencir M, Colakoglu M, Ozen S.

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**OBJECTIVE:** This study had two aims: (1) to investigate the prevalence of familial Mediterranean fever (FMF) and Behçet's disease (BD) in school students in Denizli, a province in western Turkey; and (2) to determine whether the previously suggested "zero patient design" was reliable for use in a prevalence survey.

**METHODS:** The field survey was performed in two stages. In the first stage 7,389 students (3,847 females and 3,542 males) were asked to fill out a questionnaire in the classroom. In the questionnaire, filtering questions for FMF (the presence of recurrent attacks of fever accompanying abdominal pain, joint pain/swelling,

and/or chest pain) and BD (presence of aphthous stomatitis) were asked. The second stage consisted of two parts. In the first, 3225 questionnaires were completed by 1778 female and 1447 male students calculated according to the zero patient design, who were selected randomly from among 7389 students for evaluation. Students with any suspicion of FMF and Behçet's disease were called to the hospital for detailed investigation. In the second step the remaining students were evaluated.

RESULTS: Out of 3225 children questioned in the first step, 156 claimed recurrent abdominal pain and/or chest pain, and/or joint pain/swelling with accompanying fever, which might suggest the presence of FMF. However, this diagnosis was excluded after further clinical evaluation. In the second step 152 students were called for detailed investigation: 2 patients, one 10 years and the other 12 years old, were diagnosed as having FMF. None were diagnosed to have Behçet's disease.

CONCLUSION: The prevalence of FMF in Turkey in general is about 0.093%. The prevalence rate found in this survey was lower (0.027%) which may be due to the historic background of the region. This is the first study that has shown that the "zero patient design" can be used in an epidemiological survey.

PMID: 15515779 [Indexed for MEDLINE]

4352. Clin Exp Rheumatol. 2004 Jul-Aug;22(4 Suppl 34):S4-7.

Therapeutic approaches to familial Mediterranean fever. What do we know and where are we going to?

Amital H, Ben-Chetrit E.

PMID: 15515775 [Indexed for MEDLINE]

4353. J Obstet Gynaecol. 1999 Sep;19(5):541-2.

Familial Mediterranean fever in a pregnant woman.

Keriakos R(1), Roberts JK, Sidra L.

Author information:

(1)Department of Obstetrics and Gynaecology, Tameside Hospital,  
Ashton-under-Lyne, UK.

DOI: 10.1080/01443619964445

PMID: 15512389

4354. Semin Arthritis Rheum. 2004 Oct;34(2):549-52.

The outcome of pregnancy in the wives of men with familial mediterranean fever treated with colchicine.

Ben-Chetrit E(1), Berkun Y, Ben-Chetrit E, Ben-Chetrit A.

Author information:

(1)Department of Medicine, Hadassah University Hospital, POB 12000, Jerusalem, Israel. eldad@hadassah.org.il

**OBJECTIVE:** To evaluate the outcome of pregnancies of normal women married to men with familial Mediterranean fever (FMF), some of whom took colchicine during the conception with their wives.

**PATIENTS AND METHODS:** We followed the outcome of pregnancies and deliveries of 60 wives of FMF patients; 53 of the husbands were taking colchicine during that time. As a control group we screened the outcome of pregnancy and delivery from 230 healthy women married to healthy men.

**RESULTS:** The 60 FMF patients- wives had 222 pregnancies, of which 206 ended in term delivery with 209 live births. Sixteen pregnancies ended in spontaneous abortions (7%). Three of the newborns in the study group were born with congenital malformations. In the control group, of 788 pregnancies, 127 ended in abortions (16%). Six of the newborns were born with congenital malformations. The rate of the late abortions (second trimester) in both groups was comparable.

**CONCLUSIONS:** The results of our study indicates that neither FMF nor colchicine increases the rate of abortions or congenital malformations. Therefore we believe that there is no need to discontinue colchicine treatment in men with FMF before the conception with their wives.

PMID: 15505771 [Indexed for MEDLINE]

4355. Clin Chem. 2004 Nov;50(11):1974-8.

In silico prediction of the deleterious effect of a mutation: proceed with caution in clinical genetics.

Tchernitchko D(1), Goossens M, Wajcman H.

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When a sequence variation is found in a candidate gene for a disease, it is important to establish whether this change is neutral or responsible for the observed disorders in a patient. To answer this question, in the absence of further experimental investigations, several simulation programs have been proposed to predict whether a nonsynonymous single-nucleotide polymorphism is likely to have or not have a deleterious effect on the phenotype. In this work, we tested two such programs, PolyPhen and SIFT, using two kinds of targets. The first ones concerned the products of the hemoglobin and glucose-6-phosphate dehydrogenase genes, which are abundantly documented. The second concerned two systems for which much less information is available: (a) the TNFRSF1A gene, implicated in tumor necrosis factor receptor-associated periodic syndrome, and (b) the MEFV gene, which is believed to be involved in familial Mediterranean fever. Our data suggest that, from a practical point of view, these programs should not be used to decide, in the absence of other tests or arguments, whether the sequence variation found in a patient is or is not responsible for the disease. The consequence of an erroneous prediction may be disastrous in the perspective of genetic counseling.

DOI: 10.1373/clinchem.2004.036053

PMID: 15502081 [Indexed for MEDLINE]

4356. Semin Pediatr Infect Dis. 2004 Oct;15(4):220, 292-4.

Recurrent fever in a healthy-appearing child.

Edwards MS(1), Millon JC, Perez MD.

Author information:

(1)Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, TX, USA. morvene@bcm.tmc.edu

PMID: 15494944 [Indexed for MEDLINE]

4357. Ann Pharmacother. 2004 Dec;38(12):2074-7. Epub 2004 Oct 19.

Acute colchicine intoxication during clarithromycin administration.

Rollot F(1), Pajot O, Chauvelot-Moachon L, Nazal EM, Kélaïdi C, Blanche P.

Author information:

(1)Internal Medicine, Cochin Hospital, Paris, France.

**OBJECTIVE:** To report a case of colchicine intoxication occurring with institution of clarithromycin.

**CASE SUMMARY:** A 76-year-old man with familial Mediterranean fever (FMF) had received colchicine 1.5 mg daily for 6 years. The patient underwent 7 days of clarithromycin, amoxicillin, and omeprazole treatment for *Helicobacter pylori*-associated gastritis. Fever, abdominal pain, and diarrhea occurred 3 days after treatment initiation. On day 8, dehydration, pancytopenia, metabolic acidosis, and increased lipase level necessitated hospitalization. Alopecia was observed 2 weeks later. The patient recovered fully after the colchicine dosage was reduced to 0.5 mg/day and rehydration was performed. The previous dosage was then reinstituted without adverse reaction. An objective causality assessment revealed that the adverse event was probable.

**DISCUSSION:** Continuous colchicine administration is used in treatment of microcrystalline arthritis, Behcet's disease, and FMF. Colchicine is primarily eliminated through biliary excretion. Renal elimination and cytochrome P450 metabolism play a less significant role. Colchicine is also a substrate of P-glycoprotein, a transporter involved in cellular efflux and elimination of numerous drugs. Three cases of intoxication have been reported when colchicine was combined with erythromycin, josamycin, or clarithromycin. Macrolides are

inhibitors of P-glycoprotein and cytochrome P450-dependent enzymes and may decrease colchicine's biliary excretion through P-glycoprotein inhibition.

CONCLUSIONS: Coadministration of colchicine and macrolides may impair colchicine elimination, resulting in excess drug exposure and toxicity. To this end, colchicine should be used with extreme caution in patients receiving P-glycoprotein inhibitors, particularly if they are elderly and/or renally compromised.

DOI: 10.1345/aph.1E197

PMID: 15494379 [Indexed for MEDLINE]

4358. Clin Nephrol. 2004 Sep;62(3):226-8.

A possible favorable effect of colchicine in IgA nephropathy in a carrier of a MEFV mutation.

Koukoui L(1), Blau A, Kopolovic J, Pras M, Livneh A.

Author information:

(1)Department of Medicine F, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

IgA nephropathy is the most common primary glomerulopathy. Currently, no satisfactory treatment is available and as a result, a significant proportion of affected patients progress to end-stage renal disease. We present a patient with IgA nephropathy in whom continuous colchicine treatment induced remission, which has lasted for 22 years. The patient was a carrier of a mutation in the FMF gene (MEFV). This case raises hopes for a better prognosis in at least one subgroup of IgA nephropathy, consisting of patients who happen to be heterozygous carriers of MEFV mutations.

PMID: 15481855 [Indexed for MEDLINE]

4359. Acta Biomed. 2004 Aug;75(2):92-9.

Autoinflammatory diseases: the hereditary periodic fever syndromes.

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Human autoinflammatory diseases (HAIDs) are a heterogeneous group of genetically determined affections characterized by seemingly unprovoked inflammation, in the absence of autoimmune or infective causes. The hereditary periodic fever syndromes (HPFSs) are a HAID subset consisting of three main nosologic entities: familial Mediterranean fever (FMF), hyperimmunoglobulinemia D and periodic fever syndrome (HIDS), and tumor necrosis factor receptor superfamily 1A-associated periodic syndrome (TRAPS). FMF and HIDS are autosomal recessive diseases, while TRAPS is dominantly inherited. Although each HPFS presents genetic and phenotypic peculiarities, globally these affections share an intermittent expression, in form of acute attacks of fever variably associated with serosal, synovial and/or cutaneous inflammation, usually self-limiting. Amyloidosis is the most severe, life-threatening complication of FMF and TRAPS, whereas it has not been till now reported in HIDS. The HPFS molecular bases have been recently identified. In this paper, the most recent information on HPFSs is reviewed and summarized.

PMID: 15481697 [Indexed for MEDLINE]

4360. Ann Rheum Dis. 2004 Nov;63(11):1527.

Interferon alfa in protracted arthritis of familial Mediterranean fever: a robust alternative for synovectomy.

Ureten K, Calgüneri M, Onat AM, Ozçakar L, Ertenli I, Kiraz S.

DOI: 10.1136/ard.2003.019471

PMCID: PMC1754794

PMID: 15479914 [Indexed for MEDLINE]

4361. N Z Med J. 2004 Aug 6;117(1199):U1007.



Familial Mediterranean fever.

Konstantopoulos K, Kanta A, Lilakos K.

Comment on

N Z Med J. 2004 May 21;117(1194):U894.

PMID: 15475974 [Indexed for MEDLINE]

4362. Reumatismo. 2004 Jul-Sep;56(3):147-55.

[Hyper-IgD syndrome and other hereditary periodic fever syndromes].

[Article in Italian]

Scolozzi R(1), Boccafogli A, Vicentini L.

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Hereditary periodic fever syndromes are a group of systemic disorders characterized by recurrent attacks of systemic inflammation (autoinflammation) without infectious or autoimmune cause. The hyper-IgD syndrome (HIDS) is a rare autosomal recessive inflammatory disorder characterized by recurrent fever, increased serum IgD (normal value < 100 U/ml) and generalized inflammation (lymphadenopathy, arthralgias/arthritis, abdominal complaints, skin rash, and headache). The attacks persist during the entire life although frequency and severity tend to diminish with age. HIDS is caused by specific mutations in the gene encoding mevalonate kinase, resulting in depressed enzymatic activity. At present the therapy for the syndrome is only supportive. Other than HIDS, other hereditary systemic inflammatory disorders have been described: the Familial Mediterranean Fever, the tumour necrosis factor receptor associated periodic syndrome (TRAPS), a disease related to the mutations of one of the TNF receptors, the Familial Cold Urticaria and the Muckle-Wells syndrome. The differential diagnosis with other causes of periodic fever is crucial for assessing

appropriate management and treatment.

PMID: 15470520 [Indexed for MEDLINE]

4363. Eur J Neurol. 2004 Oct;11(10):716-7.

The coexistence of familial Mediterranean fever with multiple sclerosis.

Yücesan C, Canyiğit A, Türkçapar N.

DOI: 10.1111/j.1468-1331.2004.00877.x

PMID: 15469460 [Indexed for MEDLINE]

4364. Am J Med. 2004 Oct 1;117(7):516-9.

Necrotizing vasculitis associated with familial Mediterranean fever.

Hatemi G(1), Masatlioglu S, Gogus F, Ozdogan H.

Author information:

(1)Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical School, Istanbul University, Istanbul, Turkey.

DOI: 10.1016/j.amjmed.2004.02.050

PMID: 15464709 [Indexed for MEDLINE]

4365. Ann Rheum Dis. 2005 May;64(5):750-2. Epub 2004 Sep 30.

E148Q is a disease-causing MEFV mutation: a phenotypic evaluation in patients with familial Mediterranean fever.

Topaloglu R(1), Ozaltin F, Yilmaz E, Ozen S, Balci B, Besbas N, Bakkaloglu A.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is one of the periodic fever syndromes. It is common among Turks, Jews, Arabs, and Armenians. Several mutations in the MEFV gene, including E148Q, have been identified as causing this disease. It has been suggested that the E148Q mutation is the mildest mutation and some reports have questioned its disease association.

**OBJECTIVE:** To evaluate the phenotypic features of the patients with E148Q mutation.

**SUBJECTS:** 26 patients homozygous for E148Q, 10 compound heterozygous for E148Q, and eight complex cases were assessed.

**RESULTS:** Although four of the 26 patients with E148Q/E148Q were asymptomatic at the time of evaluation, abdominal pain was seen in 77% of the patients, fever in 66%, arthralgia in 50%, arthritis in 15.4%, and vomiting in 23.8%. Compound heterozygotes and complex cases had a higher frequency of abdominal pain, fever, arthralgia, arthritis, myalgia, and chest pain than subjects who were homozygous for E148Q, but none of these symptoms reached statistical significance. None of our patients had amyloidosis but two with E148Q/E148Q had a family history of amyloidosis and one had rapidly progressive glomerulonephritis secondary to vasculitis, which progressed to chronic renal failure.

**CONCLUSIONS:** Patients homozygous for E148Q have a heterogeneous clinical presentation. Most are symptomatic and colchicine treatment is required in these patients.

DOI: 10.1136/ard.2004.026963

PMCID: PMC1755471

PMID: 15458961 [Indexed for MEDLINE]

4366. Arthritis Rheum. 2004 Sep;50(9):2966-9.

First report of systemic reactive (AA) amyloidosis in a patient with the hyperimmunoglobulinemia D with periodic fever syndrome.

Obici L(1), Manno C, Muda AO, Picco P, D'Osualdo A, Palladini G, Avanzini MA, Torres D, Marciano S, Merlini G.

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Systemic reactive (AA) amyloidosis, leading to renal failure, is a severe complication of most hereditary periodic fever syndromes. The risk of developing this life-threatening condition varies widely among these disorders, being higher for patients affected by familial Mediterranean fever and tumor necrosis factor receptor-associated periodic syndrome. In spite of an acute-phase response during attacks, amyloidosis has never, to date, been described in patients affected with the hyperimmunoglobulinemia D with periodic fever syndrome (HIDS). This is the first report to describe the occurrence of renal AA amyloidosis causing severe nephrotic syndrome in a young Italian man affected with HIDS. The diagnosis of HIDS was established according to clinical, laboratory, and genetic criteria as required by the international Nijmegen HIDS registry. In this patient, 2 mutations in the mevalonate kinase gene were identified, one of which, the leucine-to-arginine substitution at codon 265, is novel.

DOI: 10.1002/art.20490

PMID: 15457465 [Indexed for MEDLINE]

4367. Best Pract Res Clin Rheumatol. 2004 Oct;18(5):647-61.

Palindromic rheumatism and other relapsing arthritis.

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Patients with recurrent or relapsing arthritis are frequently seen in rheumatological practice. Besides crystal arthritis, the most frequent cause of recurrent arthritis, there are several diseases that may present clinically as intermittent mono- or polyarthritis. Palindromic rheumatism is the paradigm of this type of condition, but other diseases such as systemic autoinflammatory disorders (periodic fever syndromes), Whipple's disease, arthritis associated with hyperlipidemia, intermittent hydrarthrosis and other diseases should be taken into account in the differential diagnosis of patients with recurrent arthritis. In this chapter, we discuss recent developments in these diseases with special emphasis on palindromic rheumatism, a common condition whose close

relationship with rheumatoid arthritis remains intriguing.

DOI: 10.1016/j.berh.2004.05.005

PMID: 15454124 [Indexed for MEDLINE]

4368. Rheumatol Int. 2005 May;25(4):319-20. Epub 2004 Sep 21.

Selective serotonin reuptake inhibitors in familial Mediterranean fever: are we treating depression or inflammation?

Ozçakar L, Onat AM, Kaymak SU, Ureten K, Akinci A.

DOI: 10.1007/s00296-004-0511-8

PMID: 15449025 [Indexed for MEDLINE]

4369. Nephrol Dial Transplant. 2004 Oct;19(10):2678.

Microalbuminuria in the course of familial Mediterranean fever.

Baskin E, Saatci U.

Comment on

Nephrol Dial Transplant. 2003 Mar;18(3):532-8.

DOI: 10.1093/ndt/gfh285

PMID: 15388834 [Indexed for MEDLINE]

4370. Clin Pediatr (Phila). 2004 Sep;43(7):605-8.

Once-daily use of colchicine in children with familial Mediterranean fever.

Koşan C(1), Ozkan B.

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Patients with familial Mediterranean fever routinely take daily multiple doses of colchicine to prevent acute attacks and to reduce the risk of amyloidosis. However, although there is no research in this regard in the literature, some clinicians believe that the use of colchicine in children as daily single dose may cause toxic side effects. The efficiency and the side effects of the administration of daily single dose versus daily multiple doses of colchicine were evaluated in the treatment of patients with familial Mediterranean fever. Thirty-nine patients being observed at Atatürk University Medical Faculty Pediatrics outpatient clinic with the diagnosis of familial Mediterranean fever were randomly divided into 2 groups. Group I consisted of 20 patients who continued taking colchicine in 2 or 3 divided doses daily as they did before the study. Group II comprised 19 patients who were given the total daily colchicine dose at 1 time. Patients were re-examined at 30-day intervals and both groups maintained this regimen for an average duration of 8 months. There was no difference between these 2 groups with respect to frequency of side effects, number of attacks, and acute phase response. Therefore, the daily colchicine dose can be given to children once daily.

DOI: 10.1177/000992280404300703

PMID: 15378145 [Indexed for MEDLINE]

4371. Behav Med. 2004 Winter;29(4):167-72.

The feeling of fatigue--fatigue severity by unidimensional versus composite questionnaires.

Naschitz JE(1), Rozenbaum M, Shaviv N, Fields MC, Enis S, Babich JP, Manor H, Yeshurun D, Sabo E, Rosner I.

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The authors' purpose in this study was to compare the perception of fatigue severity as measured by different fatigue questionnaires. The authors evaluated 3 groups of patients in a cross-sectional study: chronic fatigue syndrome (CFS, n = 20), non-CFS fatigue (n = 20), and familial Mediterranean fever (FMF n = 25). In

addition, the authors tracked 7 patients with CFS longitudinally for severity of fatigue. The severity of fatigue-related symptoms was assessed with 2 questionnaires: the unidimensional Chalder's Fatigue Severity Scale (CH) and the composite Fatigue Impact Scale (FI) which has 3 subscales--cognitive, physical, and social--and a total score. In the cross-sectional study, correlations between CH and FI cognitive scores were  $r = .78$  ( $p < .0001$ ), CH versus FI physical scores  $r = .603$  ( $p < .0001$ ), CH versus FI social scores  $r = .66$  ( $p < .0001$ ), and CH versus FI total scores  $r = .74$  ( $p < .0001$ ). In the longitudinal survey of CFS patients, the authors compared 30 questionnaires revealing correlations of CH versus FI cognitive scores  $r = .64$  ( $p = .0004$ ), CH versus FI physical  $r = .68$  ( $p = .0001$ ), CH versus FI social  $r = .87$  ( $p < .0001$ ), and CH versus FI total  $r = .90$  ( $p < .0001$ ). Fatigue severity as assessed by the unidimensional CH scale and the composite FI scale is comparable. The simple CH scale may be adequate for the assessment of the feeling of fatigue, in general, and for monitoring the severity of fatigue in CFS, in particular.

DOI: 10.3200/BMED.29.4.167-174

PMID: 15369197 [Indexed for MEDLINE]

4372. Ann Rheum Dis. 2004 Oct;63(10):1356-7.

Tumour necrosis factor receptor associated periodic syndrome (TRAPS) with central nervous system involvement.

Minden K, Aganna E, McDermott MF, Zink A.

DOI: 10.1136/ard.2003.016006

PMCID: PMC1754768

PMID: 15361406 [Indexed for MEDLINE]

4373. J Exp Med. 2004 Sep 6;200(5):551-8.

The PYRIN connection: novel players in innate immunity and inflammation.

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Periodic fever syndromes (PFSs) comprise a subset of the hereditary autoinflammatory disorders that are defined by recurrent self-resolving attacks of systemic inflammatory reactions in the absence of infection or autoimmunity. Recent advances have led to the discovery that members of a new family of genes, the PYRIN family, account for several hereditary PFSs. Here we discuss new insights into the function of PYRIN proteins and the molecular basis of PFSs.

DOI: 10.1084/jem.20032234

PMCID: PMC2212741

PMID: 15353551 [Indexed for MEDLINE]

4374. Clin Rheumatol. 2005 Apr;24(2):155-7. Epub 2004 Sep 4.

Avascular necrosis of the femoral head foreshadowing familial Mediterranean fever: apropos of three cases.

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We reported here on three patients in whom the diagnosis of familial Mediterranean fever was established after avascular necrosis of the femoral head had been detected. The pathogenesis and the management of this rare concomitance are discussed in the light of the relevant literature.

DOI: 10.1007/s10067-004-0986-4

PMID: 15351872 [Indexed for MEDLINE]

4375. Transplant Proc. 2004 Jul-Aug;36(6):1796-8.

Renal amyloidosis followed more than 5 years: report of 12 cases.



Kaaroud H(1), Boubaker K, Béji S, Abderrahim E, Moussa FB, Turki S, Goucha R, Hedri H, El Younsi F, Kheder A, Maiz HB.

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Renal involvement with amyloidosis is common but causes patient survival to be poor, rarely reaching 5 years. In this study, we retrospectively reviewed clinical and biological characteristics as well as treatments and outcomes of patients with renal amyloidosis followed for more than 5 years. Between 1975 and 2003, 485 patients were diagnosed with renal amyloidosis including only 12 patients who were followed more than 5 years. The six men and six women of mean age 42.4 years (range 18 to 66 years) displayed renal signs of lower limb edema in all cases; hypertension in four cases, proteinuria on urinalysis in all cases with microscopic hematuria in five cases. Biological tests showed nephrotic syndrome in 11 patients, normal renal function in nine patients, and renal failure in three patients whose mean creatinine was 481.6 micromol/L (range 294 to 726). The amyloidosis was AA type in 11 cases and non-AA in one case. An etiologic survey revealed spondylarthropathy in one patient, pulmonary tuberculosis in two patients, chronic bronchitis in three patients, hepatic hydatid cyst in one patient, Mediterranean familial fever in two patients, Crohn's disease in one patient, Hodgkin's lymphoma in one patient, and multiple myeloma in one patient. Specific treatment was initiated with colchicine in seven patients. At a 110-month mean follow-up (range 53 to 153 months), remission of nephrotic syndrome was observed in four cases, progression to chronic renal failure in two patients, and to end-stage renal failure in five cases (range 53 to 196 months), with stabilization of renal function in seven patients. In conclusion, primary amyloid disease should be optimally suppressed in patients with renal involvement. The role of this treatment in remission of renal amyloidosis is not well established. This efficacy of the treatment has been demonstrated in some patients with improved survival.

DOI: 10.1016/j.transproceed.2004.07.022

PMID: 15350480 [Indexed for MEDLINE]

[Nuclei and nucleolar organizing regions in chromosomes of lymphocytes on different stages of periodic disease].

[Article in Russian]

Karalova EM, Abroian LO, Akopian LO, Karagezian KG, Magakian IuA.

By scanning cytomorphometry a cytological study was first performed on the behavior of nuclei and nucleolar organizing regions (NOR) in chromosomes of peripheral blood lymphocytes of healthy men and of patients with periodic disease (familial Mediterranean fever, FMF) on different stages of development, including its complication with amyloidosis. The volume and total surface of nuclei, the sum total volume and sum total surface of NOR, the mean number of NOR for one nucleus and distribution of nuclei according to NOR number were measured. It is shown that the parameters of nuclei and NOR for patients with FMF on all stages clearly and trustworthy differ from those for healthy men. They are sufficiently informative, can be successfully used in clinical practice and even serve as an early diagnostic test for amyloidosis complication.

PMID: 15346796 [Indexed for MEDLINE]

4377. Intern Med. 2004 Jul;43(7):612-4.

The efficacy of interferon-alpha in a patient with resistant familial Mediterranean fever complicated by polyarteritis nodosa.

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Familial Mediterranean fever (FMF) is a recurrent self-limiting polyserositis. Polyarteritis nodosa (PAN) complicating FMF is very rare. Here, we present a 17-year-old male patient with FMF who subsequently developed PAN 2 weeks after hepatitis A infection. This case was also complicated with perirenal haematoma,

and right nephrectomy was performed. The clinical condition of the patient was improved after therapy with intravenous and oral corticosteroid and intravenous cyclophosphamide. However, the FMF attacks and vasculitic skin lesions again occurred while he was using colchicine plus immunosuppressive agents a few months later. Interferon-alpha therapy was administered and the attacks were resolved within 3 months. He has not experienced any other symptom during the follow-up period of 28 months.

PMID: 15335192 [Indexed for MEDLINE]

4378. Arthritis Rheum. 2004 Aug;50(8):2651-9.

Shedding of mutant tumor necrosis factor receptor superfamily 1A associated with tumor necrosis factor receptor-associated periodic syndrome: differences between cell types.

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**OBJECTIVE:** To investigate the effect of mutations in tumor necrosis factor receptor superfamily 1A (TNFRSF1A) on the ability of the receptors to be cleaved from the cell surface upon stimulation. The mutations we studied are associated with clinically distinct forms of TNF receptor-associated periodic syndrome (TRAPS). We also investigated different cell types within the same form of TRAPS.

**METHODS:** The shedding of TNFRSF1A in response to stimulation with phorbol myristate acetate was assessed in leukocytes and dermal fibroblasts from patients with C33Y TRAPS, and in HEK 293 cell lines stably transfected with constructs containing wild-type TNFRSF1A and/or TNFRSF1A mutants identified in TRAPS patients.

**RESULTS:** The shedding of TNFRSF1A differed between cell types within the same form of TRAPS. In particular, dermal fibroblasts, but not leukocytes, from C33Y TRAPS patients demonstrated reduced shedding of TNFRSF1A. Shedding of both wild-type and mutant TNFRSF1A from the transfected HEK 293 cells showed minor

differences, but was in all cases induced to a substantial extent.

CONCLUSION: Differences in TNFRSF1A shedding are not purely a function of the TNFRSF1A structure, but are also influenced by other features of genetic makeup and/or cellular differentiation. It is unlikely that a defect in TNFRSF1A shedding per se can fully explain the clinical features that are common to TRAPS patients with different TNFRSF1A mutations.

DOI: 10.1002/art.20380

PMID: 15334481 [Indexed for MEDLINE]

4379. Clin Sci (Lond). 2005 Jan;108(1):37-46.

Search for disease-specific cardiovascular reactivity patterns: developing the methodology.

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Aberrations of CVR (cardiovascular reactivity), an expression of autonomic function, lack specificity for a particular disorder. Recently, a CVR pattern particular to chronic fatigue syndrome has been observed. In the present study, we aimed to develop methodologies for assessing disease-specific CVR patterns. As a prototype, a population of 50 consecutive patients with FMF (familial Mediterranean fever) was studied and compared with control populations. A 10 min supine/30 min head-up tilt test with recording of the heart rate and blood pressure or the pulse transit time was performed. Five studies were conducted applying different methods. In each study, statistical analysis identified independent predictors of CVR in FMF. Based on regression coefficients of these predictors, a linear DS (discriminant score) was computed for every subject. Each study established an equation to assess CVR, calculate DS for FMF and determine the sensitivity and specificity of the DS cut-off. In each of the five studies, abnormal CVR was observed in FMF patients. The best accuracy (88% sensitivity and 90.1% specificity for FMF) was obtained by a method based on beat-to-beat heart

rate and pulse transit time recordings. Data was processed by fractal and recurrence quantitative analysis with recordings in FMF patients compared with a mixed control population. Identification of disease-specific CVR patterns was possible with the methodologies described in the present study. In FMF, disease-specific CVR may be explained by the interplay between neuroendocrine loops specific to FMF with cardiovascular homeostatic mechanisms. Recognition of disease-specific CVR patterns may advance the understanding of homeostatic mechanisms and have implications in clinical practice.

DOI: 10.1042/CS20040092

PMID: 15330754 [Indexed for MEDLINE]

4380. Trends Immunol. 2004 Sep;25(9):457-60.

A common pathway in periodic fever syndromes.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease due to mutations in pyrin, which normally inhibits pro-interleukin-1beta (IL-1beta) cytokine processing to the active form. A novel role for pyrin has been proposed by Shoham et al., who studied patients with an autosomal dominant disease called pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome. They demonstrated an interaction between pyrin and proline serine threonine phosphatase-interacting protein 1 (PSTPIP1), the protein involved in PAPA, and thus revealed a biochemical pathway common to both FMF and PAPA.

DOI: 10.1016/j.it.2004.07.007

PMID: 15324736 [Indexed for MEDLINE]

4381. J Intern Med. 2004 Sep;256(3):247-53.

Effect of inflammatory attacks in the classical type hyper-IgD syndrome on immunoglobulin D, cholesterol and parameters of the acute phase response.

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**BACKGROUND:** Classical type hyper-immunoglobulin D (IgD) syndrome (HIDS) is an hereditary auto-inflammatory disorder, characterized by recurrent episodes of fever, lymphadenopathy, abdominal distress and a high serum concentration of IgD. It is caused by mevalonate kinase deficiency.

**OBJECTIVE:** To further characterize the acute phase response during fever attacks in HIDS in order to improve diagnosis.

**SUBJECTS:** Twenty-two mevalonate kinase-deficient HIDS patients.

**METHODS:** Blood samples were drawn during and in between febrile attacks, and concentrations of C-reactive protein (CRP), ferritin, procalcitonin, pentraxin 3, IgD and cholesterol in several lipoprotein fractions were determined.

**RESULTS:** The marked acute phase response at the time of a fever attack in classical type HIDS is reflected by a rise in CRP accompanied by a moderate but statistically significant rise in procalcitonin and pentraxin 3. In only two of 22 patients, procalcitonin concentration rose above 2 ng mL<sup>-1</sup> during fever attack, compatible with the noninfectious nature of these attacks. Ferritin does not reach the high concentrations found in adult-onset Still's disease. Despite the defect in mevalonate kinase, a component of cholesterol metabolism, serum cholesterol did not change during attacks. IgD concentration is elevated regardless of disease activity, although there is appreciable variation during life. Its role in HIDS remains unclear.

**CONCLUSION:** The combination of high CRP concentration plus procalcitonin concentration <2 ng mL<sup>-1</sup> in a symptomatic HIDS patient might indicate a febrile attack without (bacterial) infection; this observation warrants further investigation for its usefulness as a marker in clinical practice.

DOI: 10.1111/j.1365-2796.2004.01359.x

PMID: 15324368 [Indexed for MEDLINE]

[Recurrent bouts of fever accompanied by abdominal pain and emesis].

[Article in German]

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A 34 year-old Turkish patient was admitted to hospital several times with the same symptoms of abdominal pain, fever up to 39.2 degrees C and vomiting. The diagnosis always was an acute attack of chronic pancreatitis. The inflammation scores in the blood were high and he had a moderate increase in pancreatic enzymes. He always got well in a few days on a strict diet and regime of analgesics. Taking these symptoms and his ethnic affiliation into consideration, differential diagnosis should include familial Mediterranean fever (FMF). Therapy with colchicine should be initiated even if genetic testing does not reveal the mutation characteristics for FMF. Immediate and consistent therapy helps to avoid amyloid nephropathy as the most dangerous complication of this disease.

DOI: 10.1007/s00108-004-1270-z

PMID: 15322706 [Indexed for MEDLINE]

4383. Int J Obstet Anesth. 1998 Oct;7(4):271-4.

Anaesthesia for caesarean section in a patient with systemic amyloidosis secondary to familial Mediterranean fever.

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The anaesthetic management of a 33-year-old primigravid woman at 29 + 5 weeks' gestation with familial Mediterranean fever (FMF), secondary amyloidosis, renal allograft with deteriorating renal function and cardiac impairment for emergency

caesarean section is described. Pathophysiology and management options are discussed. Cautious induction of epidural anaesthesia together with continuous invasive monitoring produced a good outcome for mother and baby.

PMID: 15321193

4384. Rheumatology (Oxford). 2004 Nov;43(11):1405-8. Epub 2004 Aug 17.

Treatment of renal amyloidosis with etanercept in tumour necrosis factor receptor-associated periodic syndrome.

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**OBJECTIVE:** To describe the effect of Etanercept treatment in systemic AA amyloidosis in tumour necrosis factor receptor-associated periodic syndrome (TRAPS).

**METHODS:** Etanercept therapy was given to a 27 year old woman, with systemic amyloidosis and nephrotic syndrome, and to her 51 year old father, also affected by TRAPS, who had previously undergone renal transplant for amyloidosis. Serum SAA levels, plasma cytokines, glomerular filtration rate and serum amyloid P scanning were monitored.

**RESULTS:** Etanercept treatment resulted in initial clinical resolution of nephrotic syndrome in the 27 year old female. Both subjects demonstrated improvements in GFR and initial reduction or stabilisation of amyloid deposits on SAP scanning.

**CONCLUSION:** Etanercept may reverse or slow the progression of systemic AA amyloidosis in subjects with C33Y TNFRSF1A mutation. Treatment may however need to be continuous and life-long to prevent progression to end stage disease.

DOI: 10.1093/rheumatology/keh357

PMID: 15316120 [Indexed for MEDLINE]



Mutant forms of tumour necrosis factor receptor I that occur in TNF-receptor-associated periodic syndrome retain signalling functions but show abnormal behaviour.

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Tumour necrosis factor (TNF)-receptor-associated periodic syndrome (TRAPS) is a hereditary autoinflammatory disorder involving autosomal-dominant missense mutations in TNF receptor superfamily 1A (TNFRSF1A) ectodomains. To elucidate the molecular effects of TRAPS-related mutations, we transfected HEK-293 cells to produce lines stably expressing high levels of either wild-type (WT) or single mutant recombinant forms of TNFRSF1A. Mutants with single amino acid substitutions in the first cysteine-rich domain (CRD1) were produced both as full-length receptor proteins and as truncated forms lacking the cytoplasmic signalling domain (deltasig). High-level expression of either WT or mutant full-length TNFRSF1A spontaneously induced apoptosis and interleukin-8 production, indicating that the mutations in CRD1 did not abrogate signalling. Consistent with this, WT and mutant full-length TNFRSF1A formed cytoplasmic aggregates that co-localized with ubiquitin and chaperones, and with the signal transducer TRADD, but not with the inhibitor, silencer of death domain (SODD). Furthermore, as expected, WT and mutant deltasig forms of TNFRSF1A did not induce apoptosis or interleukin-8 production. However, whereas the WT full-length TNFRSF1A was expressed both in the cytoplasm and on the cell surface, the mutant receptors showed strong cytoplasmic expression but reduced cell-surface expression. The WT and mutant deltasig forms of TNFRSF1A were all expressed at the cell surface, but a proportion of the mutant receptors were also retained in the cytoplasm and co-localized with BiP. Furthermore, the mutant forms of surface-expressed deltasig TNFRSF1A were defective in binding TNF-alpha. We conclude that TRAPS-related CRD1 mutants of TNFRSF1A possess signalling properties associated with the cytoplasmic death domain, but other behavioural features of the mutant receptors are abnormal, including intracellular

trafficking and TNF binding.

DOI: 10.1111/j.1365-2567.2004.01942.x

PMCID: PMC1782552

PMID: 15312137 [Indexed for MEDLINE]

4386. Gene. 2004 Aug 18;338(1):25-34.

Structural, expression, and evolutionary analysis of mouse CIAS1.

Anderson JP(1), Mueller JL, Rosengren S, Boyle DL, Schaner P, Cannon SB, Goodyear CS, Hoffman HM.

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Mutations in the human CIAS1 (hCIAS1) gene have been identified in a continuum of inflammatory disorders including familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal onset multisystem inflammatory disease (NOMID). CIAS1 codes for the protein Cryopyrin, which appears to play a role in innate immune function by regulating the production of proinflammatory cytokines. Human and mouse Cryopyrin are highly conserved and consist of three functional domains including a pyrin domain, an NACHT domain, and a leucine-rich repeat (LRR) domain that are characteristics of the NALP family of proteins. The pyrin and NACHT domains of Cryopyrin and other NALP proteins are highly conserved among primate and nonprimate mammals, suggesting purifying selection throughout mammalian evolution. Cryopyrin expression is also very similar in human and mouse with mouse CIAS1 mRNA expression found primarily in peripheral blood leukocytes consistent with the postulated inflammatory function. We also detected significant expression in mouse eye and skin tissue, which is consistent with symptoms observed in human Cryopyrin-associated diseases.

DOI: 10.1016/j.gene.2004.05.002

PMCID: PMC4348074

PMID: 15302403 [Indexed for MEDLINE]

4387. Am J Med. 2004 Aug 1;117(3):208-10.

Beneficial response to interleukin 1 receptor antagonist in traps.

Simon A, Bodar EJ, van der Hilst JC, van der Meer JW, Fiselier TJ, Cuppen MP, Drenth JP.

PMID: 15300976 [Indexed for MEDLINE]

4388. Hum Mutat. 2004 Sep;24(3):194-8.

Infevers: an evolving mutation database for auto-inflammatory syndromes.

Touitou I(1), Lesage S, McDermott M, Cuisset L, Hoffman H, Dode C, Shoham N, Aganna E, Hugot JP, Wise C, Waterham H, Pugnere D, Demaille J, Sarrauste de Menthier C.

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The Infevers database (<http://fmf.igh.cnrs.fr/infevers/>) was established in 2002 to provide investigators with access to a central source of information about all sequence variants associated with periodic fevers: Familial Mediterranean fever (FMF), TNF Receptor Associated Periodic Syndrome (TRAPS), Hyper IgD Syndrome (HIDS), Familial Cold Autoinflammatory Syndrome/Muckle-Wells Syndrome/Chronic Infantile Neurological Cutaneous and Articular Syndrome (FCAS/MWS/CINCA). The prototype of this group of disorders is FMF, a recessive disease characterized by recurrent bouts of unexplained inflammation. FMF is the pivotal member of an expanding family of autoinflammatory disorders, a new term coined to describe illnesses resulting from a defect of the innate immune response. Therefore, we decided to extend the Infevers database to genes connected with autoinflammatory diseases. We present here the biological content of the Infevers database, including the introduction of two new entries: Crohn/Blau and Pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA syndrome). Infevers has a range of query capabilities, allowing for simple or complex interrogation of the database. Currently, the database contains 291 sequence variants in related genes (MEFV,

TNFRSF1A, MVK, CARD15, PSTPIP1, and CIAS1), consisting of published data and personal communications, which has revealed or refined the preferential mutational sites for each gene. This database will continue to evolve in its content and to improve in its presentation.

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DOI: 10.1002/humu.20080

PMID: 15300846 [Indexed for MEDLINE]

4389. Clin Rheumatol. 2004 Aug;23(4):333-7. Epub 2004 May 1.

Continuity of cytokine activation in patients with familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is a recessively inherited inflammatory disorder, characterized by recurrent attacks of fever and polyserositis. It has been considered that miscellaneous cytokines take part in the pathogenesis of the disease. The aim of this study was to investigate serum levels of soluble interleukin-2 receptor (sIL-2R), interleukin-6 (IL-6), and interleukin-10 (IL-10) in patients with FMF. The study included 42 patients with FMF (3 females, 39 males, mean age: 24.43 years) and 20 healthy volunteers as the control group (18 males, 2 females, mean age: 23.2 years). The patients were chosen according to Eliakim criteria. After recording their history and performing an examination, leukocyte counts, erythrocyte sedimentation rates (ESR), C-reactive protein (CRP), fibrinogen, sIL-2R, IL-6, and IL-10 levels were measured before and during attacks. A significant increase was found in leukocyte (  $p<0.001$ ), ESR (  $p<0.001$ ), CRP (  $p<0.001$ ), and fibrinogen (  $p<0.001$ ) levels of the patient group in the attack period compared to those in the quiescent state. sIL-2R (  $p=0.019$ ) and IL-6 (  $p<0.001$ ) levels showed significant increases during attacks compared to the levels before an attack. There was no significant difference between IL-10 levels. The levels of the three cytokines were significantly high both before and

during the attacks compared to the control group. As a result, the elevation of sIL-2R and IL-6 levels both before and during the attacks compared to control group suggests the existence of continuous cytokine activation in the patients. No significant increase in the IL-10 levels in spite of the significant rise of sIL-2R and IL-6 during attacks supports the notion of inflammation and also reveals that compensation by anti-inflammatory IL-10 does not seem to occur.

DOI: 10.1007/s10067-004-0925-4

PMID: 15293095 [Indexed for MEDLINE]

4390. Rheumatol Int. 2005 Aug;25(6):442-6. Epub 2004 Jul 30.

A comparison of clinical findings of familial Mediterranean fever patients with and without amyloidosis.

Cefle A(1), Kamali S, Sayarlioglu M, Inanc M, Ocal L, Aral O, Konice M, Gul A.

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**OBJECTIVE:** This study investigates the clinical and demographic characteristics of familial Mediterranean fever (FMF) patients with and without amyloidosis.

**PATIENTS AND METHODS:** The clinical data of 503 patients with FMF (females:males 250:253) were reviewed. Fifty of these patients had amyloidosis (f:m 23:27).

**RESULTS:** The ages of attack onset in patients with and without amyloidosis were 7.8+/-6.2 and 11.1+/-8.5, respectively ( $P<0.05$ ). The time between disease onset and diagnosis was longer in patients with amyloidosis than those without (187.6+/-99.4 months and 132.5+/-110.2 months, respectively,  $P<0.001$ ). More patients in the amyloidosis group had positive family histories of FMF (68% vs 54%,  $P<0.05$ ). The frequencies of chest pain (78% vs 51%,  $P<0.001$ ), arthritis (80% vs 60%,  $P<0.01$ ), and erysipelas-like erythema (44% vs 16%,  $P<0.001$ ) were higher in the amyloidosis group.

**CONCLUSION:** In the amyloidosis group, FMF-related manifestations of chest pain, arthritis, and erysipelas-like erythema are more frequent. Our results also support that long periods between disease onset and diagnosis are associated with a high risk of developing amyloidosis.

4391. Joint Bone Spine. 2004 Jul;71(4):284-90.

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS): definition, semiology, prognosis, pathogenesis, treatment, and place relative to other periodic joint diseases.

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Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is an autosomal dominant inherited condition of periodic fever and pain. Most patients are of northern European descent. The attacks manifest as fever and pain in the joints, abdomen, muscles, skin, or eyes, with variations across patients. An acute-phase response occurs during the attacks. Patients with TRAPS are at risk for AA amyloidosis, the most common targets being the kidneys and liver. Soluble TNFRSF1A is usually low between the attacks and may be normal during the attacks, when TNF levels are high. TNFRSF1A is found in abnormally high numbers on leukocyte cell membranes. TRAPS is the first condition for which naturally occurring mutations in a TNF receptor were found; the mutations affect the soluble TNFRSF1A gene in the 12p13 region. In some patients, the pathogenesis involves defective TNFRSF1A shedding from cell membranes in response to a given stimulus. Thus, TRAPS is a model for a novel pathogenic concept characterized by failure to shed a cytokine receptor. This review compares TRAPS to other inherited periodic febrile conditions, namely, familial Mediterranean fever, Muckle-Wells syndrome, cold urticaria, and hyper-IgD syndrome. The place of TRAPS relative to other intermittent systemic joint diseases is discussed. Colchicine neither relieves nor prevents the attacks, whereas oral glucocorticoid therapy is effective when used in dosages greater than 20 mg/day. The pathogenic hypothesis involving defective TNFRSF1A shedding suggests that medications targeting TNF may be effective in TRAPS.

4392. Rheumatology (Oxford). 2004 Oct;43(10):1292-9. Epub 2004 Jul 27.

A novel mutation (T61I) in the gene encoding tumour necrosis factor receptor superfamily 1A (TNFRSF1A) in a Japanese patient with tumour necrosis factor receptor-associated periodic syndrome (TRAPS) associated with systemic lupus erythematosus.

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**OBJECTIVE:** To identify potential mutations in the tumour necrosis factor receptor superfamily 1A gene (TNFRSF1A) in a Japanese female patient with recurrent fever complicated by systemic lupus erythematosus (SLE), and in her family members.

**METHODS:** DNA sequencing of exons 1-10 of the TNFRSF1A gene was performed to determine mutations that might be associated with the tumour necrosis factor receptor-associated periodic syndrome (TRAPS). Moreover, the TNFRSF1A gene was examined in Japanese patients with autoimmune diseases, including SLE, rheumatoid arthritis (RA), mixed connective tissue disease (MCTD) and Behçet's disease, and in healthy Japanese controls. Enzyme-amplified sensitivity immunoassay (EASIA) analysis was used to assess serum levels of TNF, the 55-kDa TNF receptor (TNFRSF1A) and the 75-kDa TNF receptor (TNFRSF1B). Membrane TNFRSF1A expression was analysed on the surface of peripheral blood mononuclear cells by flow cytometry.

**RESULTS:** A novel mutation, a heterozygous C to T transition in exon 3 which substitutes an isoleucine for a threonine at position 61 (T61I) was detected in the TNFRSF1A gene derived from the genomic DNA of a Japanese female TRAPS patient. Two nieces and one nephew, all with a similar clinical phenotype, also possessed the same TNFRSF1A mutation. We further demonstrated the same mutation in five of 60 SLE patients (8.3%) and in five of 120 healthy individuals (4.2%), with no significant differences. Although high titres of serum TNF and soluble TNFRSF1B protein were observed in this patient, low titres of soluble TNFRSF1A

protein were detected. However, a defect in TNFRSF1A shedding in vitro was not observed in monocytes derived from this patient.

CONCLUSION: This is the first report of a TRAPS patient associated with SLE with a novel TNFRSF1A mutation (T61I).

DOI: 10.1093/rheumatology/keh320

PMID: 15280569 [Indexed for MEDLINE]

4393. J Med Microbiol. 2004 Aug;53(Pt 8):787-90.

Is there any relationship between *Chlamydomydia pneumoniae* infection and juvenile idiopathic arthritis?

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The role of *Chlamydomydia pneumoniae* in the development and exacerbation of juvenile idiopathic arthritis (JIA) was investigated. Blood samples were taken from 60 JIA patients during an active disease period and for 4 weeks after. Synovial fluid samples were obtained from 20 of the 60 patients. In addition, 22 patients with familial Mediterranean fever (FMF) during the active period and 35 healthy children were included in the study as control groups. Synovial fluid samples were also obtained from three children with FMF. IgG, IgM and IgA levels against *C. pneumoniae* in serum samples were studied by immunofluorescence and IgG antibody and PCR studies were performed for *C. pneumoniae* DNA in synovial fluid samples. Twenty-nine (48.3 %) patients with JIA, 18 (81.8 %) patients with FMF and 22 (62.8 %) healthy children were found to be pre-infected with *C. pneumoniae*. Pre-infection with *C. pneumoniae* among FMF patients was found to be significantly higher than among those with JIA. We did not find a significant difference between JIA patients and healthy children. Chronic *C. pneumoniae* infection was observed only in six JIA patients, one FMF patient and two healthy children. Synovial fluid antibodies were found at higher than 1/512-fold dilution in one JIA patient and four times higher than normal serum in three JIA patients. *C. pneumoniae* DNA was not detected in any synovial fluid sample from FMF or JIA



patients by PCR. In conclusion, *C. pneumoniae* infection does not have a triggering or a progressive effect on the clinical situation in JIA aetiopathogenesis, as a result of a multifactorial aetiology. New, extensive and serial studies (especially PCR studies of synovial tissue) are needed in order to confirm the indirect results.

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DOI: 10.1099/jmm.0.45583-0

PMID: 15272067 [Indexed for MEDLINE]

4394. Rev Med Liege. 2004 May;59(5):320-5.

[Familial Mediterranean fever].

[Article in French]

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Familial Mediterranean Fever (FMF) is an hereditary disease that especially affects people living around the Mediterranean sea. It is characterized by recurring fever and abdominal pain, eventually associated with localised pleuritis, synovitis or skin inflammation. The most serious complication is amyloidosis, which can lead to terminal renal failure. The attacks and complications can be avoided by life long administration of colchicine. Two independent French and American teams discovered the gene responsible for the disease in 1997. It encodes for a protein named pyrin/marenostrin involved in the homeostasis the inflammatory mechanisms. The main mutations have been identified and are henceforth accessible for molecular screening.

PMID: 15264584 [Indexed for MEDLINE]

4395. Acta Med Austriaca. 2004 Feb;31(1):8-12.

Periodic fever syndromes--a clinical overview.

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Most hereditary periodic fever syndromes known today have their onset in the first year of life. Only two, namely Familial Mediterranean Fever (FMF) and TNF-Receptor Associated Periodic Syndrome (TRAPS) occur later, with most patients having become symptomatic by their twentieth birthday. Therefore this review will concentrate on FMF and TRAPS, the latter being a very rare disease, while the former has become somewhat more common in mid-Europe as a result of migration.

PMID: 15259591 [Indexed for MEDLINE]

4396. Clin Chem Lab Med. 2004;42(6):590-4.

Activity of eosinophils and immunoglobulin E concentration in the peritoneal fluid of women with endometriosis.

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Autoinflammatory phenomena, including autoantibody production and atopy, have been regarded as associated with endometriosis. The present study investigates the activity of eosinophils and the distribution of immunoglobulin E concentrations in the peritoneal fluid of women with early endometriosis. The study group consisted of 30 patients with laparoscopically diagnosed early endometriosis. The healthy control group consisted of 18 females with no evident changes in the abdominal cavity and no endometrial foci. Concentrations of immunoglobulin E in serum and peritoneal blood were determined by enzyme

immunoassay. The activity of eosinophils was estimated according to the expression of the early activation molecule CD69 by the flow cytometry method. The concentrations of immunoglobulin E in the peripheral blood and peritoneal fluid were similar in both groups. However, the count of CD69+ eosinophils was higher in the peritoneal fluid of women with endometriosis. The results indicate that activated eosinophils accumulate in the peritoneal fluid in early endometriosis and can play a significant role in the pathogenesis of the disease.

DOI: 10.1515/CCLM.2004.102

PMID: 15259373 [Indexed for MEDLINE]

4397. Neth J Med. 2004 Apr;62(4):119-20, 139.

Two patients with recurrent fever and wine red discolouration of the eyelids.

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PMID: 15255081 [Indexed for MEDLINE]

4398. Eur J Haematol. 2004 Aug;73(2):123-7.

Periodic fever, mild arthralgias, and reversible moderate and severe organ inflammation associated with the V198M mutation in the CIAS1 gene in three German patients--expanding phenotype of CIAS1 related autoinflammatory syndrome.

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Dominant mutations in the CIAS1 gene cause a spectrum of autoinflammatory diseases such as familial cold autoinflammatory syndrome, FCAS, which is characterized by episodes of urticaria, arthralgia, fever and conjunctivitis after generalized exposure to cold. We here describe patients of two German families with the 592G-->A, V198M mutation, which has been described to induce FCAS before. However, in our patients the clinical phenotype was very different from this disease. They never had urticaria, cold induced fever or conjunctivitis; instead the following symptoms occurred: Very regular periodic fever, irregular severe febrile episodes, relatively mild arthralgia, dry cough, cardiomyopathy, nephropathy and euthyroid thyroiditis all being reversible. We conclude that the clinical phenotype associated with mutations in the CIAS1 gene is much broader than assumed before.

DOI: 10.1111/j.1600-0609.2004.00270.x

PMID: 15245511 [Indexed for MEDLINE]

4399. Internist (Berl). 2004 Aug;45(8):904-11.

[Hereditary periodic fever].

[Article in German]

Lamprecht P(1), Timmann C, Ahmadi-Simab K, Gross WL.

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Familial Mediterranean fever (FMF), hyperimmunoglobulinemia D periodic fever syndrome (HIDS), and tumor necrosis factor receptor-associated periodic syndrome (TRAPS) are hereditary periodic fever syndromes. FMF is caused by mutations in the Mediterranean fever gene, HIDS by mutations in the mevalonat-kinase gene, and TRAPS by mutations in the TNF-receptor superfamily 1A gene. Impaired function of the encoded proteins, i.e. pyrin in FMF, mevalonat-kinase in HIDS, and the p55 TNF-receptor in TRAPS, induces a dysregulated cytokine balance. Clinical manifestations are relapsing fever, serositis, arthralgia, myalgia, and miscellaneous forms of rash. The diagnosis is made through molecular genetic analysis of mutations of the MEFV-gene (FMF), MVK-gene (HIDS), or TNFRSF1A-gene

(TRAPS). Colchicine is the therapy of choice in FMF. HIDS is treated symptomatically. Impaired TNF-alpha regulation in TRAPS can be treated with etanercept.

DOI: 10.1007/s00108-004-1254-z

PMID: 15243709 [Indexed for MEDLINE]

4400. Lupus. 2004;13(5):339-43.

Rationale for interleukin-6 blockade in systemic lupus erythematosus.

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Interleukin-6 (IL-6) is a pleiotropic cytokine with a wide range of biological activities that plays an important role in immune regulation and inflammation. Among other actions, it induces terminal differentiation of B lymphocytes into antibody-forming cells and the differentiation of T cells into effector cells. IL-6 also has multiple potent proinflammatory effects. An association between IL-6 and lupus was demonstrated in murine models of SLE and blocking IL-6 improved lupus in all models tested. Data from several studies suggest that IL-6 plays a critical role in the B cell hyperactivity and immunopathology of human SLE, and may have a direct role in mediating tissue damage. Based on these data, we propose that blocking the effect of IL-6 in humans may improve lupus by interacting with the autoinflammatory process both systemically and locally.

DOI: 10.1191/0961203304lu1023oa

PMCID: PMC2014821

PMID: 15230289 [Indexed for MEDLINE]

4401. Scand J Rheumatol. 2004;33(3):133-9.

The genetic background of tumour necrosis factor receptor-associated periodic

syndrome and other systemic autoinflammatory disorders.

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Systemic autoinflammatory disorders are hereditary diseases with symptoms of acute inflammation and a rise in serum acute phase proteins as a consequence, but with no signs of autoimmunity. By the end of the 1990s, four types of hereditary periodic fever had been described in the medical literature: familial Mediterranean fever, hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), tumour necrosis factor receptor-associated periodic fever syndrome (TRAPS) and Muckle-Wells syndrome. Since then, the number of diseases classified as systemic autoinflammatory disorders has increased to eight. In patients of Nordic descent, cases of HIDS and TRAPS have been reported. We provide an overview of the genetic background and main clinical aspects of the different autoinflammatory disorders, with an emphasis on TRAPS.

PMID: 15228182 [Indexed for MEDLINE]

4402. Arthritis Rheum. 2004 Jun;50(6):1951-8.

Molecular analysis of the MVK and TNFRSF1A genes in patients with a clinical presentation typical of the hyperimmunoglobulinemia D with periodic fever syndrome: a low-penetrance TNFRSF1A variant in a heterozygous MVK carrier possibly influences the phenotype of hyperimmunoglobulinemia D with periodic fever syndrome or vice versa.

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**OBJECTIVE:** To describe biochemical findings and the spectrum of mevalonate kinase (MVK) gene mutations as well as an associated TNFRSF1A low-penetrance variant in a series of patients with clinical features of the hyperimmunoglobulinemia D with periodic fever syndrome (HIDS).

**METHODS:** The MVK gene was sequenced in 8 children and 1 adult (including 2 siblings) fulfilling the clinical criteria for HIDS. In addition, sequencing of exons 2, 3, 4, and 6 of the TNFRSF1A gene was performed in patients with only one or no MVK mutation. Mevalonate kinase (MK) enzyme activity in leukocytes and renal excretion of mevalonic acid were also measured.

**RESULTS:** Mutations in the coding region of the MVK gene were detected in 6 patients, and the most common mutation was V377I. Among these patients were 2 novel mutations, both of which were located in exon 6. These novel mutations resulted in the substitution of tryptophan (TGG) by a stop codon (TGA) at amino acid position 188 (W188X) and in the exchange of valine (GTG) for alanine (GCG) at amino acid position 203 (V203A). In 1 patient, a combination of one MVK (V377I) mutation and one TNFRSF1A (R92Q) mutation was present. The patient's clinical phenotype resembled a mixture of variant-type HIDS and tumor necrosis factor receptor-associated periodic syndrome (TRAPS). Her IgD values varied between normal and slightly increased, and the MK activity was in the low-normal range, while urinary mevalonate concentrations were always normal.

**CONCLUSION:** The genotype findings indicate that a relatively small number of genes may be involved in the clinical manifestation of HIDS, with low-penetrance TNFRSF1A variants possibly influencing the HIDS phenotype or MVK mutations contributing to TRAPS.

DOI: 10.1002/art.20264

PMID: 15188372 [Indexed for MEDLINE]

4403. Cir Cir. 2004 Mar-Apr;72(2):135-8.

[Familial Mediterranean fever in Mexico City. A 20-year follow-up].

[Article in Spanish]

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Familial Mediterranean fever (MFF) is an autosomic recessive, inherited inflammatory disease principally seen in persons from the Mediterranean area. Clinical findings include fever, abdominal pain, and pleuritis. The most severe complication of MFF is renal amyloidosis, manifested as nephrotic syndrome, which evolves into chronic renal failure. In this study, we described clinical findings, evolution, and response to treatment in 52 patients diagnosed with MFF living in Mexico City in whom the most important clinical features were fever and abdominal pain. Differing from previous reported series of patients from the Mediterranean area, patient developed renal amyloidosis during the 20-year follow-up, which suggests that an environmental factor might have a significant influence in development of renal amyloidosis.

PMID: 15175132 [Indexed for MEDLINE]

4404. J Rheumatol. 2004 Jun;31(6):1139-42.

Influence of Serum Amyloid A (SAA1) and SAA2 gene polymorphisms on renal amyloidosis, and on SAA/C-reactive protein values in patients with familial mediterranean fever in the Turkish population.

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**OBJECTIVE:** To evaluate the effect of serum amyloid A (SAA) 1 and SAA2 gene polymorphisms on SAA levels and renal amyloidosis in Turkish patients with familial Mediterranean fever (FMF).

**METHODS:** SAA1 and SAA2 gene polymorphisms and SAA levels were determined in 74 patients with FMF (39 female, 35 male; median age 11.5 yrs, range 1.0-23.0). All patients were on colchicine therapy. SAA1 and SAA2 gene polymorphisms were



analyzed using polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP). SAA and C-reactive protein (CRP) values were measured and SAA/CRP values were calculated.

**RESULTS:** The median SAA level was 75 ng/ml (range 10.2-1500). SAA1 gene polymorphisms were: a/a genotype in 23 patients (31.1%), a/beta genotype in 30 patients (40.5%), a/g genotype in one patient (1.4 %), beta/beta genotype in 14 patients (18.9%), beta/g genotype in 5 patients (6.8 %), and g/g genotype in one patient (1.4%). Of the 23 patients who had a/a genotype for the SAA1 polymorphism, 7 patients had developed renal amyloidosis (30.4%) compared to only one patient without this genotype (1/51; 2.0%);  $p < 0.001$ . SAA2 had no effect on renal amyloidosis. SAA1 and SAA2 genotypes had no significant effect on SAA levels. SAA/CRP values were significantly lower in patients with the SAA1a/a genotype, compared to other SAA1 genotypes: 0.16 (0.025-1.96) versus 0.23 (0.012-28.20),  $p < 0.05$ .

**CONCLUSION:** SAA1a/a genotype is one genetic factor that confers a significant risk for amyloidosis in the Turkish FMF population. Neither the SAA1 nor SAA2 genotypes had a significant effect on SAA level.

PMID: 15170927 [Indexed for MEDLINE]

4405. Int J Hematol. 2004 Apr;79(3):235-7.

E148Q/M694I mutation in 3 Japanese patients with familial Mediterranean fever.

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We describe 3 unrelated Japanese patients with familial Mediterranean fever (FMF) due to a compound heterozygous E148Q/M694I mutation in the MEFV gene. The first patient is a 38-year-old man who also has chronic myelogenous leukemia (CML). Because genomic DNA analysis of the patient's nail revealed the E148Q/M694I mutation, we concluded that the individual mutations were obtained congenitally. Interferon alpha therapy was effective against not only the CML but also the FMF.

The second patient is a 42-year-old man with consanguineous parents and a 14-year history of recurrent lower abdominal and back pain associated with fever. He successfully responded to colchicine treatment. The third patient is a 23-year-old woman who has a family history of FMF and since the age of 11 years has had recurrent chest and abdominal pain with fever. The onset of FMF was at an early age in this case, in contrast with the late onset of the disease in the first 2 cases. This patient's mother also has a heterozygous M694I mutation and experienced the same symptoms until 30 years of age. Our data suggest that it should be recognized that there are more FMF patients in Japan than previously expected and that the frequency of the E148Q/M694I mutation may be significant in Japanese FMF patients.

PMID: 15168590 [Indexed for MEDLINE]

4406. Clin Rheumatol. 2004 Jun;23(3):230-4. Epub 2004 Apr 17.

Bone mineral density in children with familial Mediterranean fever.

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The aim of this study was to evaluate bone mineral content (BMC), serum and urinary bone turnover parameters in patients with familial Mediterranean fever (FMF), an autosomal recessive disease characterized by recurrent episodes of inflammation of serous membranes. Demographic characteristics and MEFV mutations were defined in 48 children diagnosed with FMF (23 F, 25 M; median age 7.0 years (3.0-10.0)). We evaluated the blood counts, acute-phase proteins and serum and urinary bone turnover parameters during attack-free periods. The BMC and BA (bone area) of vertebrae L1-L4 were measured by DEXA. Thirty-eight age-, sex- and ethnicity-matched healthy children constituted the control group. Mean L1-L4 BMC in Group I (patients with two mutations) and II (patients with no or single mutations) were 15.49 $\pm$ 5.99 g and 15.68 $\pm$ 4.89 g, respectively, both significantly lower than the mean L1-L4 BMC of control patients, which was

19.59+/-6.7 g ( $p<0.05$ ). Mean L1-L4 BMD in Group I, Group II and the control group were 0.466+/-0.066 g/cm<sup>2</sup>, 0.487+/-0.085 g/cm<sup>2</sup> and 0.513+/-0.079 g/cm<sup>2</sup>, respectively. Mean z-scores in Group I, Group II and the control group were -1.87+/-0.74, -1.55+/-0.92 and -1.39+/-0.84, respectively. Mean L1-L4 BMD and z-score of Group I were lower than in the control group ( $p<0.05$ ). ESR and SAA (serum amyloid A) levels were higher in Group I patients: 28.3+/-14.5 mm/h and 350+/-62 mg/l in Group I; and 20.5+/-11.7 mm/h and 190+/-68 mg/l in Group II, respectively. In conclusion, FMF patients had lower BMC, BMD and z-scores than a control group. We suggest that decreased BMD, BMC and z-score in FMF patients may be secondary to subclinical inflammation.

DOI: 10.1007/s10067-004-0874-y

PMID: 15168151 [Indexed for MEDLINE]

4407. Cell. 2004 May 28;117(5):561-74.

Inflammatory caspases: linking an intracellular innate immune system to autoinflammatory diseases.

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Caspases not only play an essential role during apoptotic cell death, but a subfamily of them-the inflammatory caspases-are associated with immune responses to microbial pathogens. Activation of inflammatory caspases, such as caspase-1 and caspase-5, occurs upon assembly of an intracellular complex, designated the inflammasome. This results in the cleavage and activation of the proinflammatory cytokines IL-1 $\beta$  and IL-18. Mutations in one of the scaffold proteins of the inflammasome, NALP3/Cryopyrin, are associated with autoinflammatory disorders underscoring the importance of regulating inflammatory caspase activation.

DOI: 10.1016/j.cell.2004.05.004

PMID: 15163405 [Indexed for MEDLINE]

4408. Scand J Rheumatol. 2004;33(2):123-5.

An unusual presentation of familial Mediterranean fever with prolonged hip pain and amyloidosis.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent self-limiting attacks of joint, chest and abdominal associated with fever. We present an unusual case of FMF with prolonged arthritis and amyloidosis. Familial Mediterranean fever should be considered in the differential diagnosis of prolonged hip pain, even in the absence of symptoms or signs of FMF.

PMID: 15163115 [Indexed for MEDLINE]

4409. N Z Med J. 2004 May 21;117(1194):U894.

Familial Mediterranean fever: 36 years to diagnosis.

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Comment in

N Z Med J. 2004 Aug 6;117(1199):U1007.

PMID: 15156212 [Indexed for MEDLINE]

4410. Br J Dermatol. 2004 May;150(5):1029-31.

A case of familial cold autoinflammatory syndrome confirmed by the presence of a CIAS1 mutation.

Shpall RL, Jeffes EW, Hoffman HM.

DOI: 10.1111/j.1365-2133.2004.05927.x

PMID: 15149524 [Indexed for MEDLINE]

4411. Hum Mutat. 2004 Jun;23(6):621-8.

An improved electronic microarray-based diagnostic assay for identification of MEFV mutations.

Moutereau S(1), Narwa R, Matheron C, Vongmany N, Simon E, Goossens M.

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Recent technological advances, such as DNA chip devices that allow automated, high-throughput genotyping, promise to considerably improve the detection capability of single-nucleotide polymorphisms (SNPs) in clinically relevant genes. We used the NanoChip(R) Molecular Biology Workstation (Nanogen, [www.nanogen.com](http://www.nanogen.com)) and recently introduced microelectronic array technology to develop a detection method for the more frequent mutations involved in familial Mediterranean fever (FMF), an autosomal recessive disease that affects several ethnic groups in the Mediterranean population, whose early diagnosis is crucial if severe complications are to be prevented. We adapted the previously described Nanogen procedures to FMF mutation analysis, introducing modifications that notably improve the technique. First, as the original procedure makes use of costly dye-tagged reporter sequences, we devised a universal reporter strategy, which was first evaluated and validated on the robust, previously established factor V Leiden and factor II (prothrombin) NanoChip diagnostic assays. FMF (MEFV), factor V (F5), and factor II (F2) genotypes identified using this improved system were totally concordant with results of other genotyping methods (denaturing gradient gel electrophoresis [DGGE], SSCP, and RFLP analysis).

Second, we showed that the target sequences loaded on the NanoChip cartridges can be rehybridized several times in a highly reproducible manner, allowing sequential analysis of mutations. Thus, we devised a strategy that allows us to monitor the possible interference of additional mutations or SNPs at probe or stabilizer sequences. Finally, a comparative cost per sample analysis demonstrates that the accurate and reproducible FMF mutation detection assay we developed can be readily implemented in the clinical laboratory setting at reasonable expense.

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DOI: 10.1002/humu.20045

PMID: 15146467 [Indexed for MEDLINE]

4412. Genet Test. 2004 Spring;8(1):65-8.

Reverse hybridization vs. DNA sequencing in the molecular diagnosis of Familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is an autosomal recessive inflammatory disorder predominantly affecting people living in or originating from areas around the Mediterranean Sea. It is caused by a number of mutations within the MEFV gene, which differently affect the severity of the disease phenotype. Because patients usually present with rather nonspecific clinical symptoms, MEFV genotyping can confirm and refine FMF diagnosis and improve treatment of affected individuals. We have performed a method comparison study on 100 Lebanese FMF patients to evaluate the potential of a rapid reverse-hybridization teststrip-based assay (FMF StripAssay) to serve as a first-line screening test for our population. When results obtained by reverse-hybridization and DNA sequencing of exons 2, 3, 5, and 10 were compared, the FMF StripAssay identified 144/149 mutations, and correctly typed all 12 different MEFV mutations covered. We conclude that reverse-hybridization provides a very rapid, accurate and

easy-to-perform screening method, and, in combination with more comprehensive diagnostic methods, represents an efficient strategy for FMF genotyping.

DOI: 10.1089/109065704323016049

PMID: 15140375 [Indexed for MEDLINE]

4413. *Pediatr Nephrol*. 2004 Jul;19(7):821. Epub 2004 May 4.

High factor VIII levels during attacks of familial Mediterranean fever.

Akar N, Ekím M, Gürman C.

DOI: 10.1007/s00467-004-1499-8

PMID: 15127284 [Indexed for MEDLINE]

4414. *Best Pract Res Clin Rheumatol*. 2003 Dec;17(6):929-44.

Musculoskeletal disorders in secondary amyloidosis and hereditary fevers.

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Amyloidosis remains a severe potential complication of many chronic inflammatory disorders, foremost of rheumatoid arthritis. It is not exactly known why some patients develop a progressive amyloidosis while others do not, although latent deposits may be present. It is likely that more potent anti-inflammatory drugs recently used in rheumatoid arthritis have led to a decrease of amyloid-associated (AA) amyloidosis. However, overt amyloidosis remains a severe complication of some chronic inflammatory disorders and it has a poor prognosis. Hereditary fevers are a group of diseases characterized by intermittent bouts of clinical inflammation with focal organ involvement, mainly abdomen, musculoskeletal system and skin. The most frequent is familial Mediterranean fever which affects patients of Mediterranean descent all over the world. Three other types have been recently characterized clinically as well as genetically. A

thorough diagnosis is warranted, as clinical and therapeutic management is specific for each of these diseases.

DOI: 10.1016/j.berh.2003.09.002

PMID: 15123044 [Indexed for MEDLINE]

4415. Nephron Clin Pract. 2004;96(4):c131-5.

Association of FMF-related (MEFV) point mutations with secondary and FMF amyloidosis.

Atagunduz MP(1), Tuglular S, Kantarci G, Akoglu E, Direskeneli H.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is the major cause of AA amyloidosis in Turkey. M694V mutation in MEFV gene was suggested to be associated with severe clinical features and amyloidosis of FMF.

**METHODS:** In this study, the frequencies of three FMF-related MEFV mutations (M694V, M680I and V726A) were investigated in FMF patients with (AA-FMF, n = 37) and without amyloidosis (non-AA-FMF, n = 35), in patients with secondary amyloidosis related to non-FMF inflammatory conditions (S-AA, n = 19) and in a non-inflammatory control group (n = 185) by molecular genetic studies using polymerase chain reaction with the ARMS (amplification refractory mutation system) method.

**RESULTS:** Both AA and non-AA-FMF patients had significantly higher MEFV mutations compared to non-inflammatory controls (81 and 62.7% respectively vs. 4.2%,  $p = 0.0001$ ). AA-FMF patients carried significantly more MEFV mutations than non-AA-FMF patients ( $p = 0.01$ ). M694V was the most common mutation in both FMF groups (63.5 vs. 51.4%), however allele frequency ( $p = 0.17$ ) and the number of homozygous patients for this mutation did not differ between the groups ( $p = 0.77$ ). Although lower compared to FMF patients, S-AA patients also had a significantly higher incidence of MEFV mutations than non-inflammatory controls (21 vs. 4.2%) ( $p = 0.0002$ ). M694V was the only MEFV mutation in this group.

**CONCLUSION:** MEFV mutations are found to be increased both in FMF and non-FMF associated secondary amyloidosis in our study; however, no clear association



between M694V and amyloidosis is observed, except in the non-FMF group. Our results suggest that MEVF mutations may also serve as a severity marker for other inflammatory conditions.

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DOI: 10.1159/000077375

PMID: 15122067 [Indexed for MEDLINE]

4416. Clin Pharmacol Ther. 2004 May;75(5):476-83.

Simvastatin treatment for inflammatory attacks of the hyperimmunoglobulinemia D and periodic fever syndrome.

Simon A(1), Drewe E, van der Meer JW, Powell RJ, Kelley RI, Stalenhoef AF, Drenth JP.

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Hyperimmunoglobulinemia D (hyper-IgD) and periodic fever syndrome, a hereditary autoinflammatory syndrome, is characterized by lifelong recurrent episodes of fever and inflammation. No effective treatment is known. It is caused by a defect of mevalonate kinase, an enzyme that follows 3'-hydroxy-3'-methylglutaryl-coenzyme A (HMG-CoA) reductase in the isoprenoid pathway. We wanted to test the hypothesis that inhibition of HMG-CoA reductase would ameliorate the inflammatory attacks. Six patients with hyper-IgD syndrome and proven mevalonate kinase deficiency were followed up for 2 treatment periods with either simvastatin, 80 mg/d, or placebo for 24 weeks, separated by a 4-week washout period in a double-blind fashion. Simvastatin resulted in a drop in urinary mevalonic acid concentration in all patients and decreased the number of febrile days in 5 of 6 patients. No side effects were observed. These data offer preliminary evidence for the hypothesis that simvastatin may improve inflammatory attacks in the hyper-IgD syndrome. This highlights the anti-inflammatory properties of HMG-CoA reductase inhibition.

DOI: 10.1016/j.clpt.2004.01.012

PMID: 15116060 [Indexed for MEDLINE]

4417. Arch Dermatol. 2004 Apr;140(4):479-84.

Periodic fever with atypical dyshidrosis--quiz case.

Papadopoulos EJ(1), Jaffe ES, Elgart GW, Raffeld M, Turner ML.

Author information:

(1)National Institutes of Health, Bethesda, MD, USA.

DOI: 10.1001/archderm.140.4.479-a

PMID: 15096381 [Indexed for MEDLINE]

4418. Rev Med Suisse Romande. 2003 Apr;123(4):233-4.

[Genetics facilitates the diagnosis of "complex" diseases: an example].

[Article in French]

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A case of Familial Mediterranean Fever is described. Advances in human genetics have simplified the diagnosis of some "complex" diseases.

PMID: 15088553 [Indexed for MEDLINE]

4419. Arthritis Rheum. 2004 Apr;50(4):1355; author reply 1355-6.

Genetic heterogeneity in familial Mediterranean fever: comment on the article by Cazeneuve et al.

Gul A.

Comment on

Arthritis Rheum. 2003 Aug;48(8):2324-31.

DOI: 10.1002/art.20143

PMID: 15077328 [Indexed for MEDLINE]

4420. Arthritis Rheum. 2004 Apr;50(4):1354-5; author reply 1355-6.

Diagnostic value of MEFV gene analysis in familial Mediterranean fever must still be assessed in non-classically affected populations: comment on the article by Cazeneuve et al.

Touitou I.

Comment on

Arthritis Rheum. 2003 Aug;48(8):2324-31.

DOI: 10.1002/art.20144

PMID: 15077326 [Indexed for MEDLINE]

4421. Int Urol Nephrol. 2003;35(2):207-8.

Development of Peyronie's disease during long-term colchicine treatment.

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Author information:

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Colchicine has been reported to be a safe and effective medication in the treatment of early phase of Peyronie's disease (PD). However here we reported two patients, presenting with PD during high dose colchicine treatment for familial mediterranean fever (FMF).

PMID: 15072497 [Indexed for MEDLINE]

4422. Genes Immun. 2004 Jun;5(4):289-93.

Allelic variants in genes associated with hereditary periodic fever syndromes as susceptibility factors for reactive systemic AA amyloidosis.

Aganna E(1), Hawkins PN, Ozen S, Pettersson T, Bybee A, McKee SA, Lachmann HJ, Karenko L, Ranki A, Bakkaloglu A, Besbas N, Topaloglu R, Hoffman HM, Hitman GA, Woo P, McDermott MF.

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We investigated the hypothesis that low-penetrance mutations in genes (TNFRSF1A, MEFV and NALP3/CIAS1) associated with hereditary periodic fever syndromes (HPFs) might be risk factors for AA amyloidosis among patients with chronic inflammatory disorders, including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), Crohn's disease, undiagnosed recurrent fevers and HPFs themselves. Four of 67 patients with RA plus amyloidosis had MEFV variants compared with none of 34 RA patients without amyloid (P value=0.03). The E148Q variant of MEFV was present in two of the three patients with TNF receptor-associated periodic syndrome (TRAPS) complicated by amyloid in two separate multiplex TRAPS families containing 5 and 16 affected members respectively, and the single patient with Muckle-Wells syndrome who had amyloidosis was homozygous for this variant. The R92Q variant of TNFRSF1A was present in two of 61 JIA patients with amyloidosis, and none of 31 nonamyloidotic JIA patients. No HPF gene mutations were found in 130 healthy control subjects. Although allelic variants in HPFs genes are not major susceptibility factors for AA amyloidosis in chronic inflammatory disease, low-penetrance variants of MEFV and TNFRSF1A may have clinically significant proinflammatory effects.

DOI: 10.1038/sj.gene.6364070

PMID: 15071491 [Indexed for MEDLINE]

4423. *Pediatr Med Chir.* 2003 Jul-Aug;25(4):289-91.

[Familial Mediterranean Fever: a case of dominant transmission with variable penetrance].

[Article in Italian]

Porrello M(1), Ciaccio C, Gallerano P, Gesù M, Forni G, Mancuso A.

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Familial Mediterranean Fever is an autosomal recessive disease occurring in Mediterranean and Middle Eastern populations. It is caused by mutations affecting both alleles of MEFV, a gene that encodes a neutrophil protein called pyrin. We describe a case of dominant transmission with variable penetrance.

PMID: 15070275 [Indexed for MEDLINE]

4424. *Am J Pharmacogenomics.* 2004;4(2):109-18.

Identifying mutations in autoinflammatory diseases: towards novel genetic tests and therapies?

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Autoinflammatory diseases are defined as illnesses caused by primary dysfunction of the innate immune system. This new concept includes a broad number of disorders, but the spotlight has been focused for the past two years on periodic fevers (familial Mediterranean fever [FMF]; mevalonate kinase deficiency [MVK]; tumor necrosis factor [TNF] receptor-associated periodic syndrome [TRAPS]; cryopyrin-associated periodic syndrome [CAPS]), Crohn's disease and Blau

syndrome, thanks to the recent understanding of their molecular basis. Indeed, until recently, these conditions were defined only by phenotypical features, the main ones being recurrent attacks of fever, abdominal pain, arthritis, and cutaneous signs, which sometimes overlap, obscuring diagnosis. The search for distinguishing signs such as periorbital edema in TRAPS, and the use of specific functional tests where available, are valuable. Needless to say, molecular screening of the causative genes has dramatically improved patient quality-of-life by providing early and accurate diagnosis, subsequently allowing for the appropriate treatment. Some patients, however, remain hard to manage despite the advent of new genetic tests, and/or due to the lack of effective treatment. The original clinical link between the aforementioned diseases can now be confirmed by a molecular one, following the exciting discovery that most of the altered proteins are related to the death domain fold (DDF) superfamily involved in inflammation and apoptosis. These molecules mediate the regulation of nuclear factor-kappa B (NF-kappa B) activation, cell apoptosis, and interleukin-1 beta secretion through cross-regulated and, sometimes, common signaling pathways. Knowledge of the defective step in autoinflammation has already led to the elucidation of the mechanisms of action of existing drugs and may allow the development of new therapies.

PMID: 15059033 [Indexed for MEDLINE]

4425. Turk J Gastroenterol. 2003 Dec;14(4):276-9.

Familial Mediterranean fever with massive recurrent ascites: a case report.

Cekin AH(1), Dalbudak N, Künefecı G, Gür G, Boyacıoğlu S.

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A 35-year-old woman had a history of recurrent massive ascites for 12 years. She had been examined to identify the etiology of ascites and was placed on antituberculous and subsequently steroid treatment at another center before admission to our hospital for fever, abdominal distention and abdominal pain. She had massive ascites with serum-ascites albumin gradient of 1.0 g/dl. We could not

find any cause for ascites including tuberculosis. We thus performed exploratory laparotomy of the abdomen. There was no evidence of tuberculosis, peritoneal diseases or of any gynecological reason for ascites. Biopsies taken from the peritoneum revealed fibrinous peritonitis. Since she had a history of attacks of abdominal pain in her childhood, she was screened for mutations causing familial Mediterranean fever and was found to be homozygous for M694V. After definitive diagnosis of familial Mediterranean fever, she was put on colchicine treatment and relief of symptoms and reduction in ascites were seen on follow-up. To our knowledge this is the first documented case of massive ascites due to familial Mediterranean fever.

PMID: 15048606 [Indexed for MEDLINE]

4426. Clin Rheumatol. 2004 Apr;23(2):186-7. Epub 2004 Feb 24.

Helicobacter pylori infection in Turkish children with familial Mediterranean fever: is it a cause of persistent inflammation?

Ozaltin F, Bakkaloglu A, Saltik IN, Demir H, Duzova A, Bulun A, Besbas N, Topaloglu R, Ozen S.

DOI: 10.1007/s10067-003-0839-6

PMID: 15045642 [Indexed for MEDLINE]

4427. Clin Rheumatol. 2004 Apr;23(2):177-8. Epub 2004 Feb 24.

A patient with hyper-IgD syndrome in Antalya, Turkey.

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Hyper-IgD syndrome is a periodic fever syndrome that presents with recurrent episodes of high fever accompanied by lymphadenopathy, abdominal distress,

arthralgias or arthritis, headache and skin lesions. The diagnosis is based on clinical grounds and elevated serum IgD levels (>100 U/ml), but requires a high index of suspicion, and a mevalonate kinase enzyme defect. Most patients are from western Europe but there are others identified in other countries. We describe a 17-year-old patient who had been followed with the diagnosis of familial Mediterranean fever for a long time before she was diagnosed with hyper-IgD syndrome.

DOI: 10.1007/s10067-003-0858-3

PMID: 15045637 [Indexed for MEDLINE]

4428. *Pediatr Int.* 2004 Feb;46(1):81-4.

Familial mediterranean fever medicated with an herbal medicine in Japan.

Komatsu M(1), Takahashi T, Uemura N, Takada G.

Author information:

(1)Department of Pediatrics, Akita University School of Medicine, Akita, Japan.

DOI: 10.1111/j.1328-0867.2004.01831.x

PMID: 15043671 [Indexed for MEDLINE]

4429. *An Med Interna.* 2004 Mar;21(3):143-7.

[Autoinflammatory disorders: a new concept in hereditary periodic fever syndromes].

[Article in Spanish]

Horcada Rubio ML(1), Delgado Beltrán C, Armas Ramírez C.

Author information:

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At last year the great scientific advances in genetics and molecular biology have



led to a bigger knowledge about we nowadays call "Autoinflammatory syndromes", characterized by recurrent inflammatory episodes genetically determined and not mediated by autoimmunity. In this group, they are included the hereditary periodic fever syndromes: familial mediterranean fever (FMF), hyper Ig-D syndrome (HIDS), TNF-receptor-associated periodic syndrome (TRAPS), Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS), CINCA syndrome. The past 6 year have witnessed the identification of genes causing these diseases. Some of these genes encode proteins with a common domain (PYRIN domain). These protein are part of regulatory pathway of inflammation and apoptosis. The purpose of this article, is to carry out review of the genetic, clinical, molecular and rheumatologic aspect of these syndromes, in part unknown. Although they are not common, they are not absent in our diary clinical practise. Their study and research we will be able to obtain new knowledge that lead us to solve the complex inflammatory process.

PMID: 15043497 [Indexed for MEDLINE]

4430. Immunity. 2004 Mar;20(3):319-25.

NALP3 forms an IL-1beta-processing inflammasome with increased activity in Muckle-Wells autoinflammatory disorder.

Agostini L(1), Martinon F, Burns K, McDermott MF, Hawkins PN, Tschopp J.

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Comment in

Immunity. 2004 Mar;20(3):243-4.

Mutations within the NALP3/cryopyrin/CIAS1 gene are responsible for three autoinflammatory disorders: Muckle-Wells syndrome, familial cold autoinflammatory syndrome, and CINCA. The NALP3 protein is homologous to NALP1, which is a component of the inflammasome, a molecular platform that activates the proinflammatory caspases-1 and -5. NALP3 (and other members of the NALP family) lacks the C-terminal, CARD-containing sequence of NALP1, and its role in caspase

activation is unclear. Here, we report that NALP2 and NALP3 associate with ASC, the CARD-containing protein Cardinal, and caspase-1 (but not caspase-5), thereby forming an inflammasome with high proIL-1 $\beta$ -processing activity. Macrophages from Muckle-Wells patients spontaneously secrete active IL-1 $\beta$ . Increased inflammasome activity is therefore likely to be the molecular basis of the symptoms associated with NALP3-dependent autoinflammatory disorders.

PMID: 15030775 [Indexed for MEDLINE]

4431. Br J Dermatol. 2004 Mar;150(3):581-8.

Toxic epidermal necrolysis-like reaction secondary to colchicine overdose.

Arroyo MP(1), Sanders S, Yee H, Schwartz D, Kamino H, Strober BE.

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Colchicine is a microtubule-inhibiting drug used to treat gout, familial Mediterranean fever and many other skin diseases. Intoxication with colchicine affects multiple organs, often fatally. Cutaneous sequelae of colchicine toxicity are rare. We describe the clinical and histological features of a toxic epidermal necrolysis-like exanthem in a patient who lethally overdosed on colchicine.

DOI: 10.1111/j.1365-2133.2004.05838.x

PMID: 15030347 [Indexed for MEDLINE]

4432. Ann Dermatol Venereol. 2004 Feb;131(2):183-6.

[Unusual cutaneous lesions of familial Mediterranean fever].

[Article in French]

Bafounta ML(1), Doumat-Batch F, Vasseur E, Staroz F, Clerici T, Saiag P.

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(1)Service de Dermatologie, CHU Ambroise Paré, UFR Paris-Ouest, Boulogne.

**BACKGROUND:** Familial mediterranean fever belongs to the periodic fever syndromes. During the attacks, fever is associated with abdominal pain, arthralgia, or both. Cutaneous involvement occurs in 7 to 46 p. 100 of cases and mainly consists in erysipelas-like erythema. We report on three patients treated for familial Mediterranean fever who developed unusual cutaneous lesions.

**OBSERVATIONS:** All the patients had long past history of familial mediterranean fever without cutaneous involvement except, for the third patient who had pseudo-erysipela. The first patient had diffuse Sweet's syndrome-like lesions, the second developed long lasting panniculitis of the thigh and the third had a persistent and lichenified erysipela-like plaque. In two patients, skin histology revealed an inflammatory infiltrate with neutrophils. In all cases, an increase in the colchicine dose led to the rapid resolution of the lesions.

**DISCUSSION:** In our 3 case reports, the lesions were particular because of their atypical clinical appearance, their long duration, and they differed from the usual pseudo-erysipela aspect. Histopathologically, the lesions were similar to pseudo-erysipela, which has led some authors to hypothesize that cutaneous lesions of familial mediterranean fever belong to neutrophilic dermatoses. This hypothesis is supported by the response to the increase in colchicine doses.

PMID: 15026746 [Indexed for MEDLINE]

4433. Hum Mutat. 2004 Apr;23(4):399.

The west side story: MEFV haplotype in Spanish FMF patients and controls, and evidence of high LD and a recombination "hot-spot" at the MEFV locus.

Aldea A(1), Calafell F, Aróstegui JI, Lao O, Rius J, Plaza S, Masó M, Vives J, Buades J, Yagüe J.

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Mutations at the MEFV gene cause, with various degrees of penetrance, familial

Mediterranean fever (FMF). This disease is more prevalent in the Middle East than elsewhere, and most studies have focused on those populations. However, FMF occurs also in the Western Mediterranean and these populations should be taken into account for a complete view of FMF. We have analyzed intragenic MEFV SNPs in Spanish and Chueta (descendants of converted Jews) FMF patients and controls, and this constitutes the first systematic survey of normal MEFV SNP haplotype structure and variability. Our findings have allowed us to systematize the nomenclature of MEFV haplotypes and show that there is strong linkage disequilibrium (LD) at the MEFV locus and an intragenic recombination hot spot. The high local LD, regardless the recombination hot spot, is responsible for the limited diversity of the MEFV control haplotypes found in the Spanish population and it suggests that it may be a common feature to all Mediterranean populations. The MEFV mutation spectrum in Spain is quite diverse, and similar to those of France and Italy. On the contrary, the Chueta spectrum was poorer and closer to that of North African Jews, suggesting a direct connection with the Jewish diaspora.

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DOI: 10.1002/humu.9229

PMID: 15024744 [Indexed for MEDLINE]

4434. Rheumatology (Oxford). 2004 Apr;43(4):526-7.

Periodic fever due to a novel TNFRSF1A mutation in a heterozygous Chinese carrier of MEFV E148Q.

Stojanov S, Lohse P, McDermott MF, Renner ED, Kéry A, Mirakian R, Hammond LJ, Aganna E, Hoffmann F, Zellerer S, Belohradsky BH.

DOI: 10.1093/rheumatology/keh066

PMID: 15024140 [Indexed for MEDLINE]

4435. J Biol Chem. 2004 May 21;279(21):21924-8. Epub 2004 Mar 12.

Cryopyrin-induced interleukin 1beta secretion in monocytic cells: enhanced activity of disease-associated mutants and requirement for ASC.

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Several autoinflammatory disorders are associated with missense mutations within the nucleotide-binding oligomerization domain of cryopyrin. The mechanism by which cryopyrin mutations cause inflammatory disease remains elusive. To understand the molecular bases of these diseases, we generated constructs to express three common cryopyrin disease-associated mutations, R260W, D303N, and E637G, and compared their activity with that of the wild-type protein. All cryopyrin mutant proteins tested were found to induce potent NF-kappaB activity when compared with the wild-type protein. This activation was dependent on the expression of ASC, an adaptor protein previously suggested to mediate cryopyrin signaling. When the disease-associated mutants were expressed in monocytic THP-1 cells (which express endogenous ASC), each induced spontaneous IL-1beta secretion, whereas wild-type protein did not. In the absence of stimuli, wild-type cryopyrin was unable to bind to ASC, whereas the three mutants coimmunoprecipitated with ASC, suggesting a mechanism involved in the constitutive activation of mutant proteins. The induction of cryopyrin activity by enforced oligomerization in THP-1 cells resulted in ASC binding and the secretion of IL-1beta, an effect that was abolished by the inhibition of ASC expression with small interfering RNAs. Thus, cryopyrin-mediated IL-1beta secretion requires ASC in monocytic cells. Further, these results indicate that cryopyrin disease-associated mutants are constitutively active and able to induce NF-kappaB activation and IL-1beta secretion at least in part by an increased ability to interact with ASC.

DOI: 10.1074/jbc.M401178200

PMID: 15020601 [Indexed for MEDLINE]

4436. Ann Rheum Dis. 2004 Apr;63(4):438-43.

Non-isotopic RNase cleavage assay for mutation detection in MEFV, the gene responsible for familial Mediterranean fever, in a cohort of Greek patients.

Ritis K(1), Giaglis S, Spathari N, Micheli A, Zonios D, Tzoanopoulos D, Deltas CC, Rafail S, Mean R, Papadopoulos V, Tzioufas AG, Moutsopoulos HM, Kartalis G.

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**BACKGROUND:** The MEFV gene is responsible for familial Mediterranean fever (FMF). Several disease associated mutations have been identified. The range of genetic variation in MEFV in Greek patients has not been determined.

**OBJECTIVE:** To describe a method that facilitates the routine screening of the entire coding sequence of MEFV (excluding exon 1).

**METHODS:** The non-isotopic RNase cleavage assay (NIRCA) was optimised and used as a first step screening method to screen exons 2 to 10 of MEFV. Exons 2 and 10 were analysed separately at DNA level, while exons 3 to 9 were analysed together at cDNA level. The sample group consisted of 26 FMF patients diagnosed using established clinical criteria, six asymptomatic relatives, 12 patients with atypical clinical manifestations, nine patients suffering from various inflammatory diseases, and three normal individuals. All were analysed by NIRCA for mutations in the MEFV gene and direct sequencing was applied subsequently to confirm the results.

**RESULTS:** MEFV mutations were identified in 25 of 26 typical FMF patients and in two of 12 patients with atypical manifestations. NIRCA results were in concordance with sequencing findings in all sequences analysed, suggesting that the method is highly reliable in this disease. Sixteen alterations of MEFV were identified (eight missense mutations and eight single nucleotide polymorphisms).

**CONCLUSIONS:** NIRCA can be used for rapid screening of the coding sequence of the MEFV gene in patients suspected of suffering from FMF.

PMCID: PMC1754936

PMID: 15020340 [Indexed for MEDLINE]

4437. BMC Med Genet. 2004 Feb 10;5:4.

Amyloidosis in familial Mediterranean fever patients: correlation with MEFV genotype and SAA1 and MICA polymorphisms effects.

Medlej-Hashim M(1), Delague V, Chouery E, Salem N, Rawashdeh M, Lefranc G, Loiselet J, Mégarbané A.

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**BACKGROUND:** Familial mediterranean fever (FMF) is a recessively inherited disease characterized by recurrent crises of fever, abdominal, articular and/or thoracic pain. The most severe complication is the development of renal amyloidosis. Over 35 mutations have been discovered so far in the gene responsible for the disease, MEFV. This article aims at determining a correlation between the MEFV genotype and the occurrence of amyloidosis in FMF patients, in addition to the study of the modifying effects of the SAA1 (type 1 serum amyloid A protein) and MICA (Major Histocompatibility Complex (MHC) class-I-chain-related gene A) genes on this severe complication.

**METHODS:** Fourteen MEFV mutations were screened and the SAA1 and MICA polymorphisms tested in 30 FMF patients with amyloidosis and 40 FMF patients without amyloidosis.

**RESULTS:** The M694V and V726A allelic frequencies were, respectively, significantly higher and lower in the group with amyloidosis, compared to the control FMF group. The beta and gamma SAA1 alleles were more frequently encountered in the group without amyloidosis, whereas the alpha allele was significantly more observed in FMF patients with amyloidosis ( $p < 0.025$ ). All the MICA alleles were encountered in both patients' groups, but none of them was significantly associated with amyloidosis.

**CONCLUSIONS:** The results suggest a protective effect of the SAA1 beta and gamma alleles on the development of amyloidosis and show the absence of a MICA modifying effect on amyloidosis development. Testing these polymorphisms on a larger sample will lead to more definite conclusions.

DOI: 10.1186/1471-2350-5-4

PMCID: PMC356915

PMID: 15018633 [Indexed for MEDLINE]

4438. *Pediatr Nephrol.* 2004 May;19(5):539-43. Epub 2004 Mar 11.

Variable expression of vasculitis in siblings with familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent and self-limited attacks of serosal inflammation with abdominal pain, chest pain, and arthritis usually accompanied by fever. Different vasculitides such as polyarteritis nodosa (PAN) and Henoch-Schönlein syndrome (HSS) may be associated with FMF. We report two sisters of a Turkish family with FMF who developed distinct vasculitides. The younger sister developed severe PAN with perirenal hematoma at the age of 13 years, the older sister presented with severe HSS and acute renal failure at the age of 19 years. Neither sister developed amyloidosis until the age of 30 years. This observation suggests that early events in the pathogenesis of PAN and HSS are generally quite similar.

DOI: 10.1007/s00467-004-1440-1

PMID: 15015067 [Indexed for MEDLINE]

4439. J Investig Med. 2004 Jan;52(1):58-61. doi: 10.1136/jim-52-01-28.

Neutrophil adhesion molecule expression in familial Mediterranean fever: discordance between the intravascular regulation of beta2 integrin and L-selectin expression in acute attack.

Molad Y(1), Fridenberg A, Bloch K, Langevitz P, Mukamel M, Sulkes J, Pras M, Livneh A.

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**BACKGROUND:** To determine the surface expression of neutrophil beta2 integrin (CD11b/CD18) and L-selectin (LS) adhesion molecules in patients with familial Mediterranean fever (FMF) and to investigate the in vitro regulation of their expression in response to chemoattractant stimuli.



**METHODS:** Neutrophil surface expression of CD11b and LS molecules was analyzed by flow cytometry in anticoagulated whole blood drawn from FMF patients and normal controls, and the in vitro regulation of these molecules induced by the chemoattractant N-formyl-methionyl-leucyl-phenylalanine (FMLP) was assayed.

**RESULTS:** Patients during acute FMF attacks showed a statistically significant increased neutrophil surface CD11b compared with normal controls (mean fluorescence intensity: 22.8 +/- 13.7 vs 12.8 +/- 10.41, respectively; p = .03). There was no difference in LS expression between the groups. Neutrophils of FMF patients regulate CD11b and LS expression induced by chemoattractant (FMLP) stimulation to a degree similar to that in controls.

**CONCLUSIONS:** beta2 Integrin is up-regulated during an acute attack of FMF in dissociation with LS expression, suggesting a unique nonchemoattractant-mediated neutrophil activation.

DOI: 10.1136/jim-52-01-28

PMID: 14989371 [Indexed for MEDLINE]

4440. Isr Med Assoc J. 2004 Feb;6(2):103-6.

New pieces in the puzzle of autoinflammatory disorders.

Tweezer-Zaks N(1), Langevitz P, Livneh A.

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PMID: 14986469 [Indexed for MEDLINE]

4441. J Med Genet. 2004 Mar;41(3):e24.

Subcellular localisation of marenostriin/pyrin isoforms carrying the most common mutations involved in familial Mediterranean fever in the presence or absence of its binding partner ASC.

Cazeneuve C, Papin S, J  ru I, Duquesnoy P, Amselem S.

PMCID: PMC1735693

PMID: 14985395 [Indexed for MEDLINE]

4442. Rheumatology (Oxford). 2004 Apr;43(4):410-5. Epub 2004 Feb 24.

Clinical and genetic aspects of the hereditary periodic fever syndromes.

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Hereditary periodic fever syndromes are a group of diseases characterized by intermittent bouts of clinical inflammation with focal organ involvement, mainly of the abdomen, musculoskeletal system and skin. The most frequent is familial Mediterranean fever, which affects patients of Mediterranean descent all over the world. Three other types have recently been characterized clinically and genetically. A thorough diagnosis is warranted, as clinical and therapeutic management is specific for each of these diseases. The underlying mechanisms of these inflammatory diseases appear to be specific for each type, involving so far unknown proteins, and have already opened new avenues in our understanding of the inflammatory response.

DOI: 10.1093/rheumatology/keh157

PMID: 14983109 [Indexed for MEDLINE]

4443. Semin Arthritis Rheum. 2004 Feb;33(4):273-82.

Colchicine nonresponsiveness in familial Mediterranean fever: clinical, genetic, pharmacokinetic, and socioeconomic characterization.

Lidar M(1), Scherrmann JM, Shinar Y, Chetrit A, Niel E, Gershoni-Baruch R,

Langevitz P, Livneh A.

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**OBJECTIVES:** To identify the ethnic, clinical, genetic, and pharmacokinetic correlates of colchicine treatment failure in patients with familial Mediterranean fever (FMF).

**METHODS:** Fifty-nine FMF patients, unresponsive to a daily dose of  $> \text{or } = 2 \text{ mg}$  colchicine, were compared with 51 colchicine-responsive patients by clinical, demographic, and socioeconomic assessment, FMF gene (Mediterranean Fever [MEFV]) mutation and serum amyloid A1 (SAA1) gene polymorphism analysis, and plasma and white blood cell colchicine level determination.

**RESULTS:** Colchicine responders and nonresponders were comparable with respect to gender, age, duration and onset of the disease, and various demographic parameters. The 2 cohorts were found to carry mainly the M694V MEFV mutation and had a similar number of homozygotes or compound heterozygotes. Predominance of the alpha/beta alleles of SAA1 and comparable plasma and polymorphonuclear colchicine concentrations characterized both groups. Nonresponders were from lower socioeconomic backgrounds, had less education, and a more severe form of disease. A statistically significant 2-fold elevation of colchicine concentration in the mononuclear cells (MNC) of responders was found.

**CONCLUSIONS:** Colchicine treatment failure in FMF is associated with inadequate colchicine MNC concentration, probably resulting from a genetic defect unrelated to the underlying FMF.

PMID: 14978665 [Indexed for MEDLINE]

4444. QJM. 2004 Mar;97(3):141-51.

Patterns of cardiovascular reactivity in disease diagnosis.

Naschitz JE(1), Rosner I, Rozenbaum M, Fields M, Isseroff H, Babich JP, Zuckerman E, Elias N, Yeshurun D, Naschitz S, Sabo E.

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**BACKGROUND:** Aberrations of cardiovascular reactivity (CVR), an expression of autonomic function, occur in a number of clinical conditions, but lack specificity for a particular disorder. Recently, a CVR pattern particular to chronic fatigue syndrome was observed.

**AIM:** To assess whether specific CVR patterns can be described for other clinical conditions.

**METHODS:** Six groups of patients, matched for age and gender, were evaluated with a shortened head-up tilt test: patients with chronic fatigue syndrome (CFS) (n = 20), non-CFS fatigue (F) (n = 15), neurally-mediated syncope (SY) (n = 21), familial Mediterranean fever (FMF) (n = 17), psoriatic arthritis (PSOR) (n = 19) and healthy subjects (H) (n = 20). A 10-min supine phase was followed by recording 600 cardiac cycles on tilt (5-10 min). Beat-to-beat heart rate (HR) and pulse transit time (PTT) were measured. Results were analysed using conventional statistics, recurrence plot analysis and fractal analysis.

**RESULTS:** Multivariate analysis evaluated independent predictors of the CVR in each patient group vs. all other groups. Based on these predictors, equations were determined for a linear discriminant score (DS) for each group. The best sensitivities and specificities of the DS, consistent with disease-related phenotypes of CVR, were noted in the following groups: CFS, 90.0% and 60%; SY, 93.3% and 62.5%; FMF, 90.1% and 75.4%, respectively.

**DISCUSSION:** Pathological disturbances may alter cardiovascular reactivity. Our data support the existence of disease-related CVR phenotypes, with implications for pathogenesis and differential diagnosis.

PMID: 14976271 [Indexed for MEDLINE]

4445. *Pediatr Nephrol.* 2004 May;19(5):536-8. Epub 2004 Feb 12.

Polyarteritis nodosa in a case of familial Mediterranean fever.

Bakkaloğlu SA(1), Muzaç S, Akpek S, Söylemezoğlu O, Buyan N, Hasanoğlu E.

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We describe a 7-year-old boy with familial Mediterranean fever (FMF) complicated by polyarteritis nodosa (PAN) with distinct angiographic findings. On admission, he had abdominal pain, arthralgia, and severe fibromyalgia. During hospitalization, he displayed maculopapular eruptions, high blood pressure, gastrointestinal bleeding, and persistent constitutional symptoms mimicking a vasculitic process, most probably PAN. Renal angiography showed a perfusion defect compatible with a renal infarction secondary to a vasculitic process. He responded well to pulse methylprednisolone therapy with colchicine. We emphasize the rare association of FMF and PAN and the non-aneurysmal angiographic signs of PAN.

DOI: 10.1007/s00467-003-1390-z

PMID: 14963762 [Indexed for MEDLINE]

4446. Arthritis Rheum. 2004 Feb;50(2):607-12.

Spectrum of clinical features in Muckle-Wells syndrome and response to anakinra.

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Comment in

Arthritis Rheum. 2004 Feb;50(2):345-9.

Arthritis Rheum. 2005 Jul;52(7):2226-7.

Arthritis Rheum. 2004 Nov;50(11):3738-9; author reply 3739-40.

OBJECTIVE: Mutations in the NALP3/CIAS1/PYPAF1 gene are associated with the autoinflammatory diseases Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS), and neonatal-onset multisystem inflammatory disease (NOMID), which is also known as chronic infantile neurologic, cutaneous, articular (CINCA) syndrome. Molecular studies suggest that NALP3 is involved in the processing of interleukin-1beta (IL-1beta), prompting us to investigate

whether IL-1 blockade may be therapeutic in patients with MWS.

**METHODS:** We reviewed the clinical features of 3 members of a family, all of whom had MWS associated with the NALP3 variant V200M (also designated V198M), and evaluated the response of their inflammatory disease to treatment with the recombinant human IL-1 receptor antagonist anakinra. The subjects kept a diary of symptoms and underwent fortnightly clinical and laboratory assessments, including measurement of the serum amyloid A protein concentration.

**RESULTS:** Each subject had fever, rashes, arthralgia, conjunctivitis, sensorineural deafness, and an intense acute-phase response characteristic of MWS. However, additional features were identified, including exacerbation of their disease by cold and neurologic manifestations, that have hitherto been described only in FCAS and NOMID, respectively. Clinical and serologic evidence of active inflammatory disease resolved rapidly and completely during treatment with anakinra.

**CONCLUSION:** The remarkable response of MWS to anakinra suggests that IL-1 $\beta$  has a fundamental role in the pathogenesis of inflammation associated with mutations in the NALP3 gene, and supports study of IL-1 inhibition in patients with NOMID/CINCA syndrome or FCAS. The clinical features of the various syndromes associated with mutations in the NALP3 gene may overlap to a greater extent than has previously been recognized.

DOI: 10.1002/art.20033

PMID: 14872505 [Indexed for MEDLINE]

4447. Arthritis Rheum. 2004 Feb;50(2):345-9.

Genomic-based therapy: targeting interleukin-1 for autoinflammatory diseases.

Hoffman HM, Patel DD.

Comment in

Arthritis Rheum. 2004 Nov;50(11):3738-9; author reply 3739-40.

Comment on

Arthritis Rheum. 2004 Feb;50(2):607-12.

DOI: 10.1002/art.20032

PMID: 14872474 [Indexed for MEDLINE]

4448. Eur J Hum Genet. 2004 Mar;12(3):255.

FMF revisited.

Manna R, La Regina M, Nucera G, Gasbarrini G, Touitou I.

Comment on

Eur J Hum Genet. 2004 Feb;12(2):85-6.

DOI: 10.1038/sj.ejhg.5201170

PMID: 14872202 [Indexed for MEDLINE]

4449. Kidney Int. 2004 Mar;65(3):1118-27.

Renal amyloidosis in familial Mediterranean fever.

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DOI: 10.1111/j.1523-1755.2004.00485.x

PMID: 14871446 [Indexed for MEDLINE]

4450. Curr Opin Allergy Clin Immunol. 2002 Dec;2(6):511-6.

The autoinflammatory syndromes.

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**PURPOSE OF REVIEW:** To review the remarkable recent progress in our understanding of a range of inflammatory conditions in humans that until recently appeared unrelated. The term autoinflammatory disease has been proposed to describe a group of disorders characterized by attacks of seemingly unprovoked inflammation without significant levels of autoantibodies and autoreactive T cells.

**RECENT FINDINGS:** As the link between the innate immune response and disease susceptibility has become more apparent, some remarkable associations have emerged. The majority of hereditary periodic fevers are due to mutations in the pyrin and tumour necrosis factor receptor superfamilies of molecules, both of which are intimately involved in innate immunity. Pyrin/marenostrin protein is mutated in familial Mediterranean fever, while mutations in a related protein, cryopyrin, are associated with Muckle-Wells/familial cold urticaria and chronic infantile neurologic cutaneous and articular syndrome. Both of these proteins interact with the apoptotic speck-like protein involved in caspase-1 activation and regulation of nuclear factor kappa B transcription; furthermore cryopyrin contains regions of homology with the nucleotide-binding oligomerization domain 2 protein, which is associated with susceptibility to Crohn's disease. Variants in the leucine-rich repeat domain of nucleotide-binding oligomerization domain are found in approximately 20% of patients with Crohn's disease, depending on ethnic background, while mutations in the NACHT domain are associated with a rare dominant granulomatous disease called Blau syndrome.

**SUMMARY:** The study of autoinflammatory disease has progressed from genetics to definition of the functional defects in these patients. Although a direct association between defective innate immune responses to bacterial components and these diseases has not been formally established, much ongoing research is aimed towards confirmation of that hypothesis.

DOI: 10.1097/01.all.0000044536.45448.2d

PMID: 14752334 [Indexed for MEDLINE]

4451. Apoptosis. 2004 Jan;9(1):5-18.

TMS1/ASC: the cancer connection.

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TMS1/ASC is a bipartite protein comprising two protein-protein interaction domains, a pyrin domain (PYD) and a caspase recruitment domain (CARD). Proteins containing these domains play pivotal roles in regulating apoptosis and immune response pathways, and mutations in a number of PYD- and CARD-containing proteins have been linked to autoinflammatory diseases and cancer. Indeed, one of the ways in which TMS1/ASC was identified was as a target of methylation-mediated silencing in breast cancer cells. This review discusses the mounting evidence supporting a correlation between the silencing of TMS1/ASC expression and cancer. In addition, it addresses the reported functions of TMS1/ASC that include apoptosis, activation of inflammatory caspases and regulation of NF-kappa B, and discusses the potential ways in which loss of TMS1/ASC contributes to carcinogenesis.

DOI: 10.1023/B:APPT.0000012117.32430.0c

PMID: 14739594 [Indexed for MEDLINE]

4452. Ann Trop Paediatr. 2003 Dec;23(4):259-63.

Pyrexia of unknown origin in children: a review of 102 patients from Turkey.

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Pyrexia of unknown origin (PUO) has not been appropriately investigated in Turkish children and therefore a study was undertaken to determine the causes of PUO and to evaluate which clinical procedures are useful in establishing a diagnosis. A total of 102 children fitting the classical PUO criteria seen in our clinic between 1995 and 2002 were investigated retrospectively. Infections, collagen vascular disorders, malignancy and miscellaneous conditions constituted 44.2%, 6.8%, 11.7% and 24.5% of cases, respectively, while 12.8% of the cases remained undiagnosed. Enteric fever, brucellosis and respiratory tract infections were the most commonly encountered infections, whereas familial Mediterranean

fever was the commonest non-infectious disorder. Biopsy, aspiration, serology, bacteriology, radiology and observation of the clinical course were the most useful diagnostic procedures.

DOI: 10.1179/027249303225007833

PMID: 14738573 [Indexed for MEDLINE]

4453. Clin Exp Rheumatol. 2003 Jul-Aug;21(4 Suppl 30):S53-4; author reply S54.

Familial Mediterranean fever: is low mortality from tuberculosis a specific advantage for MEFV mutations carriers? Mortality from tuberculosis among Muslims, Jewish, French, Italian and Maltese patients in Tunis (Tunisia) in the first half of the 20th century.

Cattan D.

Erratum in

Clin Exp Rheumatol. 2003 Nov-Dec;21(6):802.

Comment on

Clin Exp Rheumatol. 2002 Jul-Aug;20(4 Suppl 26):S57-8.

PMID: 14727462 [Indexed for MEDLINE]

4454. Clin Exp Rheumatol. 2003 Jul-Aug;21(4 Suppl 30):S49-52.

Familial Mediterranean fever in 2003. Pathogenesis and management.

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PMID: 14727461 [Indexed for MEDLINE]

4455. Clin Exp Rheumatol. 2003 Jul-Aug;21(4 Suppl 30):S41-3.

Benign cystic mesothelioma: a rare cause of ascites in a case with familial Mediterranean fever.

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Benign cystic mesothelioma (BCM) is a rare neoplasm of the peritoneum, consisting of solitary or multiple cysts arising from mesothelial cells. Here we report a patient with a previous diagnosis of familial Mediterranean fever (FMF) presenting with abdominal distension and ascites which were found to be due to BCM. The co-existence of these two entities has not been reported previously. Ascites as the presenting feature of BMC is also a rare observation.

PMID: 14727459 [Indexed for MEDLINE]

4456. Clin Exp Rheumatol. 2003 Jul-Aug;21(4 Suppl 30):S38-40.

Colchicine-induced leukopenia in a patient with familial Mediterranean fever: the cause and a possible approach.

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A young patient with familial Mediterranean fever (FMF) developed leukopenia each time she took colchicine. However, when she discontinued the drug the white cell and the platelets counts increased but she experienced FMF attacks. Later it was found that the patient also had concomitant cytomegalovirus (CMV) infection. This

complex situation posed several diagnostic and therapeutic issues concerning the real cause for the leukopenia and the possible approach to take in such conditions. We propose that when an essential drug (such as colchicine for FMF) causes leukopenia, one should look for concurrent CMV or another viral infection. If there is no such infection, it is suggested that the mechanism leading to leukopenia be clarified. In the case of bone marrow suppression, colchicine should be continued with injections of G-CSF, whereas if the bone marrow is hypercellular it is suggested to use steroids and colchicine concomitantly.

PMID: 14727458 [Indexed for MEDLINE]

4457. Clin Exp Rheumatol. 2003 Jul-Aug;21(4 Suppl 30):S35-7.

MEFV mutations are increased in Behçet's disease (BD) and are associated with vascular involvement.

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**OBJECTIVE:** A high prevalence of Behçet's disease (BD) among familial Mediterranean fever (FMF) patients has been described recently and a weak association of BD and certain MEFV gene mutations, originally linked to FMF, has been reported in an ethnically mixed population from France. We further investigated the presence of MEFV mutations in BD patients from Turkey, a country with a high prevalence of both disorders.

**METHODS:** The frequencies of three FMF-related MEFV mutations (M694V, M680I and V726A) were investigated in BD patients (n = 57) by molecular genetic studies using a polymerase chain reaction with the ARMS method. All patients fulfilled the International Study Group Criteria for the diagnosis of BD and patients with FMF-like symptoms or a chronic inflammatory disease were excluded.

**RESULTS:** Fifteen BD patients were found to carry one single MEFV mutation (26%), compared to 9.1% in the control group (p = 0.003, OR: 3.5, 95% CI: 1.6-7.6).

Among 20 BD patients with vascular involvement, 11 (55%) had MEFV mutations compared to 4 patients (11%) in the non-vascular group (p = 0.001, OR: 10, 95%

CI: 2.5-39.3). M694V was the dominant mutation in our study group (11 out of 15 patients with mutated alleles). Six out of 7 female patients with vascular involvement carried MEFV mutations in contrast to 5 out of 13 male patients (85.7% versus 38.4%,  $p = 0.07$ , OR: 0.1, 95% CI: 0.009-1.14). No association with other clinical manifestations was observed.

CONCLUSION: MEFV mutations, originally linked to FMF, may act as a genetic susceptibility factor for other inflammatory disorders such as vascular BD.

PMID: 14727457 [Indexed for MEDLINE]

4458. Rheumatol Int. 2005 May;25(4):255-9. Epub 2004 Jan 15.

MEFV mutations in familial Mediterranean fever: association of M694V homozygosity with arthritis.

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OBJECTIVE: Familial Mediterranean fever (FMF) is an autosomal recessive recurrent polyserositis with a higher prevalence in some ethnic groups, including Turks. Mutations in the FMF gene (MEFV) were found associated with FMF. The aim of this study was to analyze MEFV gene mutations in FMF patients to gain insight into the mutation phenotype correlation.

OBJECTIVES: We analyzed the most frequent mutations (M680I, M694V, V726A, and E148Q) in a group of young male Turkish FMF patients using an amplification refractory mutation system and a commercial kit.

RESULTS: M694V mutation was detected in 80% of the patients. After making a strict diagnostic discrimination between arthralgia and arthritis, arthritis was present in 71% of homozygous and 29.4% of heterozygous patients for M694V mutation. Other mutations were not found to correlate with specific symptoms or findings.

CONCLUSION: The homozygosity of M694V mutation in the MEFV gene is associated with arthritis in FMF patients.

4459. Ann Rheum Dis. 2004 Feb;63(2):187-90.

Decreased prevalence of atopy in paediatric patients with familial Mediterranean fever.

Sackesen C(1), Bakkaloglu A, Sekerel BE, Ozaltin F, Besbas N, Yilmaz E, Adalioglu G, Ozen S.

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**BACKGROUND:** A number of inflammatory diseases, including familial Mediterranean fever (FMF), have been shown to be driven by a strongly dominated Th1 response, whereas the pathogenesis of atopic diseases is associated with a Th2 response.

**OBJECTIVE:** Because dominance of interferon gamma has the potential of inhibiting Th2 type responses-that is, development of allergic disorders, to investigate whether FMF, or mutations of the MEFV gene, have an effect on allergic diseases and atopy that are associated with an increased Th2 activity.

**METHOD:** Sixty children with FMF were questioned about allergic diseases such as asthma, allergic rhinitis, and atopic dermatitis, as were first degree relatives, using the ISAAC Study phase II questionnaire. The ISAAC Study phase II was performed in a similar ethnic group recruited from central Anatolia among 3041 children. The same skin prick test panel used for the ISAAC Study was used to investigate the presence of atopy in patients with FMF and included common allergens.

**RESULTS:** The prevalences of doctor diagnosed asthma, allergic rhinitis, and eczema were 3.3, 1.7, and 3.3%, respectively, in children with FMF, whereas the corresponding prevalences in the ISAAC study were 6.9, 8.2, and 2.2%, respectively. Only the prevalence of allergic rhinitis was significantly different between the two groups ( $p < 0.001$ ). The prevalence of atopy in these patients with FMF (4/60 (7%)) was significantly lower than in the children of the population based study (20.6%) ( $p < 0.001$ ).

**CONCLUSION:** Family Mediterranean fever seems to be protective against development of atopic sensitisation and allergic rhinitis.

PMCID: PMC1754884

PMID: 14722209 [Indexed for MEDLINE]

4460. Isr Med Assoc J. 2003 Oct;5(10):746-7.

Infantile familial Mediterranean fever.

Brik R(1), Shinawi M, Gershoni-Baruch R.

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Comment on

Isr Med Assoc J. 2003 Oct;5(10):739-40.

PMID: 14719476 [Indexed for MEDLINE]

4461. Isr Med Assoc J. 2003 Oct;5(10):739-40.

Periodic fever in infants: familial Mediterranean fever only?

Ben-Chetrit E.

Comment in

Isr Med Assoc J. 2003 Oct;5(10):746-7.

PMID: 14719474 [Indexed for MEDLINE]

4462. J Rheumatol. 2003 Dec;30(12):2620-3.

Intravenous colchicine for treatment of patients with familial Mediterranean fever unresponsive to oral colchicine.

Lidar M(1), Kedem R, Langevitz P, Pras M, Livneh A.

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**OBJECTIVE:** To evaluate the efficacy and safety of weekly intravenous (IV) colchicine, in addition to oral colchicine therapy, in a subset of patients with familial Mediterranean fever (FMF) unresponsive to oral colchicine prophylaxis.

**METHODS:** Thirteen patients with frequent FMF attacks, despite oral doses of 2-3 mg/day colchicine, were treated with weekly IV injections of 1 mg colchicine for 12 weeks in an open-label pilot study. Patients were evaluated periodically for the number and severity of their attacks, use of analgesics, and erythrocyte sedimentation rate (ESR).

**RESULTS:** A 50% reduction in attack frequency and attack severity in at least one site was achieved by 10 and 6 of the 13 study patients, respectively ( $p < 0.001$  and  $p < 0.01$ ). Mean number of abdominal attacks declined significantly from  $4.2 \pm 3.0$  per patient at baseline to  $1.9 \pm 2.6$  attacks at the end of the third month of the study ( $p = 0.0002$ ). The mean severity of abdominal attacks declined from a baseline of  $6.1 \pm 0.95$  to  $3.9 \pm 2.8$  after 3 months ( $p = 0.02$ ). Comparable significant change was observed in chest attacks, ESR, and number of analgesic tablets used. Joint attacks were unrelieved during the study period. The treatment was safe and well tolerated, without side effects.

**CONCLUSION:** Treatment with weekly IV colchicine injections in addition to oral colchicine therapy is effective and safe in patients with FMF refractory to oral colchicine.

PMID: 14719203 [Indexed for MEDLINE]

4463. Rheumatol Int. 2005 Jan;25(1):60-4. Epub 2004 Jan 8.

A case of familial Mediterranean fever and polyarteritis nodosa complicated by spontaneous perirenal and subcapsular hepatic hemorrhage requiring multiple arterial embolizations.



Akar S(1), Goktay Y, Akinci B, Tekis D, Biberoglu K, Birlik M, Onen F, Tunca M, Akkoc N.

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The association of familial Mediterranean fever (FMF) and polyarteritis nodosa (PAN) has been well established. These patients have been reported to have an overall better prognosis than other PAN patients. Herein we report a patient with FMF and PAN who died of sepsis following a severe course of recurrent bleeding episodes which required multiple embolization attempts. The 39-year-old Turkish male presented with abdominal pain of 1-month duration. He had been diagnosed with FMF at the age of 24. On admission, he had pallor with general ill appearance. Rebound tenderness was obtained in the right upper abdominal quadrant. He had mild anemia, leukocytosis, thrombocytosis, and hypoalbuminemia. On the 2nd day of his admission, he developed hypotension with a rapid decline in hemoglobin level. Abdominal angiography showed multiple aneurysms in the branches of renal arteries, superior mesenteric artery, and hepatic arterial system including left renal infarct, suggesting PAN. He was put on high-dose steroids and oral cyclophosphamide. Despite medical treatment, he developed intense abdominal pain, hypotension, tachycardia, and a rapid fall in hemoglobin on four occasions. Active bleeding sites were embolized in two different angiography sessions. Although the patient experienced no more recurrent bleeding, he died of multiorgan dysfunction syndrome resulting from sepsis 6 weeks after admission. Polyarteritis nodosa associated with FMF may follow a grave course despite immunosuppressive therapy. Arterial embolization should be considered in the presence of bleeding aneurysms in addition to immunosuppressive therapy.

DOI: 10.1007/s00296-003-0424-y

PMID: 14712330 [Indexed for MEDLINE]

4464. Turk J Pediatr. 2003 Jul-Sep;45(3):198-202.

Analysis of the modifying effects of SAA1, SAA2 and TNF-alpha gene polymorphisms on development of amyloidosis in FMF patients.

Yilmaz E(1), Balci B, Kutlay S, Ozen S, Ertürk S, Oner A, Beşbaş N, Bakkaloğlu A.

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The aim of this study was to examine whether polymorphisms at serum amyloid A (SAA) and tumor necrosis factor-alpha (TNF-alpha) genes are associated with development of amyloidosis in familial Mediterranean fever (FMF) patients. Seventy-three FMF patients with amyloidosis and 100 other FMF patients without amyloidosis of known genotypes and 100 healthy control subjects were analyzed. There was a significant difference in the frequency of alpha/alpha genotype at the SAA1 locus between FMF patients with amyloidosis and controls and FMF patients without amyloidosis. The frequencies of the alpha/alpha genotype and alpha alleles at SAA1 locus were significantly higher in the FMF patients with amyloidosis. The frequencies of the alpha allele at SAA1 locus in FMF patients with amyloidosis, without amyloidosis and controls were 85.6%, 49.5% and 42.5%, respectively. We demonstrated that alpha/alpha genotype at SAA1 gene might have modifying effects on the development of amyloidosis. Determination of genotypes at SAA1 locus can play a key role in conferring genetic susceptibility and patient's prognosis to renal amyloidosis.

PMID: 14696796 [Indexed for MEDLINE]

4465. Am J Gastroenterol. 2003 Dec;98(12):2594-604.

Abdominal and digestive system associations of familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is a hereditary episodic febrile syndrome that is expressed by acute spells of fever, painful manifestations in the abdomen, chest and joints, and slow development of nephropathic amyloidosis. Despite the

recent cloning of the FMF gene (MEFV) and the identification of about 40 disease-related mutations, the diagnosis is still clinically dependent, and the pathogenesis and most of the clinical heterogeneity remain to be explained. Because episodic abdominal pain affects 95% of FMF patients, most of them are seen by gastroenterologists and undergo complete or partial abdominal imaging before the diagnosis is made. Focusing on recent advances in FMF, this article reviews both common and infrequent manifestations that a gastroenterologist may encounter during workups of FMF patients. These include episodic abdominal pain, paralytic or mechanical ileus, constipation, diarrhea, ascites, malabsorption, bowel infarction, and bleeding, arising directly from FMF or secondary to FMF common associations such as amyloidosis, vasculitides, inflammatory bowel disease, irritable bowel syndrome, or colchicine side effects. This article will help the gastroenterologist to cope with most clinical situations related to the abdominal and alimentary tract in patients with FMF.

DOI: 10.1111/j.1572-0241.2003.08784.x

PMID: 14687803 [Indexed for MEDLINE]

4466. Am J Med Genet A. 2004 Jan 1;124A(1):67-73.

A severe autosomal-dominant periodic inflammatory disorder with renal AA amyloidosis and colchicine resistance associated to the MEFV H478Y variant in a Spanish kindred: an unusual familial Mediterranean fever phenotype or another MEFV-associated periodic inflammatory disorder?

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Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurring short attacks of fever and serositis. Secondary AA amyloidosis is the worst complication of the disease and often determines the prognosis. The MEFV gene, on chromosome 16p13.3, is responsible for the disease and around 30 mutations have been reported to date. Colchicine is the standard FMF treatment today, and prevents both attacks and amyloid deposition in 95% of patients. Here we describe a three-generation Spanish kindred with five family

members affected by a severe periodic inflammatory disorder associated with renal AA amyloidosis and colchicine unresponsiveness. Clinical diagnosis of definite FMF disease was made based on the Tel-Hashomer criteria set. Genetic analyses revealed that all subjects were heterozygous for the new H478Y MEFV variant, segregating with the disease. In addition, mutations in the TNFRSF1A and CIAS1/PYPAF1/NALP3 genes, related to the dominantly inherited autoinflammatory periodic syndromes, were ruled out. However, the dominant inheritance of the disease, the long fever episodes with a predominant joint involvement, and the resistance to colchicine in these patients raise the question of whether the periodic syndrome seen in this kindred is a true FMF disease with unusual manifestations or rather another MEFV-associated periodic syndrome. We conclude that the new H478Y MEFV mutation is the dominant pathological variant causing the inflammatory periodic syndrome in this kindred and that full-length analyses of the MEFV gene are needed to obtain an adequate diagnosis of patients with clinical suspicion of a hereditary periodic fever syndrome, especially those from non-ancestral populations.

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DOI: 10.1002/ajmg.a.20296

PMID: 14679589 [Indexed for MEDLINE]

4467. Eur J Hum Genet. 2004 Feb;12(2):85-6.

Familial Mediterranean fever seems to be not uncommon in Greece.

Konstantopoulos K, Kanta A.

Comment in

Eur J Hum Genet. 2004 Mar;12(3):255.

Comment on

Eur J Hum Genet. 2003 Jan;11(1):50-6.

DOI: 10.1038/sj.ejhg.5201096

PMID: 14673474 [Indexed for MEDLINE]

4468. J Urol. 2004 Jan;171(1):391-4; discussion 394.

Acute epididymitis in boys: evidence of a post-infectious etiology.

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**PURPOSE:** We studied the etiology and management of pediatric epididymitis.

**MATERIAL AND METHODS:** We performed 1-year prospective study in children with epididymitis. All patients underwent an immediate sonographic study of the scrotum. Microbiological studies included throat and urine cultures as well as viral cultures of nasopharyngeal and stool specimens. Serological tests for group A streptococcus and *Mycoplasma pneumoniae* as well as for enteroviruses, adenoviruses, influenza and parainfluenza viruses in the appropriate seasons were performed in patients and controls.

**RESULTS:** A total of 44 patients 2 to 14 years old (mean age 9.8 +/- 3.2) were studied. Hospital admissions peaked during the summer and winter. The incidence of epididymitis was around 1.2/1,000 boys yearly. One patient had familial Mediterranean fever and another had Henoch-Schonlein purpura. Microbiological studies of the urine, throat, nasopharynx and stool yielded bacterial/viral growth in 9 patients (20.4%). Serological studies revealed significantly elevated titers to certain pathogens in patients with epididymitis compared with controls, including *M. pneumoniae* (53% vs 20%), enteroviruses (62.5% vs 10%) and adenoviruses (20% vs 0%). Most patients were treated with analgesics and 3 patients received antibiotics intravenously. Systemic and local signs and symptoms resolved gradually in 1 to 7 days.

**CONCLUSIONS:** Our results suggest that epididymitis in boys is not rare and it is mostly an inflammatory phenomenon (presumably post-infectious) with a benign course. The treatment of these patients is basically with analgesics with a little role for antibiotics.

DOI: 10.1097/01.ju.0000102160.55494.1f

PMID: 14665940 [Indexed for MEDLINE]

4469. J Immunol. 2003 Dec 15;171(12):6329-33.

Cutting edge: CIAS1/cryopyrin/PYPAF1/NALP3/CATERPILLER 1.1 is an inducible inflammatory mediator with NF-kappa B suppressive properties.

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Mutations in the cold-induced autoinflammatory syndrome 1 (CIAS1) gene have been recently linked to three chronic autoinflammatory disorders. These observations point to an important role for CIAS1 in regulating inflammatory processes. We report that TNF-alpha and ligands recognized by multiple Toll-like receptors rapidly induce CIAS1 gene expression in primary human monocytes. Transfection of full-length CIAS1 or either of two shorter, naturally occurring isoforms dramatically inhibited TNF-alpha-induced activation of NF-kappaB reporter activity. Furthermore, CIAS1 suppressed TNF-alpha-induced nuclear translocation of endogenous p65. Transcriptional activity of exogenous NF-kappaB p65 was also blocked by CIAS1. The nucleotide-binding and leucine-rich repeat regions, but not the pyrin domain of CIAS1, are responsible for this inhibition. These data suggest CIAS1/cryopyrin may act as a key regulator of inflammation, induced to dampen NF-kappaB-dependent proinflammatory signals.

PMID: 14662828 [Indexed for MEDLINE]

4470. Rev Med Interne. 2003 Dec;24(12):781-5.

[Tumor necrosis factor receptor superfamily 1A-associated periodic syndrome (TRAPS)].

[Article in French]

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**PURPOSE:** Tumor necrosis factor receptor superfamily 1A associated periodic syndrome (TRAPS) belongs to the group of hereditary fever syndromes, also called hereditary auto-inflammatory syndromes.

**CURRENT KNOWLEDGE AND KEY POINTS:** The diagnosis of TRAPS should be evoked in presence of the following clinical signs, whatever the population of the affected patients. TRAPS acute inflammatory access, of 1 to 3 weeks' duration, is characterised by the presence of fever, abdominal pain, myalgias, various types of skin rash including erysepela-like erythema. Long term inflammatory response can lead to AA amyloidosis. Genetic testing will confirm the diagnosis when showing a mutation in the extracellular part of the TNFRSF1A receptor.

Therapeutic management of TRAPS is not definitely established. Daily colchicine does not seem to prevent efficiently inflammatory attacks. Corticosteroids, in contrast can attenuate the intensity and diminish the duration of attacks.

**FUTURE PROSPECTS AND PROJECTS:** The value of biological agents that inhibits TNF action is not yet completely determined in TRAPS. Mechanisms of the disease are not yet elucidated. In some families with specific mutations, a relative soluble TNF receptor deficiency has been found in the plasma. However this mechanism does not account for what is observed in other kindreds.

PMID: 14656637 [Indexed for MEDLINE]

4471. J Emerg Med. 2003 Nov;25(4):383-5.

PFAPA syndrome mimicking familial Mediterranean fever: report of a Turkish child.

Ataş B(1), Caksen H, Arslan S, Tuncer O, Kirimi E, Odabaş D.

Author information:

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The PFAPA (Periodic Fever, Aphthous stomatitis, Pharyngitis, Adenitidis) syndrome is characterized by periodic fever, adenitis, pharyngitis, and aphthous stomatitis. Herein, we present a Turkish child with PFAPA syndrome mimicking familial Mediterranean fever because of a rare presentation. A 9-year-old boy was admitted with recurrent fever, aphthous stomatitis, sore throat, headache, and

general body pains, lasting 2 to 3 days since 3.5 years of age. He was completely symptom-free between the attacks. He was diagnosed as having familial Mediterranean fever according to the clinical findings when he was 6 years of age and Colchicum tablet was administered. Despite colchicine therapy for 8 months, his attacks did not subside; therefore, the drug was discontinued. He had high fever, a painful cervical lymphadenopathy, aphthous stomatitis, and tonsillo-pharyngitis. The patient was then diagnosed as having PFAPA syndrome. He was given a single dose of prednisolone (0.35 mg/kg/dose). His complaints dramatically and completely disappeared 3 h after administration of the drug. During the 8th month of follow-up, a similar febrile attack lasting only 1 day was noted and it was controlled with a single dose of prednisolone (0.5 mg/kg/day). At this writing the patient is in the 12th month of follow-up, and there have been no symptoms after the second attack. In conclusion, our patient shows that PFAPA syndrome can be confused with familial Mediterranean fever. We also would like to emphasize that the typical PFAPA syndrome can be easily diagnosed by detailed history-taking and physical findings.

PMID: 14654177 [Indexed for MEDLINE]

4472. Blood Cells Mol Dis. 2003 Nov-Dec;31(3):320-3.

Familial Mediterranean fever with amyloidosis associated with novel exon 2 mutation (S1791) of the MEFV gene.

Timmann C(1), Mersinli O, Kuhne K, Sievertsen J, Griebel MA, Dieckerhoff J, Horstmann RD.

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Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent attacks of fever, serositis, and a risk for AA amyloidosis. FMF is caused by mutations in the Mediterranean fever gene (MEFV), which is expressed in blood cells of the myelomonocytic differentiation pathway. We identified a novel mutation S1791 in exon 2 of MEFV in two members of a family of Turkish origin. In both cases, S1791 was in compound heterozygosity with MEFV



mutation M694V, and the characteristic clinical syndrome of FMF including amyloidosis was found. The location of S1791 in exon 2 is of interest because (1) amyloidosis in FMF has previously been found to be strongly associated with compound exon 10 mutations and (2) it supports the notion that the mechanism causing FMF is connected to the cytoplasmic rather than nuclear function of the molecule.

PMID: 14636645 [Indexed for MEDLINE]

4473. Hautarzt. 2003 Dec;54(12):1208-10.

[Recurring episodes of fever with oral aphthae, lymph node swelling and joint symptoms in a 9-year-old boy. Diagnosis: PFAPA syndrome (Marshall syndrome)].

[Article in German]

Schnopp C(1), Mempel M, Brockow K, Ring J, Abeck D.

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DOI: 10.1007/s00105-003-0632-0

PMID: 14634753 [Indexed for MEDLINE]

4474. Ann Pharmacother. 2003 Dec;37(12):1821-4.

Colchicine-induced myopathy in a teenager with familial Mediterranean fever.

Sayarlioglu M(1), Sayarlioglu H, Ozen S, Erkoc R, Gul A.

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OBJECTIVE: To report a case of colchicine-induced myopathy in a teenager with

familial Mediterranean fever (FMF).

**CASE SUMMARY:** A 15-year-old boy of Turkish origin, diagnosed as having FMF at the age of 14 years, was treated with colchicine 1.5 mg/d. He had experienced only 2 mild peritonitis attacks with fever within 1 year. The patient used the recommended dose regularly, and he described progressive proximal muscle weakness and generalized myalgias, which started 1 month before presentation. Physical examination showed proximal muscle weakness in his arms and legs. Laboratory tests revealed elevated serum creatine kinase, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase. All other laboratory values were within normal range. Electromyographic investigation revealed a myopathic pattern in proximal muscles without any neuropathic changes. A biopsy of the deltoid muscle showed vacuolar degeneration of striated muscle fibers with no inflammatory findings.

**DISCUSSION:** Colchicine, the most important drug in treatment of FMF, can cause myopathy in patients with impaired renal and hepatic function. In our patient, an objective causality scale showed that therapeutic doses of colchicine for FMF were the definite cause of myopathy, even though his renal and hepatic function were normal. The treatment of FMF attacks in patients who cannot use colchicine is an important problem. There are insufficient data about the use of immunosuppressive agents in the treatment of FMF attacks; however, we now successfully control the attacks with colchicine 0.5 mg/d and azathioprine 2 mg/kg/d.

**CONCLUSIONS:** Colchicine-induced myopathy should be excluded in patients with FMF who present with generalized muscle weakness. Clinicians should be aware that myopathy can occur in patients with FMF who have normal renal and hepatic function.

DOI: 10.1345/aph.1D188

PMID: 14632592 [Indexed for MEDLINE]

4475. Blood. 2004 Apr 1;103(7):2809-15. Epub 2003 Nov 20.

Molecular basis of the spectral expression of CIAS1 mutations associated with phagocytic cell-mediated autoinflammatory disorders CINCA/NOMID, MWS, and FCU.

Neven B(1), Callebaut I, Prieur AM, Feldmann J, Bodemer C, Lepore L, Derfalvi B, Benjaponpitak S, Vesely R, Sauvain MJ, Oertle S, Allen R, Morgan G, Borkhardt A, Hill C, Gardner-Medwin J, Fischer A, de Saint Basile G.

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NALP proteins are recently identified members of the CATERPILLER (CARD, transcription enhancer, R(purine)-binding, pyrin, lots of LRR) family of proteins, thought to function in apoptotic and inflammatory signaling pathways. Mutations in the CIAS1 gene, which encodes a member of the NALP (NACHT-, LRR-, and PYD-containing proteins) family, the cryopyrin/NALP3/PYPAF1 protein, expressed primarily in phagocytic cells, were recently found to be associated with a spectrum of autoinflammatory disorders. These include chronic infantile neurologic cutaneous and articular (CINCA) syndrome (also known as neonatal-onset multisystem inflammatory disease [NOMID]), Muckle-Wells syndrome (MWS), and familial cold urticaria (FCU). We describe herein 7 new mutations in 13 unrelated patients with CINCA syndrome and identify mutational hotspots in CIAS1 on the basis of all mutations described to date. We also provide evidence of genotype/phenotype correlations. A 3-dimensional model of the nucleotide-binding domain (NBD) of cryopyrin suggested that this molecule is structurally and functionally similar to members of the AAA+ protein family of ATPases. According to this model, most of the mutations known to affect residues of the NBD are clustered on one side of this domain in a region predicted to participate in intermolecular contacts, suggesting that this model is likely to be biologically relevant and that defects in nucleotide binding, nucleotide hydrolysis, or protein oligomerization may lead to the functional dysregulation of cryopyrin in the MWS, FCU, and CINCA/NOMID disorders.

DOI: 10.1182/blood-2003-07-2531

PMID: 14630794 [Indexed for MEDLINE]

4476. Bioinformatics. 2003 Nov 22;19(17):2171-5.

Disease-associated variants in PYPAF1 and NOD2 result in similar alterations of conserved sequence.

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Sequence variations in the gene products PYPAF1/CIAS1 and NOD2/CARD15 have been associated with several autoinflammatory diseases that, although clinically different, share a similar inflammatory pathophysiology. A multiple sequence alignment of homologous proteins demonstrates that some of the missense variants are located in highly conserved regions of the NTPase domain and possibly impair NTP-hydrolysis. Intriguingly, one of the variations, which is found identically in PYPAF1 and NOD2, is located at the same alignment position. Our findings suggest that evolutionary gene duplication can give rise to disease families because variants affect conserved sequence in a similar fashion.

PMID: 14630645 [Indexed for MEDLINE]

4477. J Paediatr Child Health. 2003 Nov;39(8):627-8.

Recurrent episodes of fever with tonsillitis, mouth ulcers and adenopathy.

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PMID: 14629532 [Indexed for MEDLINE]

4478. Nitric Oxide. 2003 Sep;9(2):103-10.

Plasma nitric oxide level in familial Mediterranean fever and its modulations by Immuno-Guard.

Panossian A(1), Hambartsumyan M, Panosyan L, Abrahamyan H, Mamikonyan G, Gabrielyan E, Amaryan G, Astvatsatryan V, Wikman G.

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Familial Mediterranean fever (FMF) is a recessively inherited inflammatory disorder, characterised by recurrent attacks of fever and serositis. Since nitric oxide (NO) is an important mediator of inflammation, the production of NO (assessed as the accumulation of nitrate and nitrite and measured by capillary electrophoresis) in blood plasma of FMF patients during acute attacks (active) and attack-free periods (inactive) of the disease has been determined and compared with NO levels found in healthy volunteers (control group C). Thirty-six FMF patients were involved in a placebo-controlled double-blind study (group A received the drug, group B the placebo) of the effects of Immuno-Guard, a novel herbal preparation which relieves the severity and longevity of FMF attacks on NO blood levels. Thirty-two FMF patients (group D) being permanently treated with colchicine were also examined with respect to their NO blood level. No significant differences were found between the NO levels in blood of inactive FMF patients and those of control group C, or between inactive colchicine-treated group D patients and inactive patients of groups A and B, a finding which is atypical for chronic inflammatory disorders. Significantly lower plasma NO levels were found in active FMF patients in groups A and B compared with inactive patients in those groups ( $p=0.031$  and  $0.036$ , respectively) and with patients of group D and the control group C ( $p=0.0235$  and  $0.0453$ , respectively). The decrease of NO in blood of FMF patients may trigger the generation of fever by initiating the production of pro-inflammatory IL-6. Plasma NO levels in inactive FMF patients were significantly increased during attack-free periods following treatment with Immuno-Guard. The preparation has a normalising effect both on NO and IL-6 blood levels in FMF patients during attacks, demonstrating a relationship between the beneficial effect of Immuno-Guard in reducing the severity of inflammatory attacks in FMF patients and the increase in NO blood levels.

PMID: 14623176 [Indexed for MEDLINE]

4479. FEBS Lett. 2003 Nov 20;554(3):520-8.

Structural localization of disease-associated sequence variations in the NACHT and LRR domains of PYPAF1 and NOD2.

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Several autoinflammatory diseases with distinct clinical manifestations have been associated with sequence variations in the gene products PYPAF1/CIAS1 and NOD2/CARD15. Both proteins belong to the PYD/CARD-containing family of apoptosis regulators and activators of pro-inflammatory caspases. To gain insight into the dysfunctional role of sequence alterations, we assembled a structure-based multiple sequence alignment of family members and related proteins. This allowed us to analyze the putative effect of the alterations on the function of nucleotide-binding (NACHT) and leucine-rich repeat (LRR) domains shared by the family members. In support of this analysis, we carefully selected template structures for the NACHT and LRR domains and mapped the genetic variations onto 3D domain models. Additionally, we propose a model of the NACHT and LRR domain complex. Our study revealed that many of the disease-associated sequence variants are located close to highly conserved sequence regions of functional relevance and are spatially adjacent in the predicted 3D structure. The implications on the domain functions such as NTP-hydrolysis or oligomerization are discussed.

PMID: 14623123 [Indexed for MEDLINE]

4480. Ann Ital Med Int. 2003 Jul-Sep;18(3):136-48.

[Familial Mediterranean fever: an ancient hereditary disease].

[Article in Italian]

Nucera G(1), La Regina M, Diaco M, Neri G, Gasbarrini G, Manna R.

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Erratum in

Ann Ital Med Int. 2003 Jul;11(7):550.

Familial Mediterranean fever (FMF) is an autosomal recessive disorder that mainly affects people living around the Mediterranean sea (i.e. Turks, Armenians, Arabs and Jews), but cases of FMF are now being increasingly diagnosed in every country of the world (including Italy). Described for the first time in 1945, it has recently become more relevant, after the discovery of the responsible gene, the MEFV gene which encodes a 781-aminoacid protein called pyrin that seems to play a role in the regulation of the inflammatory process. As the prototype of an emerging group of disorders fated to become more and more popular--the hereditary auto-inflammatory disorders--FMF is an under-diagnosed cause of fever of unknown origin. Fever is the main but not the only symptom; sterile serosites are the most common associated features. The classical clinical picture is being continuously enriched. Geno-phenotype correlations and interval-free symptoms are the new clinical insights, while fundamentally important studies attempt to enlighten its obscure pathogenesis. In spite of the introduction of alternative treatments, colchicine is still the only suitable drug for the prevention of acute episodes and the development of amyloidosis.

PMID: 14621424 [Indexed for MEDLINE]

4481. J Pediatr. 2003 Nov;143(5):658-61.

Prevalence and significance of mutations in the familial Mediterranean fever gene in Henoch-Schönlein purpura.

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**OBJECTIVES:** Based on the fact that Henoch-Schönlein purpura (HSP) occurs in approximately 5% of persons with familial Mediterranean fever (FMF), we assessed the prevalence and significance of FMF gene mutations in children with one or more episodes of HSP.

**STUDY DESIGN:** Thirty-four boys and 18 girls treated for HSP at Rambam Medical Center were interviewed and asked to donate blood. Mean age at disease onset was 6.7+/-2.4 years, and mean follow-up was 3.8+/-1.3 years. Six predominant mutations (M694V, M680I, M694I, V726A, K695R, E148Q) in the MEFV gene were studied.

**RESULTS:** Nine heterozygotes, three homozygotes and two compound heterozygotes, were identified. Altogether, five persons (10%) carried two mutated MEFV alleles, a number significantly exceeding that determined for the general Israeli population (1%-2%). Of these, three displayed genotypes associated with a mild form of disease (M694V/E148Q and V726A/V726A), and two had genotypes normally observed in disease-free persons (E148Q/K695R and E148Q/E148Q).

**CONCLUSIONS:** Occult FMF cases much more numerous than expected were identified among children presenting with HSP. Such children should be closely monitored for renal complications, and treatment with colchicine should be considered.

DOI: 10.1067/S0022-3476(03)00502-X

PMID: 14615741 [Indexed for MEDLINE]

4482. Arthritis Rheum. 2003 Nov;48(11):3298-9; author reply 3299-300.

Long-term followup needed to define role of infliximab in treatment of renal amyloidosis: comment on the case report by Elkayam et al.

Tweezer-Zaks N, Langevitz P, Livneh A.

Comment on

Arthritis Rheum. 2002 Oct;46(10):2571-3.

DOI: 10.1002/art.11316

PMID: 14613300 [Indexed for MEDLINE]

4483. Transplant Proc. 2003 Nov;35(7):2639-40.

Early detection of amyloidosis in renal allografts: electron microscopic, histochemical, immunohistochemical findings and relationship with graft survival.

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PMID: 14612050 [Indexed for MEDLINE]

4484. Eur J Pediatr. 2004 Jan;163(1):30-2. Epub 2003 Nov 11.

Tumour necrosis factor receptor-associated periodic syndrome with a novel mutation in the TNFRSF1A gene in a Japanese family.

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Tumour necrosis factor receptor-associated periodic syndrome (TRAPS) is a dominantly inherited disorder characterised by recurrent episodes of sustained fever. Here we report a case of TRAPS with a novel TNFRSF1A mutation, C70S, in a Japanese family. The mutation disrupts one of the three disulphide bonds in cysteine-rich domain 2 of TNF receptor 1, similar to the reported mutations of the same cysteine residue (C70R, C70Y). This is the first confirmed case of TRAPS in an eastern Asian population. The patient's asymptomatic sister as well as their mother with mild symptoms had the same mutation. CONCLUSION: Although tumour necrosis factor receptor-associated periodic syndrome has been reported mainly in families of northern European ancestry, our case suggests the need to include it in the differential diagnosis of patients with recurrent fever even in ethnic groups in which no case has been documented.

DOI: 10.1007/s00431-003-1338-0

PMID: 14610673 [Indexed for MEDLINE]

4485. N Engl J Med. 2003 Nov 6;349(19):1872-3; author reply 1872-3.

Molecular mechanisms of amyloidosis.

van der Hilst JC, Simon A, Drenth JP.

Comment on

N Engl J Med. 2003 Aug 7;349(6):583-96.

PMID: 14606469 [Indexed for MEDLINE]

4486. N Engl J Med. 2003 Nov 6;349(19):1872-3; author reply 1872-3.

Molecular mechanisms of amyloidosis.

Sungur CI.

Comment on

N Engl J Med. 2003 Aug 7;349(6):583-96.

DOI: 10.1056/NEJM200311063491920

PMID: 14602890 [Indexed for MEDLINE]

4487. Proc Natl Acad Sci U S A. 2003 Nov 11;100(23):13501-6. Epub 2003 Oct 31.

Pyrin binds the PSTPIP1/CD2BP1 protein, defining familial Mediterranean fever and PAPA syndrome as disorders in the same pathway.

Shoham NG(1), Centola M, Mansfield E, Hull KM, Wood G, Wise CA, Kastner DL.

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Pyrin, the familial Mediterranean fever protein, is found in association with the cytoskeleton in myeloid/monocytic cells and modulates IL-1beta processing,

NF-kappaB activation, and apoptosis. These effects are mediated in part through cognate interactions with the adaptor protein ASC, which shares an N-terminal motif with pyrin. We sought additional upstream regulators of inflammation by using pyrin as the bait in yeast two-hybrid assays. We now show that proline serine threonine phosphatase-interacting protein [PSTPIP1, or CD2-binding protein 1 (CD2BP1)], a tyrosine-phosphorylated protein involved in cytoskeletal organization, also interacts with pyrin. Recently, PSTPIP1/CD2BP1 mutations were shown to cause the syndrome of pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA), a dominantly inherited autoinflammatory disorder mediated predominantly by granulocytes. Endogenous PSTPIP1/CD2BP1 and pyrin are coexpressed in monocytes and granulocytes and can be coimmunoprecipitated from THP-1 cells. The B box segment of pyrin was necessary and the B box/coiled-coil segment sufficient for this interaction, whereas the SH3 and coiled-coil domains of PSTPIP1/CD2BP1 were both necessary, but neither was sufficient, for pyrin binding. The Y344F PSTPIP1/CD2BP1 mutation, which blocks tyrosine phosphorylation, was associated with a marked reduction in pyrin binding in pervanadate-treated cells. PAPA-associated A230T and E250Q PSTPIP1/CD2BP1 mutations markedly increased pyrin binding as assayed by immunoprecipitation and, relative to WT, these mutants were hyperphosphorylated when coexpressed with c-Abl kinase. Consistent with the hypothesis that these mutations exert a dominant-negative effect on the previously reported activity of pyrin, we found increased IL-1beta production by peripheral blood leukocytes from a clinically active PAPA patient with the A230T PSTPIP1/CD2BP1 mutation and in cell lines transfected with both PAPA-associated mutants.

DOI: 10.1073/pnas.2135380100

PMCID: PMC263843

PMID: 14595024 [Indexed for MEDLINE]

4488. Turk J Gastroenterol. 2003 Mar;14(1):71-3.

Is hyperbilirubinemia a component or just a coincidence of familial mediterranean fever: a case report and review of the literature.

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Familial Mediterranean fever is a multisystem disorder, usually seen in subjects of Mediterranean and Middle Eastern origin, characterized by recurrent bouts of fever and pain due to inflammation of the peritoneum, synovia, or pleura. In this article we report a case of Familial Mediterranean fever with recurrent abdominal pain and hyperbilirubinemia, review the literature and discuss whether the hyperbilirubinemia is co-existent or a feature of the disease.

PMID: 14593543 [Indexed for MEDLINE]

4489. Duodecim. 2003;119(18):1779-81.

[Abdominal pain in a refugee].

[Article in Finnish]

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PMID: 14587465 [Indexed for MEDLINE]

4490. Pediatr Nephrol. 2003 Dec;18(12):1313-4. Epub 2003 Oct 30.

A case of osteopoikilosis coexisting with amyloidosis of familial Mediterranean fever.

Kavukçu S, Soylu A, Türkmen M, Güneş D, Bora S, Gülay H.

DOI: 10.1007/s00467-003-1312-0

PMID: 14586673 [Indexed for MEDLINE]

4491. Clin Rheumatol. 2003 Oct;22(4-5):314-7.

Colchicine treatment in children with familial Mediterranean fever.

Ozkaya N(1), Yalçinkaya F.

Author information:

(1)Ankara University School of Medicine, Ankara, Turkey.

Prophylactic colchicine therapy has been shown to be a safe and effective method of eliminating the attacks and preventing the development of amyloidosis in patients with familial Mediterranean fever (FMF). However, information about effective dosages that control FMF attacks and prevent amyloidosis in childhood is not available. The aim of this study is to determine the 'effective colchicine dose' for children in terms of body weight and surface area. Sixty-two (34 male, 28 female) children with FMF were selected and colchicine treatment was initiated by giving 0.5-1 mg/day to each patient. The dose was gradually increased up to a maximum 2 mg/day in unresponsive patients; mean duration of therapy was 45.6 +/- 35.5 months. When the 'optimal effective dosage' (i.e. the one that reduced the frequency of attacks and ESR, CRP and fibrinogen levels during the attack-free period) was achieved, the optimal effective dose was calculated according to the body weight and body surface area for each patient. Based on these values 'mean colchicine dose' was computed for the study group and values for different age groups were evaluated. Mean colchicine doses according to the body weight and surface area of the whole group were found to be 0.03 +/- 0.02 mg/kg/day and 1.16 +/- 0.45 mg/m(2)/day, respectively. It was shown that children less than 5 years of age might need colchicine doses as high as 0.07 mg/kg/day or 1.9 mg/m(2)/day. These dosages are approximately 2.5-3 times more than the 'mean colchicine dose' for children aged 16-20 years. These results clearly show that small children need higher doses of colchicine in order to control their attacks. Thus, we conclude that colchicine, when given according to body weight or body surface area, would be more effective in childhood.

DOI: 10.1007/s10067-003-0739-9

PMID: 14579163 [Indexed for MEDLINE]

4492. Saudi Med J. 2003 Oct;24(10):1055-9.

Familial Mediterranean fever mutation frequencies and carrier rates among a mixed Arabic population.

Al-Alami JR(1), Tayeh MK, Najib DA, Abu-Rubaiha ZA, Majeed HA, Al-Khateeb MS, El-Shanti HI.

Author information:

(1)Department of Biochemistry, School of Medicine, Jordan University of Science and Technology, Irbid, Jordan.

**OBJECTIVE:** Familial Mediterranean Fever (FMF) is an autoinflammatory periodic disorder characterized by febrile and painful attacks due to inflammation involving the serosal membranes. The gene implicated in this disorder, MEFV, has been cloned and mutations in its coding regions have been identified. We aimed at identifying the frequency of MEFV mutations and carrier frequency in a mixed Arabic population.

**METHODS:** We identified 29 probands from 29 unrelated sibships segregating the disorder and representing the affected individual cohort. We screened 200 anonymous deoxyribonucleic acid (DNA) samples, representing a healthy adult cohort, for the mutations found to be common in the affected individual cohort. We also, screened anonymous DNA samples from 4 Arabic countries, namely, Egypt (231), Syria (225), Iraq (176) and the Kingdom of Saudi Arabia (107) thus enlarging our healthy adult cohort. The study was carried out between 1999 and 2002 at Jordan University of Science and Technology, Irbid and the University of Jordan, Amman, Jordan.

**RESULTS:** Out of the 58 alleles of the 29 probands, only 31 mutations were identified and M694V and V726A are the most common. The mutation E148Q was the most common among the healthy adult cohort, but was not present in affected individuals. The collective mutant allele frequency "q" was 0.101. The expected carrier rate was 18.1% (one in 5.5) while the observed carrier rate was 18.4% (one in 5.4).

**CONCLUSION:** E148Q has reduced penetrance and thus, a proportion of the individuals genetically affected with FMF remain asymptomatic. M694I and M680I are more prevalent in the affected individuals cohort, which points to their higher penetrance. The overall carrier rate is one in 5, but the selective heterozygote advantage could not be demonstrated in this study due to the relatively small sample size.

PMID: 14578967 [Indexed for MEDLINE]

4493. Clin Chem. 2003 Nov;49(11):1948-50.

Genetic testing for familial Mediterranean fever in Austria by means of reverse-hybridization teststrips.

Oberkanins C(1), Weinhäusel A, Kriegshäuser G, Moritz A, Kury F, Haas OA.

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Comment in

Clin Chem. 2003 Nov;49(11):1781-2.

PMID: 14578333 [Indexed for MEDLINE]

4494. Clin Chem. 2003 Nov;49(11):1942-5.

Clinical evaluation of a reverse hybridization assay for the molecular detection of twelve MEFV gene mutations.

Tchernitchko D(1), Legendre M, Delahaye A, Cazeneuve C, Niel F, Goossens M, Amselem S, Girodon E.

Author information:

(1)Service de Biochimie et de Génétique Moléculaire, Hôpital Henri Mondor, AP-HP, 94010 Créteil, France.

Comment in

Clin Chem. 2003 Nov;49(11):1781-2.

PMID: 14578331 [Indexed for MEDLINE]

4495. Clin Chem. 2003 Nov;49(11):1781-2.

Standardized testing for mutations in familial Mediterranean fever.

Touitou I.

Comment on

Clin Chem. 2003 Nov;49(11):1942-5.

Clin Chem. 2003 Nov;49(11):1948-50.

PMID: 14578308 [Indexed for MEDLINE]

4496. Allergol Immunopathol (Madr). 2003 Sep-Oct;31(5):294-6.

Familial presentation of occupational hypersensitivity pneumonitis caused by aspergillus-contaminated esparto dust.

Moreno-Ancillo A(1), Domínguez-Noche C, Carmen Gil-Adrados A, Cosmes PM.

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Esparto grass (*Stipa tenacissima*), which is commonly found in the Mediterranean area, has a wide variety of uses. Five plaster workers from the same family developed cough, dyspnea, malaise, and fever after exposure to the esparto fiber used in their work for the previous few years. They showed a significant decrease in symptoms when away from work. Precipitating antibodies against an esparto extract were found in the sera of all patients. Specific IgG antibodies against *Aspergillus fumigatus* were detected. *A. fumigatus* was identified after microbiologic evaluation of esparto fiber samples. The dust derived from fungi-contaminated esparto fibers can cause hypersensitivity pneumonitis in exposed subjects. The causative antigen is *A. fumigatus*. When esparto fibers were strongly contaminated by fungi, all the workers developed a clinical picture compatible with hypersensitivity pneumonitis. The coincidental finding of an



occupational and a familiar condition is unusual.

PMID: 14572421 [Indexed for MEDLINE]

4497. Praxis (Bern 1994). 2003 Sep 24;92(39):1636-9.

[The interesting case from the pediatric polyclinic].

[Article in German]

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An eleven year old girl from Turkey was diagnosed to have a periodic fever syndrome. The diagnosis of familial mediterranean fever was made by molecular analysis of a mutation in the MEFV-Gen which codes for pyrin. The disease is well-known in the mediterranean area and belongs to the periodic fever syndromes. These syndromes are discussed for their differential diagnosis focused to childhood.

DOI: 10.1024/0369-8394.92.39.1636

PMID: 14558432 [Indexed for MEDLINE]

4498. Duodecim. 2003;119(16):1567-71.

[Genetic fever--Internet consultation, mutation in the envelope].

[Article in Finnish]

Korppi M(1), Korhonen J, Lindström K, Mononen T.

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matti.korppi@uku.fi

PMID: 14535030 [Indexed for MEDLINE]

4499. Structure. 2003 Oct;11(10):1199-205.

NMR structure of the apoptosis- and inflammation-related NALP1 pyrin domain.

Hiller S(1), Kohl A, Fiorito F, Herrmann T, Wider G, Tschopp J, Grütter MG, Wüthrich K.

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Comment in

Structure. 2003 Oct;11(10):1190-1.

Signaling in apoptosis and inflammation is often mediated by proteins of the death domain superfamily in the Fas/FADD/Caspase-8 or the Apaf-1/Caspase-9 pathways. This superfamily currently comprises the death domain (DD), death effector domain (DED), caspase recruitment domain (CARD), and pyrin domain (PYD) subfamilies. The PYD subfamily is most abundant, but three-dimensional structures are only available for the subfamilies DD, DED, and CARD, which have an antiparallel arrangement of six alpha helices as common fold. This paper presents the NMR structure of PYD of NALP1, a protein that is involved in the innate immune response and is a component of the inflammasome. The structure of NALP1 PYD differs from all other known death domain superfamily structures in that the third alpha helix is replaced by a flexibly disordered loop. This unique feature appears to relate to the molecular basis of familial Mediterranean fever (FMF), a genetic disease caused by single-point mutations.

PMID: 14527388 [Indexed for MEDLINE]

4500. Pediatr Int. 2003 Oct;45(5):564-9.

## Evaluation of 80 children with prolonged fever.

Cogulu O(1), Koturoglu G, Kurugol Z, Ozkinay F, Vardar F, Ozkinay C.

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**BACKGROUND:** Several studies have been published regarding the etiology and evaluation of a child with prolonged fever, however, the reasons for the prolonged fever have changed during the years. The present study aims to determine the causes of prolonged fever, to investigate the relationship of fever using some basic laboratory tests, and to establish guidelines for the approach in those children.

**METHODS:** The charts of 80 out of 17490 hospitalized children who were seen between 1996 and 2001 with prolonged fever of longer than 2 weeks and unknown origin were reviewed in the university hospital of Izmir, Turkey. Their charts were evaluated in respect of age, sex, growth curves, educational level of their families, the duration and the magnitude of fever, causes of fever, and basic laboratory investigations such as white blood cell, blood smear, hemoglobin, erythrocyte sedimentation rate, and C-reactive protein.

**RESULTS:** Forty-four (55.00%) were boys and 36 (45.00%) were girls. Forty-four children (55.00%) were aged between 1 month and 2 years, 21 (26.25%) were aged 3-6 years, seven (8.75%) were aged 7-10 years, and eight (10.00%) were older than 10 years. The mean age was 3.87 +/- 4.17 years (range 3 months-17 years). Forty-six children (57.50%) had a prolonged fever that had lasted from 15-30 days, 18 (22.50%) from 31-60 days, and 16 (20.00%) had fever lasting more than 60 days. Final diagnosis had been reached in 70 of the 80 children (87.50%). The most common causes were infection (47/80), followed by immune deficiency (6/80), collagen tissue disorder (5/80), neoplasia (2/80), and miscellaneous (10/80) such as central fever in three, diabetes insipidus in two, familial Mediterranean fever in two, Kawasaki disease, foreign body in the respiratory system, and Crohn disease in one patient each. Among the laboratory tests white blood cell count, hemoglobin level and blood smear distribution of infection group were statistically significant.

**CONCLUSIONS:** The most common cause of fever of unknown origin remains infection. The proportion of collagen tissue disorders and neoplasia have been found to be decreased. Unusual reasons such as diabetes insipidus and foreign body in the respiratory system in the miscellaneous group have been detected. Age plays

important role in the diagnosis of prolonged fever, while some basic laboratory tests might give clues in the evaluation and may suggest a diagnosis.

PMID: 14521533 [Indexed for MEDLINE]

4501. Expert Opin Biol Ther. 2003 Oct;3(7):1041-9.

Haematopoietic stem cell transplantation for the treatment of systemic sclerosis and other autoimmune disorders.

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Systemic sclerosis (SSc) with involvement of vital organs has up to 50% 5-year mortality and no treatment is known which changes the natural history. Although components of vascular, immunological and fibrotic processes are involved, drugs such as cyclophosphamide (CY), an alkylating agent and a potent immunosuppressive, have been partially effective in uncontrolled studies. The dose of such agents is limited by the inevitable toxicity on the bone marrow, but this threshold may be superseded by first removing the patient's own haematopoietic stem cells, followed by reconstitution of the marrow after high-dose myeloablative CY or other therapy. This autologous haematopoietic stem cell transplantation (HSCT) technique has been applied to approximately 650 patients with severe autoimmune diseases worldwide, > 100 of whom had SSc. Of these, 75 are included in the Basle registry. Around 70% of patients responded with a significant (> 25%) improvement of the thickened skin and stabilisation of vital organ involvement. Approximately a third achieved a durable remission. The treatment-related mortality was 8.5%. Based on these encouraging Phase I/II study results, several multi-centre, international, prospective randomised Phase III trials are running or being planned. The preliminary data suggest that through such a jolt of heavy immunosuppression, the dysregulated autoaggressive immune system may be re-regulated. It is hypothesised that this results in fewer autoinflammatory and unwanted stimulatory signals to other systems such as vascular endothelium and fibroblasts, and these mechanisms are currently under

study.

DOI: 10.1517/14712598.3.7.1041

PMID: 14519069 [Indexed for MEDLINE]

4502. J Biol Chem. 2003 Dec 5;278(49):48839-47. Epub 2003 Sep 26.

The tumor necrosis factor alpha-dependent activation of the human mediterranean fever (MEFV) promoter is mediated by a synergistic interaction between C/EBP beta and NF kappaB p65.

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MEFV is a gene expressed specifically in myeloid cells and whose mutations underlie an autosomal recessive auto-inflammatory disease, called familial Mediterranean fever (FMF), characterized by recurrent episodes of serosal inflammation. This gene, which encodes a protein with unclear physiological functions, has been shown to be up-regulated by the pro-inflammatory cytokine tumor necrosis factor alpha (TNFalpha). However, the mechanism of this regulation is unknown, and the MEFV promoter is still to be characterized. Here, we show that 243 bp of the 5'-flanking region of the human MEFV gene are sufficient to direct high level expression of MEFV in TNFalpha-treated cells. The TNFalpha-induced expression of MEFV is dependent on both NFkappaB p65 and C/EBPbeta that bind to evolutionarily conserved sites located, in the human promoter, at positions -163 and -55, respectively. As shown by a series of transcription and gel shift assays performed with wild-type and mutated promoter sequences, these two transcription factors act differently on the TNFalpha-dependent transcription of MEFV: C/EBPbeta is the key regulatory factor required to confer cell responsiveness to TNFalpha, whereas NFkappaB p65 increases this response by means of a synergistic interaction with C/EBPbeta that is dependent on the integrity of the identified -55 C/EBP binding site. Given the phenotype of patients with FMF, this C/EBP-NFkappaB interaction may represent a key step in the control of an inflammatory response that is abnormally high in this disease. These data, which shed novel light on the pathophysiology of FMF,

represent an unusual example of cross-talk between C/EBP and NFkappaB pathways in TNFalpha signaling.

DOI: 10.1074/jbc.M305166200

PMID: 14514692 [Indexed for MEDLINE]

4503. Rheumatol Int. 2004 May;24(3):147-52. Epub 2003 Sep 12.

Cardiovascular reactivity score for the assessment of dysautonomia in familial Mediterranean fever.

Rozenbaum M(1), Naschitz JE, Yudashkin M, Sabo E, Shaviv N, Gaitini L, Zuckerman E, Yeshurun D, Rosner I.

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**OBJECTIVE:** The aim of this study was to assess the presence of dysautonomia, as manifested in abnormal cardiovascular reactivity, in patients with familial Mediterranean fever (FMF).

**METHODS:** Fifty-five consecutive patients with FMF and 23 age- and sex-matched healthy controls were evaluated. Cardiovascular reactivity was studied: (1) using recordings of blood pressure (BP) and heart rate (HR) during 10 min of recumbence and 30 min of head-up tilt test to identify clinical endpoints and (2) during tilt-test, identifying parameters acting as independent predictors of FMF reactivity and enabling computation of a cardiovascular reactivity score (CVRS).

**RESULTS:** Clinically, vasovagal reaction, postural tachycardia syndrome, and/or orthostatic hypotension were observed in ten patients (18.1%). Utilizing a derived equation, the group average CVRS in FMF was  $5.83 \pm 1.78$  (healthy group  $-7.60 \pm 5.41$ ) ( $P < 0.0001$ ). A CVRS of  $>3.25$  was associated with FMF, with 98% sensitivity and 100% specificity.

**CONCLUSION:** A very high percentage of FMF patients exhibit abnormal cardiovascular reactivity which is clinically occult but can be detected on autonomic challenge and application of the CVRS.

DOI: 10.1007/s00296-003-0344-x

4504. Arthritis Rheum. 2003 Sep;48(9):2645-51.

Favorable preliminary experience with etanercept in two patients with the hyperimmunoglobulinemia D and periodic fever syndrome.

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**OBJECTIVE:** The hyperimmunoglobulinemia D and periodic fever syndrome (HIDS; MIM 260920) is caused by recessive mutations in the mevalonate kinase gene (MVK), which encodes an enzyme involved in cholesterol and nonsterol isoprenoid biosynthesis. HIDS is characterized by persistently elevated polyclonal IgD and recurrent febrile episodes. Although abnormalities in tumor necrosis factor alpha (TNF alpha) are not the primary cause of HIDS, plasma TNF alpha levels are elevated in HIDS patients during attacks and thus may be a therapeutic target. This study assessed the effects of etanercept, a soluble p75 TNF alpha receptor-Fc fusion protein, in 2 patients with HIDS.

**METHODS:** We performed biochemical and molecular genetic analyses on 2 girls with periodic episodes of fever, skin rash, abdominal pain, and arthralgia, of whom 1 had elevated levels of serum IgD. After the diagnosis of HIDS was made, treatment with etanercept was initiated in both patients. Clinical response was recorded in a standardized diary, and serum levels of cytokines and their decoy receptors were serially measured in 1 of the 2 patients.

**RESULTS:** Urinary mevalonate levels were elevated in both girls. Patient 1 was heterozygous for a known MVK missense mutation (V377I) and a novel mutation that led to skipping of exon 3. Patient 2 was found to have V377I and a new missense mutation, S329R. Neither patient had mutations in TNFRSF1A or MEFV, the genes for the TNF receptor-associated periodic syndrome and familial Mediterranean fever, respectively. Etanercept reduced the frequency and severity of symptoms in both patients, whereas the levels of serum IgD and urine mevalonate remained unchanged.

**CONCLUSION:** Our favorable experience with etanercept for the treatment of HIDS suggests that further investigation of this therapy is warranted.

DOI: 10.1002/art.11218

PMID: 13130485 [Indexed for MEDLINE]

4505. Arthritis Rheum. 2003 Sep;48(9):2632-44.

Heterogeneity among patients with tumor necrosis factor receptor-associated periodic syndrome phenotypes.

Aganna E(1), Hammond L, Hawkins PN, Aldea A, McKee SA, van Amstel HK, Mischung C, Kusuvara K, Saulsbury FT, Lachmann HJ, Bybee A, McDermott EM, La Regina M, Arostegui JI, Campistol JM, Worthington S, High KP, Molloy MG, Baker N, Bidwell JL, Castañer JL, Whiteford ML, Janssens-Korpola PL, Manna R, Powell RJ, Woo P, Solis P, Minden K, Frenkel J, Yagüe J, Mirakian RM, Hitman GA, McDermott MF.

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**OBJECTIVE:** To investigate the prevalence of tumor necrosis factor receptor-associated periodic syndrome (TRAPS) among outpatients presenting with recurrent fevers and clinical features consistent with TRAPS.

**METHODS:** Mutational screening was performed in affected members of 18 families in which multiple members had symptoms compatible with TRAPS and in 176 consecutive subjects with sporadic (nonfamilial) "TRAPS-like" symptoms. Plasma concentrations of soluble tumor necrosis factor receptor superfamily 1A (sTNFRSF1A) were measured, and fluorescence-activated cell sorter analysis was used to measure TNFRSF1A shedding from monocytes.

**RESULTS:** Eight novel and 3 previously reported TNFRSF1A missense mutations were identified, including an amino acid deletion (Delta D42) in a Northern Irish family and a C70S mutation in a Japanese family, both reported for the first time. Only 3 TNFRSF1A variants were found in patients with sporadic TRAPS (4 of 176 patients). Evidence for nonallelic heterogeneity in TRAPS-like conditions was found: 3 members of the "prototype familial Hibernian fever" family did not possess C33Y, present in 9 other affected members. Plasma sTNFRSF1A levels were low in TRAPS patients in whom renal amyloidosis had not developed, but also in mutation-negative symptomatic subjects in 4 families, and in 14 patients (8%) with sporadic TRAPS. Reduced shedding of TNFRSF1A from monocytes was demonstrated in vitro in patients with the T50M and T50K variants, but not in those with other



variants.

CONCLUSION: The presence of TNFRSF1A shedding defects and low sTNFRSF1A levels in 3 families without a TNFRSF1A mutation indicates that the genetic basis among patients with "TRAPS-like" features is heterogeneous. TNFRSF1A mutations are not commonly associated with nonfamilial recurrent fevers of unknown etiology.

DOI: 10.1002/art.11215

PMID: 13130484 [Indexed for MEDLINE]

4506. Heart. 2003 Oct;89(10):1257-8.

Incidence of pericardial effusion during attacks of familial Mediterranean fever.

Tutar E, Yalçinkaya F, Ozkaya N, Ekim M, Atalay S.

PMCID: PMC1767885

PMID: 12975440 [Indexed for MEDLINE]

4507. Ann Rheum Dis. 2003 Oct;62(10):916-9.

Reproductive system in familial Mediterranean fever: an overview.

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Familial Mediterranean fever (FMF), amyloidosis, and colchicine may affect the reproductive system of male and female patients. Colchicine treatment improves female fertility and the outcome of pregnancy and may prevent the development of amyloidosis. However, colchicine may induce oligospermia/azoospermia, but this effect is rare. Overall, colchicine treatment improves the prognosis of patients with FMF and increases their reproductive ability.

PMCID: PMC1754343

PMID: 12972465 [Indexed for MEDLINE]

4508. J Rheumatol. 2003 Sep;30(9):2014-8.

Mutations in the gene for familial Mediterranean fever: do they predispose to inflammation?

Ozen S(1), Bakkaloglu A, Yilmaz E, Duzova A, Balci B, Topaloglu R, Besbas N.

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**OBJECTIVE:** To analyze 70 individuals who were found to have the Mediterranean fever (MEFV) gene for the presence of definite familial Mediterranean fever (FMF) and to assess if they were prone to clinical and laboratory inflammation. We also prospectively evaluated 72 patients with childhood rheumatic diseases for the presence of MEFV mutations.

**METHODS:** Seventy patients with one MEFV gene mutation were reevaluated for the presence of a clinical FMF phenotype using a new set of criteria. They were also questioned for the presence of musculoskeletal symptoms and rheumatic diseases. They were sampled for erythrocyte sedimentation rates and C-reactive protein levels. A second group with childhood rheumatic diseases were diagnosed according to international criteria.

**RESULTS:** Median age of the 70 heterozygous individuals was 12 years. About 1/3 (34.3%) were classified with clinical FMF phenotype according to the suggested criteria. Fifteen (21.4%) were classified as normal and 3 (4.3%) had recurrent abdominal pains but did not fulfill all criteria for clinical FMF. Overall, 28 (40.0%) had some form of rheumatic complaint and 15 (21.4%) had developed a rheumatic disease including Behçet's disease, a vasculitis, or acute rheumatic fever. The mean ESR and CRP levels were 45.47 +/- 33.05 mm/h and 4.00 +/- 6.73 mg/dl, respectively. Among the 72 patients with rheumatic diseases of childhood, 22 (30.5%) carried one or 2 mutations of the MEFV gene. The mutated allele frequency among patients with rheumatic diseases was significantly higher than those in controls ( $p < 0.05$ ). Within this group, among the 59 patients with juvenile idiopathic arthritis 15 had mutations in the heterozygous or homozygous form.

**CONCLUSION:** We confirm the acute phase response in the carriers for MEFV mutations. We suggest that these patients may have a tendency to develop certain manifestations due to an increased baseline of inflammation, and the presence of these mutations may affect their disease course when they develop rheumatic disease.

PMID: 12966608 [Indexed for MEDLINE]

4509. J Rheumatol. 2003 Sep;30(9):2011-3.

Th1 polarization in familial Mediterranean fever.

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**OBJECTIVE:** Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by fever and serosal inflammation accompanied with an outburst of acute phase inflammatory products and cytokines. We studied the role of T helper (Th) 1 and 2 cells in FMF to elucidate the character of the inflammation. The cytokine products of Th1 and Th2, interferon-g (IFN-g) and interleukin 4 (IL-4), respectively, were analyzed by intracellular cytokine staining and FACS analysis.

**METHODS:** We studied 34 Turkish patients with FMF (18 asymptomatic, 8 during an attack, and 8 with amyloidosis) and 14 age matched controls, as well as 11 parents of the patients who were accepted as heterozygotes for MEFV (Familial Mediterranean gene) mutations. Peripheral blood mononuclear cells were isolated and stained with monoclonal antibodies for IFN-g and IL-4. The percentage of IL-4 positive T cells was not significantly different between the groups. However, the percentage of IFN-g positive T cells in FMF patients experiencing an attack (median 25.8%, range 8.9-50.5%) was significantly higher than asymptomatic FMF patients (median 12%, range 0.1-70.7) ( $p = 0.04$ ) and age matched controls ( $n = 7$ , median 0.4%, range 0-3.9%) ( $p = 0.0001$ ). The percentage of IFN-g positive T cells in asymptomatic FMF patients was also significantly higher than age matched controls ( $p = 0.008$ ). Heterozygotes for FMF had significantly higher IFN-g production (median 2.6%, range 0-42.4%) compared to age matched controls ( $n = 7$ , median 0.2%, range 0-1.4) ( $p = 0.001$ ). IFN-g production in FMF patients with

secondary amyloidosis was also markedly increased but had a large range of variation.

CONCLUSION: Inflammation in FMF shows a Th1 polarization. We suggest that in patients with FMF the IFN- $\gamma$  concentrations may remain higher because the defective pyrin is not able to inhibit this Th1 mediated inflammation.

PMID: 12966607 [Indexed for MEDLINE]

4510. Hum Mutat. 2003 Oct;22(4):339-40.

The E148Q MEFV allele is not implicated in the development of familial Mediterranean fever.

Tchernitchko D(1), Legendre M, Cazeneuve C, Delahaye A, Niel F, Amselem S.

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Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent attacks of fever and serositis, common in populations of Armenian, Arab, Sephardic Jewish and Turkish origin. Early diagnosis is crucial to start colchicine therapy that prevents the occurrence of attacks and renal amyloidosis. In the absence of functional test for FMF, the diagnosis remains clinical and is generally confirmed by molecular analysis of the MEFV gene. More than 40 missense mutations and two in-frame deletions have been reported, most of them being located in exon 10 of the gene. The M694V (c.2080A>G) mutation, the most frequent defect, is responsible for a severe phenotype when present in the homozygous state. The E148Q (c.442G>C) sequence variant, which is situated in exon 2, is also common, but its role in FMF is controversial. In order to assess the implication of the E148Q variation in FMF, we investigated 233 patients of Sephardic Jewish origin living in France and 213 disease-free relatives of these patients. The frequency of the E148Q allele was found to be similar in the two groups (3.62% and 3.75%, respectively,  $p=0.93$ ). Most importantly, the frequency of the M694V/E148Q compound heterozygous genotype was comparable between the patients group (3.9%) and the healthy relatives group (4.2%,  $p=0.85$ ). This population-based study, therefore, strongly supports the hypothesis that E148Q is just a benign polymorphism and not a disease-causing

mutation. Considering this variant as a mutation may lead to set false positive diagnoses and to neglect the likely existence of genetic heterogeneity in FMF.

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DOI: 10.1002/humu.9182

PMID: 12955725 [Indexed for MEDLINE]

4511. Can Fam Physician. 2003 Aug;49:967-9.

Safety of colchicine therapy during pregnancy.

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Author information:

(1)Hospital for Sick Children, Toronto, Ont.

QUESTION: A 27-year-old patient in our clinic with familial Mediterranean fever (FMF) has been treated with colchicine for the last decade. She is planning her first pregnancy. What recommendations should we give her regarding use of colchicine before and during pregnancy, bearing in mind that discontinuation of colchicine could lead to complications from amyloidosis?

ANSWER: Colchicine passes through the placenta in humans, is teratogenic in animals, and raises rates of male and female infertility. Based on several patients with chromosomal anomalies, some authorities recommend that patients who require colchicine therapy during pregnancy undergo amniocentesis with karyotyping. In contrast, an increasing body of evidence suggests that colchicine use throughout pregnancy carries no substantial teratogenic or mutagenic risk when used at recommended doses. Its use prevents febrile attacks of FMF and reduces the frequency of renal complications.

PMCID: PMC2214270

PMID: 12943352 [Indexed for MEDLINE]

4512. Clin Exp Rheumatol. 2003 Jul-Aug;21(4):509-14.

## Role of A-SAA in monitoring subclinical inflammation and in colchicine dosage in familial Mediterranean fever.

Duzova A(1), Bakkaloglu A, Besbas N, Topaloglu R, Ozen S, Ozaltin F, Bassoy Y, Yilmaz E.

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**OBJECTIVES:** 1) To compare the sensitivity of serum amyloid A protein (A-SAA) and other acute phase proteins (APPs) in determining subclinical inflammation in patients with familial Mediterranean fever (FMF) during an attack-free period; 2) to define those clinical, laboratory features that may modify the A-SAA level; and 3) to evaluate the effect of an increase in the colchicine dose on the A-SAA level.

**METHODS:** A-SAA, CRP, ESR, fibrinogen and ferritin levels were measured in 183 patients [88 F, 95 M; median age 11.0 years (1.0-20.0)] with FMF during an attack-free period. Mutational analysis was available in 157 patients. The colchicine dose was increased in 26 randomly chosen patients with no attacks within the last year; laboratory studies were repeated at the end of the second month.

**RESULTS:** During an attack-free period, the median A-SAA level was 74 (6-1,500) mg/L; other APPs were within normal ranges in 49-93% of the patients. Age, gender, age at onset, age at diagnosis, the duration of treatment and the frequency of attacks had no significant effect on the A-SAA level. Homozygous and compound heterozygous patients had higher A-SAA levels than heterozygous patients [129 mg/L (8-1,500) versus 29 mg/L (6-216);  $p < 0.005$ ]. There was a dramatic decrease in the A-SAA level [from 244 mg/L (16-1,400) to 35.5 mg/L (8-1,120);  $p < 0.001$ ] and an increase in the hemoglobin ( $1.89 \pm 0.10$  mmol/L to  $1.98 \pm 0.19$  mmol/L;  $p < 0.005$ ) after the increase in colchicine dose in 26 patients.

**CONCLUSION:** Subclinical inflammation continues during an attack-free period in FMF patients. A-SAA was the best marker of subclinical inflammation. Patients who are homozygous or compound heterozygotes of MEFV mutations had higher A-SAA levels. An increase in the colchicine dose resulted in a dramatic decrease in A-SAA and an increase in hemoglobin level. These findings favor the use of A-SAA in drug monitoring.

PMID: 12942707 [Indexed for MEDLINE]

4513. Isr Med Assoc J. 2003 Aug;5(8):592-4.

The distribution of MEFV common mutations among Israeli patients with familial Mediterranean fever.

Ben-Chetrit E, Abeliovich D.

Comment in

Isr Med Assoc J. 2003 Aug;5(8):585-8.

PMID: 12929301 [Indexed for MEDLINE]

4514. Isr Med Assoc J. 2003 Aug;5(8):585-8.

Analysis of the three most common MEFV mutations in 412 patients with familial Mediterranean fever.

Zaks N(1), Shinar Y, Padeh S, Lidar M, Mor A, Tokov I, Pras M, Langevitz P, Pras E, Livneh A.

Author information:

(1)Heller Institute of Medical Research, Sheba Medical Center, Tel Hashomer, Israel.

Comment on

Isr Med Assoc J. 2003 Aug;5(8):592-4.

**BACKGROUND:** Familial Mediterranean fever is an autosomal recessive disease characterized by recurrent attacks of fever and serositis. The disease is caused by mutations in the MEFV gene, presumed to act as a down-regulator of inflammation within the polymorphonuclear cells.

**OBJECTIVES:** To present the results of 412 FMF patients genotyped for three MEFV mutations, M694V, V726A and E148Q.

**RESULTS:** The most frequent mutation, M694V, was detected in 47% of the carrier chromosomes. This mutation, especially common among North African Jewish FMF patients, was not found in any of the Ashkenazi (East European origin) patients. Overall, one of the three mutations was detected in 70% of the carrier chromosomes. M694V/M694V was the most common genotype (27%), followed by M694V/V726A (16%). The full genotype could be assessed in 57% of the patients, and one disease-causing mutation in an additional 26%. Only one patient with the E148Q/E148Q genotype was detected despite a high carrier rate for this mutation in the Jewish population, a finding consistent with a low penetrance of this genotype. The M694V/M694V genotype was observed in 15 patients with amyloidosis compared to 4 amyloidosis patients with other genotypes ( $P < 0.0001$ ).

**CONCLUSIONS:** Because of low penetrance and as yet other undetermined reasons, mutation analysis of the most common MEFV mutations supports a clinical diagnosis in only about 60% of patients with definite FMF.

PMID: 12929299 [Indexed for MEDLINE]

4515. Br J Ophthalmol. 2003 Sep;87(9):1175-83.

Behçet's disease: from Hippocrates to the third millennium.

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Behçet's disease (BD) is characterised by recurrent episodes of orogenital aphthae, systemic vasculitis, and systemic and retinal venous thrombosis. An association between HLA-B51 and BD was first identified over 20 years ago, but recently identified gene associations implicate regions both within and without the MHC in the immunological events underlying the lesions in BD. These include allelic variants within the tumour necrosis factor gene region and within the MHC class I chain related gene region, the factor V Leiden mutation, which is associated with retinal vascular occlusion, and alleles of the intercellular adhesion molecule gene. No single causative gene for BD has emerged; the evidence indicates that the underlying immune events in BD are triggered by a microbial antigen and subsequently driven by genetic influences which control leucocyte



behaviour and the coagulation pathways. Knowledge of these risk factors may permit a more accurate prognosis for a given patient, and identify new pathways for more targeted intervention than is currently available.

PMCID: PMC1771837

PMID: 12928293 [Indexed for MEDLINE]

4516. Intern Med. 2003 Aug;42(8):761-4.

A Japanese case of familial Mediterranean fever with family history demonstrating a mutation in MEFV.

Yoshida K(1), Kanaoka S, Kajimura M, Kataoka H, Takahira K, Osawa S, Sano M, Hishida A.

Author information:

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We describe a 17-year-old woman with a family history of FMF who suffered from recurrent fever accompanied by pains in the left chest and abdomen. During a five-year period she experienced attacks about once every six months. The metaraminol provocative test was positive. Genomic DNA extracted from peripheral blood lymphocytes from both her and her parents were analyzed by polymerase chain reaction (PCR), followed by cycle sequencing. We detected a mutation (ATG to ATA) in codon 694 in exon 10 of the FMF gene, MEFV, that resulted in a substitution of isoleucine for methionine (M694I) in both her and her father. This is the first Japanese case of FMF with a mutation in MEFV identified in the family history.

PMID: 12924509 [Indexed for MEDLINE]

4517. Ned Tijdschr Geneeskd. 2003 Aug 2;147(31):1530; author reply 1530.

[Turkish children with abdominal pain and fever: familial Mediterranean fever].

[Article in Dutch]

Kusadasi N, van der Meulen J.

Comment on

Ned Tijdschr Geneesk. 2003 Jun 7;147(23):1097-100.

PMID: 12924089 [Indexed for MEDLINE]

4518. J Pediatr. 2003 Jul;143(1):140-1.

MEFV gene analysis in PFAPA.

Cazeneuve C, Geneviève D, Amselem S, Hentgen V, Hau I, Reinert P.

DOI: 10.1016/S0022-3476(03)00259-2

PMID: 12915843 [Indexed for MEDLINE]

4519. J Pediatr. 2003 Jul;143(1):127-9.

Hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) in a child with normal serum IgD, but increased serum IgA concentration.

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This report describes a boy with hyperimmunoglobulinemia D and periodic fever syndrome (HIDS). The serum IgD level was normal, but the serum IgA concentration was markedly elevated. In addition, he had a history of orchitis on two occasions, a previously unreported manifestation of HIDS. This report expands the clinical and laboratory features associated with HIDS and serves to emphasize that a normal serum IgD level does not exclude the diagnosis of HIDS.

DOI: 10.1016/S0022-3476(03)00212-9

PMID: 12915839 [Indexed for MEDLINE]

4520. Eur J Med Res. 2003 Jul 31;8(7):304-6.

The importance of serial measurements of cytokine levels for the evaluation of their role in pathogenesis in familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent fever of unknown origin, renal amyloidosis, peritonitis, pleuritis and/or synovitis. There have been many studies to elucidate the etiopathogenesis of FMF. IL-6 is a cytokine that can induce the formation of serum amyloid A and C-reactive protein, both of which are important in development of amyloidosis. IL-6 was determined to be strongly associated in the etiopathogenesis of periodic fever in Chinese-pei dogs. The dogs with this syndrome experience periodic fever, arthritis, renal amyloidosis, a clinical picture very alike of human FMF. Here, we aimed to study mainly whether IL-6 had a similar etiopathogenetic role in human FMF as in Chinese-pei dogs syndrome. The median IL-6 blood levels were found to be higher in patients with acute (n=8) FMF attack (1.85 U/ml) compared to those (n=33) with asymptomatic ones (1.0 U/ml) (p=0.16). There are mainly two results: first; the study should be designed with a larger sample size of patients with acute attack in order to alleviate underestimation of significance, second; sampling time may give various results because of dynamic changes of cytokine levels during acute attack period.

PMID: 12911867 [Indexed for MEDLINE]

4521. Arthritis Rheum. 2003 Aug 15;49(4):614-6.

Colchicine myopathy in a patient with familial Mediterranean fever and normal

renal function.

Kissin EY(1), Corbo JC, Farraye FA, Merkel PA.

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DOI: 10.1002/art.11185

PMID: 12910572 [Indexed for MEDLINE]

4522. BMC Nephrol. 2003 Aug 11;4:6.

Familial Mediterranean fever, inflammation and nephrotic syndrome: fibrillary glomerulopathy and the M680I missense mutation.

Fisher PW(1), Ho LT, Goldschmidt R, Semerdjian RJ, Rutecki GW.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by inflammatory serositis (fever, peritonitis, synovitis and pleuritis). The gene locus responsible for FMF was identified in 1992 and localized to the short arm of chromosome 16. In 1997, a specific FMF gene locus, MEFV, was discovered to encode for a protein, pyrin that mediates inflammation. To date, more than forty missense mutations are known to exist. The diversity of mutations identified has provided insight into the variability of clinical presentation and disease progression.

**CASE REPORT:** We report an individual heterozygous for the M680I gene mutation with a clinical diagnosis of FMF using the Tel-Hashomer criteria. Subsequently, the patient developed nephrotic syndrome with biopsy-confirmed fibrillary glomerulonephritis (FGN). Further diagnostic studies were unremarkable with clinical workup negative for amyloidosis or other secondary causes of nephrotic syndrome.

**DISCUSSION:** Individuals with FMF are at greater risk for developing nephrotic syndrome. The most serious etiology is amyloidosis (AA variant) with renal

involvement, ultimately progressing to end-stage renal disease. Other known renal diseases in the FMF population include IgA nephropathy, IgM nephropathy, Henoch-Schönlein purpura as well as polyarteritis nodosa.

CONCLUSION: To our knowledge, this is the first association between FMF and the M680I mutation later complicated by nephrotic syndrome and fibrillary glomerulonephritis.

DOI: 10.1186/1471-2369-4-6

PMCID: PMC194618

PMID: 12908875 [Indexed for MEDLINE]

4523. Arthritis Rheum. 2003 Aug;48(8):2386-8.

Tumor necrosis factor receptor-associated periodic syndrome characterized by a mutation affecting the cleavage site of the receptor: implications for pathogenesis.

Kriegel MA(1), Hüffmeier U, Scherb E, Scheidig C, Geiler T, Kalden JR, Reis A, Lorenz HM.

Author information:

(1)University of Erlangen-Nuremberg, Erlangen, Germany.

DOI: 10.1002/art.11169

PMID: 12905494 [Indexed for MEDLINE]

4524. Arthritis Rheum. 2003 Aug;48(8):2324-31.

Familial Mediterranean fever among patients from Karabakh and the diagnostic value of MEFV gene analysis in all classically affected populations.

Cazeneuve C(1), Hovannesyan Z, Geneviève D, Hayrapetyan H, Papin S, Girodon-Boulandet E, Boissier B, Feingold J, Atayan K, Sarkisian T, Amselem S.

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Comment in

Arthritis Rheum. 2004 Apr;50(4):1355; author reply 1355-6.

Arthritis Rheum. 2004 Apr;50(4):1354-5; author reply 1355-6.

**OBJECTIVE:** Familial Mediterranean fever (FMF) is an autosomal-recessive disorder that is common in Armenian, Turkish, Arab, and Sephardic Jewish populations. Its clinical diagnosis is one of exclusion, with the patients displaying nonspecific symptoms related to serosal inflammation. MEFV gene analysis has provided the first objective diagnostic criterion for FMF. However, in the absence of an identified mutation (NI/NI genotype), both the sensitivity of the molecular analyses and the involvement of the MEFV gene in FMF are called into question. The present study was designed to further evaluate the diagnostic value of MEFV analysis in another population of Mediterranean extraction.

**METHODS:** The MEFV gene was screened for mutations in 50 patients living in Karabakh (near Armenia) who fulfilled the established criteria for FMF. In addition, we analyzed published series of patients from the above-mentioned at-risk populations.

**RESULTS:** The mutation spectrum in Karabakhian patients, which consisted of only 6 mutations (with 26% of NI alleles), differed from that reported in Armenian patients. Strikingly, among patients from Karabakh and among all classically affected populations, the distribution of genotypes differed dramatically from Hardy-Weinberg equilibrium ( $P = 0.0016$  and  $P < 0.00001$ , respectively). These results, combined with other population genetics-based data, revealed the existence of an FMF-like condition that, depending on the patients' ancestry, was shown to affect 85-99% of those with the NI/NI genotype.

**CONCLUSION:** These data illuminate the meaning of negative results of MEFV analyses and show that in all populations evaluated, most patients with the NI/NI genotype had disease that mimicked FMF and was unrelated to the MEFV gene. Our findings also demonstrate the high sensitivity of a search for very few mutations in order to perform a molecular diagnosis of MEFV-related FMF.

DOI: 10.1002/art.11102

PMID: 12905488 [Indexed for MEDLINE]

4525. Am J Kidney Dis. 2003 Aug;42(2):370-5.

Long-term outcome of live donor kidney transplantation for renal amyloidosis.

Sherif AM(1), Refaie AF, Sobh MA, Mohamed NA, Sheashaa HA, Ghoneim MA.

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**BACKGROUND:** The short-term outcome of kidney transplantation in patients with amyloidosis has been reported. The aim of this study is to investigate long-term results in patients with renal amyloidosis.

**METHODS:** We studied results of renal transplantation in 23 amyloidotic transplant recipients compared with those in a control group of 47 nonamyloidotic patients. Amyloidosis was secondary to familial Mediterranean fever (FMF) in 16 patients, whereas it was primary (idiopathic) in 7 transplant recipients. The 2 groups were homogeneous regarding age, sex, HLA matching, immunosuppression, and duration of transplantation.

**RESULTS:** Five- and 10-year actuarial graft survival rates were similar in both groups (79.35% versus 84.04% and 65.92% versus 56.61%, respectively ). Five- and 10-year actuarial patient survival rates also were similar (80% versus 94% and 68% versus 87%, respectively). Moreover, 72.4% of controls experienced at least 1 rejection episode, whereas only 43.5% of amyloidotic transplant recipients experienced 1 or more such events ( $P = 0.02$ ). Nonetheless, mean serum creatinine concentrations did not differ between the 2 groups during the observation period. Maintenance colchicine therapy prevented the recurrence of both FMF symptoms and amyloidosis. Recurrence was documented in only 1 amyloidotic transplant recipient (4.3%) 10 years posttransplantation. Significant gastrointestinal (GI) problems were more frequent in amyloidotic patients (65% versus 38%;  $P = 0.03$ ). Amyloidotic patients with GI problems, except for 2 patients, were administered cyclosporine. Eleven of these patients had FMF, which appeared to reflect the effects of both cyclosporine and colchicine. Infections were similar in the groups; whereas amyloidotic patients had significantly lower blood pressures.

**CONCLUSION:** In our experience, long-term (5 to 10 years) outcome of live related donor kidney transplantation in patients with amyloidosis is similar to that in the general transplant population.

PMID: 12900821 [Indexed for MEDLINE]

4526. Allergol Immunopathol (Madr). 2003 Jul-Aug;31(4):236-9.

PFAPA syndrome: with regard to a case.

Hernández-Bou S(1), Giner M, Plaza AM, Sierra JI, Martín Mateos MA.

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**BACKGROUND:** PFAPA syndrome (Periodic Fever, Aphthas, Pharyngitis and cervical Adenopathies) is one of the causes of periodic fever in pediatrics and it is characterised by high fever, pharyngitis, cervical adenitis and aphthous stomatitis. Its etiopathogeny is unknown. The diagnosis is clinical and the findings of laboratory are unspecified. One or two doses (1 mg/kg) of oral prednisone are enough for a fast resolution of the clinic. It is a benign syndrome and no sequels have been noticed after its disappearance, usually in four years from its beginning.

**CLINICAL CASE:** We present the case of a 10-year-old patient who has been diagnosed of PFAPA syndrome after 3 years and a half of characteristic clinical bouts, with the fulfilment of diagnostic criteria and after having excluded other entities of similar presentation.

**CONCLUSIONS:** Periodic episodes of high fever, pharyngitis and cervical adenitis with a bad response to the conventional treatment should alert us to the PFAPA syndrome. The recognition of this entity will help us to improve the diagnostic and therapeutical focusing, lowering also the anxiety that these cases produce.

PMID: 12890417 [Indexed for MEDLINE]

4527. Rinsho Ketsueki. 2003 Jun;44(6):351-7.

[Pathophysiological aspects of neutrophils--dual action of neutrophils].

[Article in Japanese]

Sasada M.



PMID: 12884812 [Indexed for MEDLINE]

4528. *Pediatr Nephrol*. 2003 Oct;18(10):1005-8. Epub 2003 Jul 23.

Low serum apolipoprotein AI levels in amyloidosis related to familial Mediterranean fever.

Işlek I(1), Simşek T, Baskin E, Simşek B, Küçüködük S, Bedir A, Bakkaloğlu A, Beşbaş N, Topaloğlu R, Ozen S, Saatçi U.

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Amyloidosis (A) related to familial Mediterranean fever (FMF) causes serious morbidity and mortality in children. Our study evaluates serum levels of apolipoprotein (Apo) AI, AII, B, and E and Apo AII/AI ratios as a non-invasive diagnostic tool for amyloidosis in children with FMF and FMF-A. Results were compared with those of patients with childhood nephrotic syndrome (NS) and healthy children (controls). Significantly lower serum levels of Apo AI (90.20+/-28.30 mg/dl) were documented in patients with FMF-A than in all other groups (FMF 126.89+/-51.07 mg/dl, NS 140.38+/-33.73 mg/dl, and controls 134.67+/-12.73 mg/dl) (  $P<0.01$ ). Diagnostic sensitivity, specificity, and predictive value for this test were 85%, 80%, and 85%, respectively. Apo AII/AI ratio results were essentially equal in all groups (  $P>0.05$ ). It is concluded that a decreased Apo AI serum level, but not Apo AII/AI ratio, is a useful, non-invasive test for the early diagnosis of FMF-A in children.

DOI: 10.1007/s00467-003-1227-9

PMID: 12883976 [Indexed for MEDLINE]

4529. *Rheumatology (Oxford)*. 2003 Aug;42(8):1021-2.

Corneal wound healing in a patient treated with colchicine for familial Mediterranean Fever (FMF).

Leibovitch I, Alster Y, Lazar M, Langevitz P, Livneh A, Loewenstein A.

DOI: 10.1093/rheumatology/keg261

PMID: 12869680 [Indexed for MEDLINE]

4530. Kidney Int Suppl. 2003 Feb;(83):S111-4.

End-stage renal disease in North Africa.

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There are many similarities in the profile of chronic renal disease in the five North African countries, reflecting their close resemblance in ethnic background, bioecology and socioeconomic standards. The incidence of renal disease is much higher than that in the West, yet the prevalence is relatively lower, which mirrors the inadequacy of medical care facilities. The principal causes of end-stage chronic renal disease (ESRD) are interstitial nephritis (14 to 32%), often attributed to environmental pollution and inadvertent use of medications; glomerulonephritis (11 to 24%), mostly mesangioproliferative and focal segmental sclerosis; diabetes (5 to 20%) and nephrosclerosis (5 to 21%). Obstructive/reflux nephropathy, attributed to urinary schistosomiasis, is common in Egypt (7%), Libya and Southern Algeria. Primary urolithiasis is a frequent cause of obstructive nephropathy in the western (hyperoxaluria) and middle (cystinuria) regions. The incidence of tuberculosis is increasing, particularly the diffuse interstitial and hematogenous forms. It is responsible also for 10 to 40% of renal amyloidosis. The latter is also frequently associated with familial Mediterranean fever. Sickle cell anemia is an important health problem in the west, leading to a wide range of glomerular and tubulointerstitial nephropathies. Takayasu disease is increasingly recognized as a cause of ischemic nephropathy and renovascular hypertension. The management of ESRD is largely influenced by late referral, co-morbidities and lack of dialysis facilities. Hemodialysis is the most frequent modality of renal replacement therapy (RRT). CAPD is used sporadically. Renal transplantation, largely from live (often unrelated) donors, is offered to less than 5% of patients with ESRD. The reported outcome of RRT generally conforms with international standards.

DOI: 10.1046/j.1523-1755.63.s83.23.x  
PMID: 12864887 [Indexed for MEDLINE]

4531. Cell Mol Life Sci. 2003 Jun;60(6):1118-34.

Isoprenoid biosynthesis in hereditary periodic fever syndromes and inflammation.

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Mevalonate kinase (MK) is an essential enzyme in the isoprenoid biosynthesis pathway which produces numerous biomolecules (isoprenoids) involved in a variety of cellular processes. The indispensability of MK and isoprenoid biosynthesis for human health is demonstrated by the identification of its deficiency as the biochemical and molecular cause of the inherited autoinflammatory disorders mevalonic aciduria and hyperimmunoglobulinemia D and periodic fever syndrome. Since the discovery of the genetic defect, considerable progress has been made in understanding the molecular, biochemical and immunological basis of MK deficiency. Important questions such as which specific protein(s) and/or signaling pathway(s) are affected, however, remain unanswered. Resolving the complete pathophysiology of this disorder is a major challenge, but eventually will give insight into the in vivo role of MK and isoprenoid biosynthesis in inflammation and fever. This may open novel options for antiinflammatory therapies in general. Here, we give a general introduction on isoprenoid biosynthesis, the regulation thereof and deficiencies therein. We review the molecular, biochemical and immunological aspects of MK deficiency and discuss the relations between isoprenoid biosynthesis and inflammation. Finally, we compare MK deficiency with other autoinflammatory syndromes.

DOI: 10.1007/s00018-003-2296-4  
PMID: 12861380 [Indexed for MEDLINE]

4532. Ann Dermatol Venereol. 2003 May;130 Spec No 1:1S53-68.

[Systemic urticarias].

[Article in French]

Hachulla E(1).

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Systemic urticaria remains a challenge in terms of etiology, investigation and management. Most of cases are urticarial vasculitis consequence of inflammatory injury of capillaries and postcapillary venules in the skin. If hypocomplementemic urticarial vasculitis syndrome is a classical cause, the majority of patients have an underlying systemic disease like systemic lupus erythematosus, Sjögren's syndrome, mixed cryoglobulinemia, Still disease or cancer. Others systemic urticaria have been reported without clearly evidence of vasculitis like in primary or acquired angioedema, hereditary periodic fever syndromes and in some thyroiditis. Diagnosis needs a step to step procedure. Treatment depends the underlying disease. Some patients respond to nonsteroidal antiinflammatory drugs, some other need corticosteroids or immunosuppression. If urticarial vasculitis seems isolated in the absence of chronic obstructive pulmonary disease, antihistamines, nonsteroidal antiinflammatory drugs, colchicine, dapsone or hydroxychloroquine must be first used.

PMID: 12843810 [Indexed for MEDLINE]

4533. Dtsch Med Wochenschr. 2003 Jul 4;128(27):1479-82.

[Familial Mediterranean fever (familial paroxysmal polyserositis)].

[Article in German]

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**HISTORY AND ADMISSION FINDINGS:** A 48-year-old Iranian man had suffered since the age of 15 from repetitive periods of fever and abdominal pain, which had led to appendicectomy and cholecystectomy. He was admitted because of pain in the left chest and fever. He showed himself to be a personality fixed on his chronic pain. He reported pressure in the left chest and slight tenderness in the abdomen. His body temperature was about 38.5 degrees C axillary.

**INVESTIGATIONS:** All routine laboratory tests were normal except CRP (183 mg/l), microalbuminuria (20 mg/l) and amyloid A-protein in serum (865 mg/l). In an X-ray of the chest a small amount of fluid was seen on both sides. A gene test confirmed mutation of the Marenostin/Pyrin gene at chromosome 16.

**DIAGNOSIS, TREATMENT AND CLINICAL COURSE:** The diagnosis of familial Mediterranean fever was based on the typical clinical history, the ethnographical background and the result of the gene test. We initiated therapy with colchicine (3 x 0.5 mg/d) that resulted in rapid improvement of the symptoms and the patient has had no further pain.

**CONCLUSION:** Mediterranean fever should be considered in cases of repeated periods of abdominal or chest pain and fever in patients with typical ethnographical background. An early diagnosis and therapy may shorten the course of the disease and prevent unnecessary surgery, prolonged periods of hospitalization, a personality structure fixed on chronic pain, and the development of amyloidosis.

DOI: 10.1055/s-2003-40286

PMID: 12840771 [Indexed for MEDLINE]

4534. *Pediatr Nephrol.* 2003 Sep;18(9):853-9. Epub 2003 Jun 27.

Familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is the most frequent periodic syndrome characterized by recurrent attacks of polyserositis. Fever, abdominal pain, chest

pain, and arthritis/arthralgia are the leading symptoms. It is an autosomal recessive disorder, which primarily affects Jewish, Armenian, Turkish, and Arab populations. The FMF gene (MEFV) has recently been cloned to chromosome 16p, which encodes pyrin. Genotype-phenotype correlation is not well established. Amyloidosis is the most severe complication of FMF. The SAA1-alpha/alpha genotype was associated with an increased risk of amyloidosis. Colchicine treatment not only decreases the frequency and severity of attacks, but also prevents amyloidosis. Certain vasculitides, namely Henoch-Schonlein purpura and polyarteritis nodosa, are more frequent among FMF patients.

DOI: 10.1007/s00467-003-1185-2

PMID: 12836090 [Indexed for MEDLINE]

4535. Rheumatol Int. 2004 Jan;24(1):43-5. Epub 2003 Jun 27.

Familial Mediterranean fever and glomerulonephritis and review of the literature.

Akpolat T(1), Akpolat I, Karagoz F, Yilmaz E, Kandemir B, Ozen S.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent and self-limited attacks of fever usually accompanied by polyserositis. Amyloidosis is its most common renal complication. A number of reports have shown vasculitic diseases such as polyarteritis nodosa and Henoch-Schönlein purpura affecting the kidney in FMF. Here we present a patient with FMF and membranoproliferative glomerulonephritis and analyze the data published on these two entities.

DOI: 10.1007/s00296-003-0329-9

PMID: 12835915 [Indexed for MEDLINE]

4536. J Nephrol. 2003 May-Jun;16(3):431-4.

Familial Mediterranean fever (FMF) and renal AA amyloidosis--phenotype-genotype

correlation, treatment and prognosis.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease, which primarily affects the population surrounding the Mediterranean basin. It is characterized by recurrent attacks of fever and peritonitis, pleuritis, arthritis or erysipelas-like erythema. Amyloidosis, causing renal failure, is one of the most severe complications of the disease. The gene associated with FMF (MEFV) has been recently isolated. Phenotype-genotype correlation studies revealed that amyloidosis was more common in FMF patients originating from North-Africa who were homozygous for the M694V mutation. Such a correlation was not found in Turkish patients. The risk of amyloidosis is increased in male FMF patients and in patients bearing polymorphism a/a in the SAA1 gene. Colchicine is the chosen drug for the treatment of FMF and can prevent amyloidosis.

PMID: 12832747 [Indexed for MEDLINE]

4537. J Nephrol. 2003 May-Jun;16(3):427-30.

From renal amyloid deposits to the identification of the culprit genes.

Pirson Y(1).

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Hereditary amyloidoses with renal involvement are classified in two groups. The first group is a growing family of autoinflammatory disorders characterized by recurrent fever attacks. Amyloidosis is caused by the deposition of amyloid A (AA) protein, which is a degradation product of a normal serum acute-phase protein: serum amyloid A (SAA). The prototype is familial Mediterranean fever

(FMF). TNF Receptor Associated Periodic Syndrome (TRAPS) is a recently recognized periodic fever syndrome, differing from FMF in several characteristics: autosomal-dominant transmission, longer duration of attacks, and lack of response to colchicine prophylaxis. The second group comprises a variety of disorders, each characterized by the deposition of a specific mutant protein. The prototype is transthyretin amyloidosis (TTR). Identification of the form of amyloidosis has clinical implications. Therefore, in a patient with a history of recurrent fever attacks and AA amyloidosis, a diagnosis of FMF or TRAPS dictates appropriate genetic counseling and management. In patients with renal amyloidosis without a history of fever, identification of the mutant protein is therapeutically crucial; therefore, when the cell type that produces the precursor is (exclusively or mainly) the hepatocyte, a liver transplantation is to be considered.

PMID: 12832746 [Indexed for MEDLINE]

4538. Ned Tijdschr Geneesk. 2003 Jun 7;147(23):1097-100.

[Turkish children with recurrent abdominal pain and fever: familial Mediterranean fever].

[Article in Dutch]

Hulsmann AR(1), Hofstra WB, Brinkman JG, van der Wielen MJ, Bakker E, Oudesluys-Murphy AM.

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Comment in

Ned Tijdschr Geneesk. 2003 Aug 2;147(31):1530; author reply 1530.

Four children of Turkish origin, three boys aged 12, 8 and 7 years, and a girl aged 5 years, presented with clinical symptoms of familial Mediterranean fever. They had the characteristic episodes of fever combined with abdominal pain, thoracic pain, general malaise or arthralgia. Familial Mediterranean fever is an



autosomal recessive genetic disorder restricted to people originating from the Middle East. The causative gene (MEFV) and many missense mutations have been identified. The clinical syndrome is characterised by self-limiting febrile episodes accompanied by inflammation of the serous membranes, resulting in peritonitis, pleuritis or synovitis. In untreated patients systemic amyloidosis may develop, which manifests as renal insufficiency. The diagnosis is based on the characteristic medical history and is confirmed by DNA analysis. Meanwhile, treatment with colchicine can be started. This is effective in 90% of affected patients. Being aware of the prevalence of familial Mediterranean fever in immigrant populations can improve the quality of life and prevent long-term complications.

PMID: 12822516 [Indexed for MEDLINE]

4539. Arch Pediatr. 2003 Jan;10(1):45-53.

[TNF receptor-associated periodic syndrome (TRAPS): clinical aspects and physiopathology of a rare familial disease].

[Article in French]

Hentgen V(1), Reinert P.

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Hereditary periodic fever syndromes are defined as recurrent attacks of generalized inflammation for which no infectious or auto-immune cause can be identified. Minimal clinical variations, a unique biochemical-specific abnormality and the mode of genetic inheritance distinguish the four main diseases: familial Mediterranean fever, hyper-immunoglobulinemia D, TNF-receptor-associated periodic syndrome (TRAPS) and Muckle Wells syndrome. It presents with prolonged attacks of fever and severe localized inflammation. TRAPS is caused by dominantly inherited mutations in the gene encoding the first TNF receptor, which result in decreased serum levels of soluble TNF-receptor leading

to inflammation due to unopposed TNF-alpha action. Corticosteroid treatment is not completely effective in most TRAPS patients. Preliminary experiences with recombinant TNF-receptor analogues in the treatment appear be promising.

PMID: 12818781 [Indexed for MEDLINE]

4540. Arch Pediatr. 2003 Apr;10(4):379-84.

[Periodic fevers: from genetics to clinical medicine].

[Article in French]

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PMID: 12818769 [Indexed for MEDLINE]

4541. Blood. 2003 Jul 1;102(1):409.

Allogenic bone marrow transplantation: not a treatment yet for familial Mediterranean fever.

Touitou I, Ben-Chetrit E, Gershoni-Baruch R, Grateau G, Kastner DL, Kone-Paut I, Livneh A, Manna R, Mansour I, Ozdogan H, Ozen S, Sarkisian T, Tunca M, Yalcinkaya F.

Comment on

Blood. 2002 Aug 1;100(3):774-7.

DOI: 10.1182/blood-2003-04-1105

PMID: 12814918 [Indexed for MEDLINE]

4542. Rev Med Interne. 2003 Jun;24(6):407-10.

[Report of the Third International Conference on familial Mediterranean fever and hereditary inflammatory diseases. La Grand Motte, September 2002].

[Article in French]

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PMID: 12814833 [Indexed for MEDLINE]

4543. Am J Med Sci. 2003 Jun;325(6):363-4.

Acute vasculitis with multiorgan involvement in a patient with familial Mediterranean fever.

Braun E(1), Schapira D, Guralnik L, Azzam ZS.

Author information:

(1)Department of Internal Medicine, Rambam Medical Center and B. Rappaport Faculty of Medicine, Technion, Haifa, Israel.

We report a rare case of a patient with long-standing familial Mediterranean fever who presented with sudden onset of dyspnea, abdominal pain, and cutaneous manifestations. Chest CT and histologic preparations disclosed pulmonary hemorrhage and signs of systemic vasculitis. Cyclophosphamide and steroid therapy were initiated, with marked improvement. Based on this and 1 other case, we propose that systemic vasculitis should be included as a clinical manifestation of FMF.

4544. Phytomedicine. 2003 May;10(4):271-85.

Double-blind, placebo-controlled, randomized, pilot clinical trial of ImmunoGuard--a standardized fixed combination of *Andrographis paniculata* Nees, with *Eleutherococcus senticosus* Maxim, *Schizandra chinensis* Bail. and *Glycyrrhiza glabra* L. extracts in patients with Familial Mediterranean Fever.

Amaryan G(1), Astvatsatryan V, Gabrielyan E, Panossian A, Panosyan V, Wikman G.

Author information:

(1)Republican Children's FMF Center, Yerevan State Medical University, Yerevan, Armenia.

Double blind, randomized, placebo controlled pilot study of ImmunoGuard--a standardized fixed combination of *Andrographis paniculata* Nees., *Eleutherococcus senticosus* Maxim., *Schizandra chinensis* Bail., and *Glycyrrhiza glabra* L. special extracts standardized for the content of Andrographolide (4 mg/tablet), Eleuteroside E, Schisandrins and Glycyrrhizin, was carried out in two parallel groups of patients. The study was conducted in 24 (3-15 years of both genders) patients with Familial Mediterranean Fever (FMF), 14 were treated with tablets of series A (verum) and 10 patients received series B product (placebo). The study medication was taken three times of four tablets daily for 1 month. Daily dose of the andrographolide--48 mg. The primary outcome measures in physician's evaluation were related to duration, frequency and severity of attacks in FMF patients (attacks characteristics score). The patient's self-evaluation was based mainly on symptoms--abdominal, chest pains, temperature, arthritis, myalgia, erysipelas-like erythema. All of 3 features (duration, frequency, severity of attacks) showed significant improvement in the verum group as compared with the placebo. In both clinical and self evaluation the severity of attacks was found to show the most significant improvement in the verum group. Both the clinical and laboratory results of the present phase II (pilot) clinical study suggest that ImmunoGuard is a safe and efficacious herbal drug for the management of patients with FMF.

DOI: 10.1078/094471103322004767

PMID: 12809357 [Indexed for MEDLINE]

4545. Clin Exp Rheumatol. 2002 Jul-Aug;20(4 Suppl 26):S65-107.

Abstracts of the III International Conference on Familial Mediterranean Fever and Hereditary Inflammatory Disorders. Montpellier, France. September 2002.

[No authors listed]

PMID: 12803182 [Indexed for MEDLINE]

4546. Rev Prat. 2003 Apr 15;53(8):820-4.

[Familial Mediterranean fever].

[Article in French]

Societe Francaise de Genetique Humaine.

PMID: 12793162 [Indexed for MEDLINE]

4547. Eur J Obstet Gynecol Reprod Biol. 2003 Jun 10;108(2):171-6.

Familial Mediterranean fever and its implications for fertility and pregnancy.

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Familial Mediterranean fever (FMF) is a recessively inherited disease of episodic fever in combination with severe abdominal pain, pleurisy, arthritis or erysipelas-like skin rashes. The disease is mainly prevalent in Sephardic Jews, Armenians, Turks and Arabs. The gene responsible for FMF was cloned in 1997. The

gene expresses a protein called pyrin which is believed to play a role in the downregulation of mediators of inflammation. Several mutations have been identified of which the homozygous form of the M694V mutation is associated with a more severe expression of FMF. Prophylactic administration of colchicine is effective in relieving most patients from their attacks and preventing the development of amyloidosis, which usually leads to end-stage renal disease. Unfortunately, there is little awareness of the disease in gynaecological practice although a FMF full blown episode may mimic an acute abdominal calamity suggesting several possible gynaecological diagnoses. FMF is also associated with subfertility. In females, infertility was mainly related to oligomenorrhea although the causes remain unclear. In male FMF patients, progression of the disease may induce testicular impairment, consequently affecting spermatogenesis. Some controversy exists as to the adverse effects of colchicine on sperm production and function although the impression is that the occurrence of sperm pathology in FMF patients, using the recommended dosage of colchicine, is very low. In pregnant FMF patients, an increased occurrence of miscarriage has been found. However, the mechanisms involved remain unclear. Although colchicine is a mitotic inhibitor and transplacental crossing of colchicine has been demonstrated, no increased risk of foetal abnormalities in colchicine-treated pregnant FMF patients has been found. Therefore, amniocentesis should not be done for reassurance alone.

PMID: 12781406 [Indexed for MEDLINE]

4548. J Behav Med. 2003 Apr;26(2):95-104.

Psychosocial correlates of incidence of attacks in children with Familial Mediterranean Fever.

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Author information:

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This study tested the relationship between psychosocial factors and incidence of Familial Mediterranean Fever (FMF) attacks. Forty-five children with FMF were

studied retrospectively. Parents assessed their child's hostility, perceived-control, illness-behavior encouragement (IBE), family dysfunction, and reported number of attacks during the last 12 months. Hostility was positively correlated with number of attacks, especially in children below age 10 and in girls. Family dysfunction was positively correlated with attacks in girls and in children at or above age 10. IBE was inversely correlated with attacks in older children. In children below age 10, number of siblings was positively correlated with attacks, and negatively correlated with attacks in the older group. Psychosocial factors explained 27% of the variability in attacks, after controlling for age and number of siblings, with hostility remaining the only significant predictor of attacks. These findings, if replicated in a prospective study, may guide interventions for preventing FMF attacks.

PMID: 12776380 [Indexed for MEDLINE]

4549. Amyloid. 2003 Mar;10(1):12-6.

Serum amyloid A1 and tumor necrosis factor-alpha alleles in Turkish familial Mediterranean fever patients with and without amyloidosis.

Akar N(1), Hasipek M, Akar E, Ekim M, Yalçinkaya F, Cakar N.

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The major complication of familial Mediterranean fever (FMF) is AA amyloidosis. The influence of FMF gene (MEFV) mutations and/or unknown environmental factors and other genetic modifiers are likely to affect the phenotypic variations of the disease and the development of amyloidosis. Serum amyloid A is a serum precursor of AA amyloid that is induced by inflammatory cytokines including TNF-alpha. Our analysis of SAA1.1 frequency in Turkish FMF-amyloidosis patients, revealed a higher frequency compared to non FMF-amyloidosis patients but the difference was not significant. On the other hand, the distribution of SAA1.1 homozygosity among FMF-amyloidosis patients was 55.5% compared to FMF-non-amyloidosis patients (30.8%) which was statistically significant revealing a 2.5 fold risk for the occurrence of amyloidosis. There was no significant difference between the

controls and FMF patients with and without amyloidosis for the TNF-alpha-308 G-A allele. It is worth noting that all TNF-alpha-308 G-A carriers (n = 6) in FMF-amyloidosis group have SAA1.1 homozygosity compared to 2/11 in FMF-non-amyloidosis group. Further evaluation of these polymorphisms may have importance and need further study.

PMID: 12762136 [Indexed for MEDLINE]

4550. Eur J Neurol. 2003 May;10(3):327-8.

Central nervous system demyelination in familial Mediterranean fever: is it a coincidence?

Karabudak R, Dogulu CF, Nurlu G, Simsek H, Saatci I.

PMID: 12752411 [Indexed for MEDLINE]

4551. Eur J Pediatr. 2003 Jul;162(7-8):449-454. doi: 10.1007/s00431-003-1223-x. Epub 2003 May 16.

Familial mediterranean fever: revisiting an ancient disease.

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Familial Mediterranean fever (FMF) is an auto-inflammatory disease characterised by periodic attacks of fever and serositis. Recent genetic and epidemiological research have highlighted the importance of this disease. FMF is the most frequent periodic fever syndrome and is transmitted in an autosomal recessive fashion. The disease is caused by mutations in the gene on the short arm of chromosome 16, coding for the protein "pyrin". Pyrin is mainly expressed in neutrophils and monocytes and is among the proteins involved in the interleukin-1



inflammatory pathway. The recurrent attacks of fever are accompanied by severe abdominal pain, arthritis and/or chest pain along with a marked increase in acute phase reactants. Among these, serum amyloid A protein is especially important since it is the precursor of the amyloid A fibrils deposited in secondary renal amyloidosis. Renal amyloidosis has a grave prognosis. Differential diagnosis from other periodic fever syndromes is especially important in western European countries. Among these hyper IgD syndrome is common in Netherlands and the tumour necrosis factor receptor-associated periodic syndrome is especially common among Scottish and Irish families. Mutation analysis of the gene may be helpful in diagnosing FMF; however, if this is not possible, a trial of colchicine is a helpful diagnostic tool. The indications for life-long colchicine treatment should be discussed with the family. CONCLUSION: Familial mediterranean fever and other auto-inflammatory syndromes should be suspected in children with recurrent febrile attacks. Early diagnosis will save the child from unnecessary work-up and kidney involvement.

DOI: 10.1007/s00431-003-1223-x

PMID: 12751000 [Indexed for MEDLINE]

4552. Clin Exp Rheumatol. 2003 Mar-Apr;21(2):277.

Epithelial cell-derived neutrophil activator-78 levels in children with familial Mediterranean fever.

Baskin E, Saatci U, Ozen S.

PMID: 12747300 [Indexed for MEDLINE]

4553. Clin Exp Rheumatol. 2003 Mar-Apr;21(2):266; author reply 266.

Familial Mediterranean fever and Behçet's disease.

Livneh A.

Comment on

Clin Exp Rheumatol. 2002 Jul-Aug;20(4 Suppl 26):S1-2.

PMID: 12747289 [Indexed for MEDLINE]

4554. *Pediatr Pulmonol.* 2003 Jun;35(6):452-5.

Pulmonary manifestations and function tests in children genetically diagnosed with FMF.

Brik R(1), Gershoni-Baruch R, Shinawi M, Barak L, Bentur L.

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Familial Mediterranean fever (FMF) is characterized by recurrent episodes of peritonitis, pleuritis, and synovitis. Among the pulmonary manifestations of FMF, pleuritis is the most common. Long-term sequelae of the respiratory system have not been described in FMF patients. We describe the pulmonary manifestations and function tests in a group of children who were found by genetic screening to be homozygous for the FMF gene. We surveyed 48 patients of Mediterranean extraction (aged 6-18 years) who were evaluated for a variety of pulmonary symptoms, and in whom clinical and genetic studies confirmed a diagnosis of FMF. All patients underwent complete pulmonary function tests, which included spirometry, body plethysmography, and single-breath carbon monoxide diffusion (Dlco). Forty percent of the Jewish patients, but only 8% of the Arab patients ( $P < 0.001$ ), suffered from pulmonary manifestations during an attack of FMF. Jewish patients who were homozygotes for the M694V mutation suffered significantly more from episodes of pleuritis, cough, and rapid, shallow breathing than Arab patients, who were either homozygotes for the V726A mutation or bore any other combination of mutations. Three patients (6%) had mild restrictive lung disease, all of them homozygotes for the M694V mutation. In 3 further patients, obstructive lung impairment was found. Pulmonary manifestations during FMF attacks are significantly more common in the Jewish population bearing the M694V mutation. Restrictive lung impairment was found in a small number of these patients with a severe course of the disease; however, the series is too small to draw conclusions about long-term sequelae of the respiratory system in FMF patients.

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DOI: 10.1002/ppul.10270

PMID: 12746942 [Indexed for MEDLINE]

4555. Curr Rheumatol Rep. 2003 Jun;5(3):195-9.

Behçet's syndrome: an update.

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The pathogenic mechanisms in Behçet's syndrome are largely unknown. An autoantigen role for human leukocyte antigen B51 has been proposed. The reasons behind the thrombophilia are also not clear. Endothelial pathology could be the main culprit. The recently proposed association between familial Mediterranean fever and Behçet's syndrome might not be well founded. The long-term prognosis is more guarded among the young and among males. However, the disease burns out in many cases. Clinicians are getting better at management, and have better understanding of the old drugs, such as colchicine, and have new and potent drugs like tumor necrosis factor-alpha inhibitors.

PMID: 12744810 [Indexed for MEDLINE]

4556. Clin Rheumatol. 2003 May;22(2):99-101.

Serum sIL-2r, IL-6, IL-10 and TNF-alpha level in familial Mediterranean fever patients.

Baykal Y(1), Saglam K, Yilmaz MI, Taslipinar A, Akinci SB, Inal A.

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In this study we investigated cytokine levels in patients with familial Mediterranean fever (FMF). Twenty patients and 20 healthy controls were included. Ten patients had acute attacks of FMF, whereas the other 10 were in the silent period. Patients with the acute exacerbation of FMF had higher soluble interleukin-2 receptor (sIL-2r), interleukin-6 (IL-6), tumour necrosis factor-alpha, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and fibrinogen levels than those in the silent period (  $P<0.001$ ) and controls (  $P<0.001$ ). In patients with acute attacks of FMF, interleukin-10 (IL-10) levels were not significantly different from those in the other patients or the controls (  $P>0.05$ ). In FMF patients IL-6, TNF-alpha, sIL-2r, ESR, CRP and fibrinogen levels increased with the acute-phase reaction, especially in the attack period. On the other hand, anti-inflammatory cytokine IL-10 levels did not increase as much as did the inflammatory cytokines. The balance between the cytokines may help us to understand the pathophysiology of FMF and to develop therapies. We conclude that the levels of the acute-phase reactants and the cytokines could be useful for diagnosis of acute exacerbations, follow-up and treatment. However, the cost of cytokine measurement analyses seems disadvantageous at present.

DOI: 10.1007/s10067-002-0682-1

PMID: 12740672 [Indexed for MEDLINE]

4557. Obstet Gynecol. 2003 May;101(5 Pt 2):1098-100.

Familial Mediterranean fever presenting as recurrent acute pelvic inflammatory disease.

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**BACKGROUND:** Recurrent acute episodes of pelvic inflammatory disease (PID) often present a diagnostic dilemma. The differential diagnosis should include reinfection, appendicitis, endometriosis, irritable bowel syndrome, colitis,

persistent ovarian cyst, and antibiotic-resistant bacterial strains.

CASE: NA young Palestinian woman presented with recurrent episodes of pelvic pain with rebound tenderness, fever, and elevated white blood cell count, erythrocyte sedimentation rate, and C-reactive protein. The patient underwent extensive workup, multiple courses of intravenous and oral antibiotics, and diagnostic laparoscopies, with continued recurrent episodes. Treatment with colchicine for suspected familial Mediterranean fever resulted in resolution of symptoms.

CONCLUSION: In patients of Mediterranean ancestry who have symptoms of recurrent PID that are refractory to conventional treatment, familial Mediterranean fever should be included in the differential diagnosis.

PMID: 12738114 [Indexed for MEDLINE]

4558. Ann Otol Rhinol Laryngol. 2003 Apr;112(4):365-9.

Update on treatment of Marshall's syndrome (PFAPA syndrome): report of five cases with review of the literature.

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Marshall's syndrome or PFAPA (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis) syndrome is a recently described pediatric periodic disease characterized by recurrent febrile episodes associated with head and neck symptoms. The origin of this syndrome is unknown, and it can last for several years. During healthy periods, patients grow normally. The differential diagnosis includes other diseases characterized by periodic fevers, such as familial Mediterranean fever, familial Hibernian fever, hyperglobulinemia D syndrome, Behçet's disease, cyclic neutropenia, juvenile rheumatoid arthritis, and several infectious diseases. Many treatments have been used, with various results, including antibiotics, nonsteroidal anti-inflammatory drugs, acetylsalicylic acid, colchicine, antiviral medicines, steroids, cimetidine, and tonsillectomy. We describe 5 new patients affected by PFAPA syndrome who were observed at the Department of Pediatric Otorhinolaryngology, Spedali Civili, Brescia, Italy, from

November 2000 to August 2001. All children underwent physical examination, bacterial, fungal, and viral cultures, chest radiography, and several laboratory studies. The patients were treated by successful tonsillectomy, and after a mean follow-up of 10 months, no recurrence was observed. An analysis of the literature is also presented with particular emphasis on the differential diagnosis of this rare illness and the results of the different therapeutic options.

DOI: 10.1177/000348940311200412

PMID: 12731633 [Indexed for MEDLINE]

4559. Tumori. 2003 Jan-Feb;89(1):80-1.

Cisplatin treatment triggers familial Mediterranean fever attacks.

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A 42-year-old familial Mediterranean fever (FMF) patient who was treated with cisplatin-based chemotherapy for adenocarcinoma of the lung developed severe and frequent attacks of FMF during treatment. Abdominal pain, arthralgia and fever occurred for a few days following each cisplatin cycle. His FMF worsened, the abdominal pain and fever lasted longer and treatment with colchicine was ineffective. It has been hypothesized that the link between cisplatin treatment and FMF attacks lies in an increased production of serotonin, IL-6, IL-1, IL-8 and TNF-alpha. These inflammatory cytokines have been reported to be overproduced during cisplatin treatment and are known to play an important role in FMF relapse. The oncologist should be made aware of the possibility of disease aggravation in FMF patients during cisplatin-based chemotherapy.

PMID: 12729367 [Indexed for MEDLINE]

4560. Genes Immun. 2003 Apr;4(3):197-203.

Common mutations in the familial Mediterranean fever gene associate with rapid

progression to disability in non-Ashkenazi Jewish multiple sclerosis patients.

Shinar Y(1), Livneh A, Villa Y, Pinhasov A, Zeitoun I, Kogan A, Achiron A.

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Ancient founder mutations in the Mediterranean fever gene, MEFV, are associated with familial Mediterranean fever, a recessive, episodic, inflammatory disease. Since these mutations are reported to express with above normal levels of acute phase reactants in healthy heterozygotes we postulated that the heterozygous phenotype could aggravate the clinical expression of ongoing autoimmune diseases. This study evaluated progression to disability in relapsing-remitting multiple sclerosis (RR-MS) patients of non-Ashkenazi and Ashkenazi origin carrying an MEFV mutation, particularly the detrimental M694V, using the expanded disability status scale (EDSS). In the non-Ashkenazi patients group (n=48), carriers (n=17) presented with a two-fold higher fraction which reached EDSS=3.0 and 6.0 compared to noncarriers (n=31) despite a comparable mean of MS duration. The median time to reach EDSS=3.0 was 2 years in the carriers vs 10 years in noncarriers (P=0.007); The median time to reach EDSS=6.0 was 6 years vs 23 years, respectively (P=0.003). M694V heterozygous patients reached both EDSS milestones earlier than other patients. Progression to disability was not enhanced in Ashkenazi RR-MS carriers (n=12, noncarriers n=59). In conclusion, non-Ashkenazi MS patients carrying one mutated MEFV gene, particularly M694V, expressed rapid progression to disability. The expressed mutation may increase inflammatory damage inflicted by autoimmune responses.

DOI: 10.1038/sj.gene.6363967

PMID: 12700594 [Indexed for MEDLINE]

4561. *Pediatr Nephrol.* 2003 Jun;18(6):521-6. Epub 2003 Apr 16.

Efficacy of colchicine therapy in amyloid nephropathy of familial Mediterranean fever.

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Comment in

Pediatr Nephrol. 2003 Dec;18(12):1311-2.

The aim of this study was to investigate the effect of colchicine therapy on the outcome of amyloid nephropathy of familial Mediterranean fever (FMF) in childhood. The diagnosis of amyloidosis type AA was confirmed by renal biopsy in 38 patients. During a mean follow-up period of 30.5 months (range 6-88 months), the patients received colchicine therapy. While 24 of these patients were compliant with the treatment, 14 patients remained non-compliant. Of the 24 compliant patients, 19 had normal renal function at the onset; in 13 the proteinuria improved, in 5 patients it remained stable, and in 1 patient it deteriorated from a proteinuric to nephrotic stage. Partial resolution of amyloidosis was demonstrated by repeat renal biopsy in 1 patient who showed complete resolution of proteinuria. In contrast, none of 14 non-compliant patients improved, and while only 1 patient was in renal failure initially, 10 patients deteriorated to renal failure during the follow-up period. The presence of tubulointerstitial injury at presentation adversely affected the prognosis. In conclusion, when used appropriately, colchicine can improve proteinuria and prevent chronic renal failure in patients with amyloid nephropathy of FMF. The presence of renal failure or tubulointerstitial injury at presentation and non-compliance with therapy are the factors decreasing the success of therapy.

DOI: 10.1007/s00467-003-1129-x

PMID: 12698329 [Indexed for MEDLINE]

4562. Ann Rheum Dis. 2003 May;62(5):479-81.

Familial Mediterranean fever associated pyrin mutations in Greece.

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**OBJECTIVE:** To search for pyrin mutations associated with familial Mediterranean fever (FMF) in Greece.

**PATIENTS AND METHODS:** 62 patients fulfilling the Tel Hashomer diagnostic criteria for definite (33) or probable (29) FMF diagnosis were studied. Eight point mutations of pyrin gene were tested by standard methods. Of the 62 patients tested, 48 were Greek, four were Jewish, seven were Armenian, and three were Arab.

**RESULTS:** 42 patients were found to be homozygotes for pyrin mutations; 11 patients were found to carry only one of the tested mutations; in nine patients no mutations were detected.

**CONCLUSION:** Molecular detection of pyrin gene mutations seems useful in confirming suspected cases, and in detecting asymptomatic cases, of Mediterranean fever in Greece. It may also be used as a screening tool within affected families.

PMCID: PMC1754548

PMID: 12695165 [Indexed for MEDLINE]

4563. Eur J Pediatr. 2003 May;162(5):305-8. Epub 2003 Mar 4.

Urinary glycosaminoglycans in the course of familial Mediterranean fever.

Baskin E(1), Saatçi U, Ciliv G, Bakkaloglu A, Besbas N, Topaloglu R, Ozen S.

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Familial Mediterranean fever (FMF) is characterised by recurrent fever and serositis. The most important complication of the disease is amyloidosis. Cheap and non-invasive methods would be important in predicting or establishing the early diagnosis of amyloidosis. For this purpose, we studied the role of urinary glycosaminoglycans (GAG). The study group included 123 FMF patients without an attack and 11 patients with FMF associated amyloidosis. Ten healthy children and ten patients with primary nephrotic syndrome served as controls. In patients with

amyloidosis, urinary GAG were lower than in patients with FMF, patients with nephrotic syndrome and controls (median and range: 8.54 mg hexuronic acid/g creatinine (1.87-25.5), 5.8 (1.7-17.26), 23.12 (8.74-28.06) and 19.25 (14.2-26.9) respectively,  $P < 0.01$ ). There was a significant negative correlation between the duration of the disease and urinary GAG ( $r = -0.43$ ,  $P = 0.002$ ). In 49 FMF patients with a low GAG, urinary GAG increased significantly after an increase in the colchicine dose (median and range: 6.64 mg hexuronic acid/g creatinine (1.77-19.39) and 9.45 mg hexuronic acid/g creatinine (2.36-28.9),  $P < 0.01$ ). **CONCLUSION:** These results suggest that urinary glycosaminoglycan levels may be a predictor of amyloidosis in patients with familial Mediterranean fever. We also suggest that effective colchicine doses may be monitored by following urinary glycosaminoglycan excretion.

DOI: 10.1007/s00431-003-1173-3

PMID: 12692710 [Indexed for MEDLINE]

4564. Arthritis Rheum. 2003 Apr;48(4):1149-55.

The contribution of genotypes at the MEFV and SAA1 loci to amyloidosis and disease severity in patients with familial Mediterranean fever.

Gershoni-Baruch R(1), Brik R, Zacks N, Shinawi M, Lidar M, Livneh A.

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**OBJECTIVE:** The clinical profile in familial Mediterranean fever (FMF), including its major manifestation, amyloidosis, is influenced by MEFV allelic heterogeneity and other genetic and/or environmental factors. In this study, we analyzed the contribution of genotypes at the MEFV and SAA1 loci to disease severity and to the development of amyloidosis, and further defined the factors affecting the clinical profile of FMF.

**METHODS:** We investigated a sample of 277 FMF patients (154 men and 123 women), including 62 patients with nephropathic amyloidosis, in whom both FMF alleles had been identified. A detailed chart review, interview, and physical examination were undertaken to determine the patients' demographic characteristics, medical history, clinical manifestations, and treatment. The disease severity score was calculated from the Tel-Hashomer key. Genotypes at the SAA1 locus (isoforms

alpha, beta, and gamma) were determined in all patients. The SAA1 13C/T polymorphism of the SAA1 promotor was analyzed in a subset of cases.

RESULTS: The male:female ratio (154:123, or 1.3) was higher among patients with amyloidosis (40:22, or 1.8) compared with patients without amyloidosis (114:101, or 1.1). Logistic regression analysis showed that homozygosity for the M694V allele (odds ratio [OR] 4.27, 95% confidence interval [95% CI] 2.01-9.07), the presence of the SAAalpha/alpha genotype (OR 2.99, 95% CI 1.47-6.09), the occurrence of arthritis attacks (OR 2.43, 95% CI 1.17-5.06), and male sex (OR 1.73, 95% CI 0.90-3.33) were significantly and independently associated with renal amyloidosis. Disease severity was mainly influenced by MEFV mutations and was not associated with genotypes at the SAA1 locus. The SAA1 13T allele was rare, being associated mainly with the SAA gamma isoform, and not related to renal amyloidosis.

CONCLUSION: Overall, disease severity and the development of amyloidosis in FMF are differentially affected by genetic variations within and outside the MEFV gene.

DOI: 10.1002/art.10944

PMID: 12687559 [Indexed for MEDLINE]

4565. Isr Med Assoc J. 2003 Feb;5(2):148-50.

Third International Conference on Familial Mediterranean Fever and Other Hereditary Inflammatory Disorders.

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(1)Heller Institute of Medical Research, Sheba Medical Center, Tel Hashomer, Israel. pninala@sheba.health.gov.il

PMID: 12674673 [Indexed for MEDLINE]

4566. Mol Cell. 2003 Mar;11(3):591-604.

Targeted disruption of pyrin, the FMF protein, causes heightened sensitivity to

endotoxin and a defect in macrophage apoptosis.

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Familial Mediterranean fever (FMF) is an inherited disorder characterized by recurrent episodes of fever and inflammation. Most patients with FMF carry missense mutations in the C-terminal half of the pyrin protein. To study the physiologic role of pyrin, we generated mice expressing a truncated pyrin molecule that, similar to FMF patients, retains the full PYRIN domain. Bacterial lipopolysaccharide (LPS) induces accentuated body temperatures and increased lethality in homozygous mutant mice. When stimulated, macrophages from these mice produce increased amounts of activated caspase-1 and, consequently, elevated levels of mature IL-1beta. Full-length pyrin competes in vitro with caspase-1 for binding to ASC, a known caspase-1 activator. Apoptosis is impaired in macrophages from pyrin-truncation mice through an IL-1-independent pathway. These data support a critical role for pyrin in the innate immune response, possibly by acting on ASC, and suggest a biologic basis for the selection of hypomorphic pyrin variants in man.

PMID: 12667444 [Indexed for MEDLINE]

4567. Cornea. 2003 Apr;22(3):191-3.

Colchicine in tear fluid of treated patients with familial Mediterranean fever.

Leibovitch I(1), Alster Y, Scherrmann JM, Azmon B, Barequet IS, Livneh A, O'Brien TP, Lazar M, Loewenstein A.

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**PURPOSE:** The study aimed to determine whether detectable concentrations of colchicine are present in the tear fluid of treated patients with familial Mediterranean fever (FMF) and thus demonstrate a possible route by which colchicine reaches the corneal surface.

**METHODS:** Tear fluid samples (50-100 microL) were collected from eight FMF patients on long-term colchicine treatment. Colchicine tear fluid concentrations were determined in all patients by radioimmunoassay using goat anticolchicine antibodies and [3H]colchicine (Dupont, Wilmington, DE).

**RESULTS:** Detectable concentrations of colchicine, with no apparent effect on the ocular surface, were found in all tear fluid samples (median, 0.46 ng/mL; range, 0.24-1.05 ng/mL).

**CONCLUSIONS:** This study provides evidence of the route by which colchicine, given systemically, reaches the corneal surface and thus gives credence to the possible inhibitory effect of this drug on corneal wound healing in the cases described in the literature.

PMID: 12658080 [Indexed for MEDLINE]

4568. Am J Gastroenterol. 2003 Mar;98(3):701.

Familial Mediterranean fever mimicking Fitz-Hugh-Curtis syndrome.

Romero-Gómez M, Corpas R, Sánchez-Muñoz D, Grande L, Caballero V.

PMID: 12650817 [Indexed for MEDLINE]

4569. Biochem Biophys Res Commun. 2003 Mar 28;303(1):69-73.

ASC is an activating adaptor for NF-kappa B and caspase-8-dependent apoptosis.

Masumoto J(1), Dowds TA, Schaner P, Chen FF, Ogura Y, Li M, Zhu L, Katsuyama T, Sagara J, Taniguchi S, Gumucio DL, Núñez G, Inohara N.

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ASC is a pro-apoptotic protein containing a pyrin domain (PD) and a caspase-recruitment domain (CARD). A previous study suggests that ASC interacts with Ipaf, a member of the Apaf-1/Nod1 protein family. However, the functional relevance of the interaction has not been determined. Here, we report that co-expression of ASC with Ipaf or oligomerization of ASC induces both apoptosis and NF-kappa B activation. Apoptosis induced through ASC was inhibited by a mutant form of Caspase-8 but not by that of Caspase-1. The PD of ASC physically interacted with Caspase-8 as well as with pyrin, the familial Mediterranean fever gene product. Caspase-8 deficiency rescued mouse fibroblasts from apoptosis induced by ASC oligomerization. Pyrin disrupted the interaction between ASC and Caspase-8, and inhibited both apoptosis and NF-kappa B activation induced by ASC. These findings suggest that ASC is a mediator of NF-kappa B activation and Caspase-8-dependent apoptosis in an Ipaf signaling pathway.

PMID: 12646168 [Indexed for MEDLINE]

4570. Eur J Hum Genet. 2003 Feb;11(2):196-200.

Carrier frequency of the V377I (1129G>A) MVK mutation, associated with Hyper-IgD and periodic fever syndrome, in the Netherlands.

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Hyper-IgD and periodic fever syndrome (HIDS) and mevalonic aciduria (MA) are two autosomal recessive disorders that both are caused by a deficient activity of the enzyme mevalonate kinase (MK) due to mutations in the encoding gene (MVK). The most frequently occurring MVK mutation, V377I (1129G>A), has been identified exclusively in HIDS patients. Other common mutations have been associated with both HIDS and MA. To estimate the incidence of MK deficiency in the Netherlands, we determined the carrier frequency of the V377I mutation in genomic DNA

extracted from anonymised newborn screening cards by PCR-RFLP. We found 14 carriers among 2138 analysed samples (1 : 153). Based on the V377I allele frequency of 42% in patients diagnosed with MK deficiency, the carrier frequency of any MVK mutation in the Dutch population can be calculated as 1 : 65. This predicts a disease incidence between 1 in 5196 and 1 in 53 656, which is far more than actually observed. Although under-diagnosis of patients with MK deficiency remains possible, this discrepancy probably is due to a reduced penetrance of V377I homozygosity. Analysis of the distribution of the V377I allele within patients carrying MVK mutations revealed that this was not according to the Hardy-Weinberg equilibrium principle, most probably due to an under-representation of V377I homozygotes in HIDS. Homozygotes for V377I might exhibit a much milder phenotype of MK deficiency or no disease-phenotype at all.

DOI: 10.1038/sj.ejhg.5200933

PMID: 12634869 [Indexed for MEDLINE]

4571. FEBS Lett. 2003 Mar 13;538(1-3):173-7.

Identification of mammalian orthologs associates PYPAF5 with distinct functional roles.

Albrecht M(1), Domingues FS, Schreiber S, Lengauer T.

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PYRIN- and CARD-containing proteins belong to a recently identified protein family involved in the regulation of apoptosis and inflammatory processes. Variations in the gene products of the family members PYPAF1 and NOD2/CARD15 have been associated with several autoinflammatory diseases. We could identify the mouse orthologs of PYPAF1, PYPAF5, NOD1, NOD2 and the rat ortholog of PYPAF5. Intriguingly, we found that PYPAF5 has been reported previously not only as regulator of NF-kappaB and caspase-1, but also as angiotensin II and vasopressin receptor. In particular, based on a comprehensive sequence analysis, we propose a structural model for this hormone receptor that is different from the model suggested previously.

PMID: 12633874 [Indexed for MEDLINE]

4572. *Pediatr Nephrol*. 2003 Feb;18(2):196-7.

A note on mutation analysis in familial Mediterranean fever.

Akar N, Akar E, Ozel D, Tekin M, Ekim M, Yalçinkaya F.

PMID: 12632594 [Indexed for MEDLINE]

4573. *Biochem Biophys Res Commun*. 2003 Mar 14;302(3):575-80.

Regulation of cryopyrin/Pypaf1 signaling by pyrin, the familial Mediterranean fever gene product.

Dowds TA(1), Masumoto J, Chen FF, Ogura Y, Inohara N, Núñez G.

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Cryopyrin, a member of the Nod protein family mutated in familial cold urticaria and Muckle-Wells syndrome, has been recently implicated in inflammation. However, the mechanism of activation and regulation of the cryopyrin signaling pathway remains poorly understood. We report here that co-expression of cryopyrin with its binding partner, ASC, induced both apoptosis and NF-kappaB activation. This signaling was mimicked by oligomerization of ASC, suggesting that cryopyrin activates downstream targets as reported for other Nod family members. Notably, pyrin, the product of the familial Mediterranean fever gene, inhibited cryopyrin-mediated apoptosis and NF-kappaB activation by disrupting the cryopyrin-ASC interaction. These results provide evidence for a cryopyrin signaling pathway activated through the induced proximity of ASC, which is negatively regulated by pyrin.



PMID: 12615073 [Indexed for MEDLINE]

4574. Rheumatol Int. 2003 Jan;23(1):41-3.

Seronegative spondyloarthropathy of familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is characterized by an autosomal inheritance pattern, Mediterranean ancestry, and history of recurrent fever. We present a 30-year-old Turkish man with FMF and accompanying seronegative spondyloarthropathy. His diagnose depended on the clinical course of his disease: recurrent fever accompanied by abdominal pain attacks together with a positive family history and his ethnic origin and sacroiliitis. We review the common manifestations of FMF and remind physicians that sacroiliac joint involvement must be kept in mind in presence of articular symptoms in a FMF patient.

PMID: 12611376 [Indexed for MEDLINE]

4575. Presse Med. 2003 Jan 11;32(1):24-6.

[The association of polyarteritis nodosa and familial Mediterranean fever].

[Article in French]

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INTRODUCTION: Some necrotizing vasculitis may be associated with familial Mediterranean fever (FMF). We report a new case of polyarteritis nodosa (PAN) that preceded the diagnosis of FMF.

**OBSERVATION:** A young woman of Turkish origin had a long childhood history of inflammatory arthralgia and myalgia, leading to the provisional diagnosis of chronic juvenile arthritis, then, after a confirmative muscle biopsy, to the diagnosis of PAN, whose outcome remained benign. At the age of 19, she was diagnosed as having FMF on clinical and genetic grounds, and colchicine led to the regression of most symptoms.

**DISCUSSION:** As with Henoch-Schönlein's purpura, PAN seems significantly associated with FMF. Its characteristics are a younger age at onset, more frequent peri-renal hematoma, overlap between classical PAN and micropolyangeitis, and overall better prognosis. In its muscular form, PAN is difficult to distinguish from protracted febrile myalgia, a recently described manifestation of FMF, in which pathological findings are poorly documented.

PMID: 12610392 [Indexed for MEDLINE]

4576. Ann Allergy Asthma Immunol. 2003 Feb;90(2):233-7.

A large kindred with familial cold autoinflammatory syndrome.

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**BACKGROUND:** Familial cold autoinflammatory syndrome (FCAS), formerly known as familial cold urticaria, is a rare condition characterized by fever, rash, and arthralgias elicited by exposure to cold. Recently, mutations responsible for FCAS were identified in a novel gene (CIAS1), making it possible to confirm the diagnosis in most patients.

**OBJECTIVE:** We present a summary of clinical data from a large family with FCAS to further define the characteristics of the disorder and to validate previously proposed clinical criteria.

**METHODS:** A total of 73 participants were evaluated by interview and questionnaire, including 36 affected individuals. Responses from the questionnaire were analyzed and comparisons of proportions were made using the Z test. DNA was isolated and genotyping was performed on all subjects. Affected

haplotypes (genotype patterns) were identified and used to confirm the diagnosis. Sequencing of the CIAS1 gene was performed in selected patients to confirm the mutation.

RESULTS: The prevalence of rash, fever/chills, joint complaints, nausea, headache, and thirst were not significantly different from previously reported proportions. There was statistically significant differences in conjunctivitis, sweating, and drowsiness with  $\alpha = 0.01$ . The mean temperature required to produce symptoms was 22 degrees C, and the average earliest onset of symptoms after exposure was 1.5 hours.

CONCLUSIONS: Applying the proposed clinical criteria, 41% of affected subjects met all six criteria, 90% met five criteria, and 100% met four criteria for FCAS. None of the unaffected subjects met more than two criteria. Using a threshold of 4 of 6 clinical criteria, the data support the diagnostic validity of the proposed clinical criteria.

DOI: 10.1016/S1081-1206(10)62147-3

PMID: 12602672 [Indexed for MEDLINE]

4577. South Med J. 2002 Dec;95(12):1400-3.

Familial Mediterranean fever.

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(1)Department of Nephrology, Ataturk University School of Medicine, Erzurum, Turkey.

BACKGROUND: The pathogenesis of familial Mediterranean fever (FMF) is unknown, and since no specific laboratory test is yet available, the diagnosis of FMF remains clinical. The purpose of this study was to review clinical characteristics of patients with FMF.

METHODS: A total of 96 patients with FMF were evaluated either retrospectively (for those diagnosed before 1997) or prospectively (for those after 1997).

RESULTS: The records of 54 male and 42 female patients were studied. All patients were Turks. Family history was positive in 72 patients (75%). Involved site was peritoneum in 73 (76%), joints in 65 (68%), and pleura in 16 (17%). Febrile myalgia occurred in 3 patients (3%), and erysipelas-like skin lesions were

observed in 2 (2%). Fever was found in 93 patients (97%). Reactive systemic (AA) amyloidosis was found in 38 patients (40%).

CONCLUSIONS: Diagnostic problems persist despite increased understanding of the pathogenesis of FMF. Amyloidosis, the most important complication of FMF, is often seen.

PMID: 12597306 [Indexed for MEDLINE]

4578. Rheumatology (Oxford). 2003 Feb;42(2):235-9.

Prospective study of anti-tumour necrosis factor receptor superfamily 1B fusion protein, and case study of anti-tumour necrosis factor receptor superfamily 1A fusion protein, in tumour necrosis factor receptor associated periodic syndrome (TRAPS): clinical and laboratory findings in a series of seven patients.

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Erratum in

Rheumatology (Oxford). 2003 May;42(5):711.

OBJECTIVE: To assess the effects prospectively of tumour necrosis factor (TNF) receptor superfamily (TNFRSF) fusion proteins TNFRSF1B (etanercept) and TNFRSF1A (p55TNFr-Ig) in patients with TNF receptor associated periodic syndrome (TRAPS).

METHODS: Seven patients with a clinical and genetic diagnosis of TRAPS received subcutaneous etanercept for 24 weeks. One of these patients had previously received an intravenous infusion of p55TNFr-Ig. Therapeutic response was assessed by comparing corticosteroid requirement, acute-phase response and an established scoring system over 20 weeks, both on and off etanercept.

RESULTS: Etanercept was well tolerated. The five corticosteroid-responsive patients required significantly less corticosteroids and demonstrated reductions in acute-phase reactants on etanercept. The two patients not requiring corticosteroids had small reductions in disease activity scores. The effect of p55TNFr-Ig in a single patient with TRAPS remains unclear.

CONCLUSIONS: Etanercept does not abolish inflammatory attacks but improves disease activity allowing corticosteroid reduction. Etanercept may be clinically useful in replacing or reducing steroid requirements in the treatment of TRAPS. A formal trial of etanercept to establish its role in clinical management is indicated.

PMID: 12595616 [Indexed for MEDLINE]

4579. Br J Radiol. 2003 Jan;76(901):22-5.

CT findings in patients with familial Mediterranean fever during an acute abdominal attack.

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The aim of this study is to present the abdominal CT findings of patients with familial Mediterranean fever (FMF) examined during an acute abdominal attack. CT scans of 17 patients (10 women and 7 men; age range 11-45 years) were retrospectively reviewed. Attention was directed to mesenteric or peritoneal abnormalities and to the presence of appendiceal pathology. Patients were divided into two groups; group A (n=14) consisted of patients with an acute abdominal attack caused by FMF, and group B (n=3) consisted of patients whose attack proved to be owing to a separate pathology requiring surgery. Characteristic CT findings of acute abdomen in FMF included mesenteric pathology (n=12), mainly of engorged vessels with thickened mesenteric folds, mesenteric lymphadenopathy (n=6) and ascites (n=6). Signs of focal peritonitis were found in four patients.

Radiologists should be familiar with such CT findings of peritoneal irritation in patients with FMF during an acute attack, and may suggest this clinical diagnosis in the proper clinical setting in a patient who has not been previously diagnosed. Alternatively, the radiologist should be aware of the possibility of a concurrent acute appendicitis or other acute abdominal pathology in patients with known FMF and should search for it.

DOI: 10.1259/bjr/32051823

PMID: 12595321 [Indexed for MEDLINE]

4580. QJM. 2003 Feb;96(2):133-42.

The head-up tilt test with haemodynamic instability score in diagnosing chronic fatigue syndrome.

Naschitz JE(1), Rosner I, Rozenbaum M, Naschitz S, Musafia-Priselac R, Shaviv N, Fields M, Isseroff H, Zuckerman E, Yeshurun D, Sabo E.

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Comment in

QJM. 2003 May;96(5):379-80.

QJM. 2003 Jun;96(6):454.

**BACKGROUND:** Studying patients with chronic fatigue syndrome (CFS), we have developed a method that uses a head-up tilt test (HUTT) to estimate BP and HR instability during tilt, expressed as a 'haemodynamic instability score' (HIS).

**AIM:** To assess HIS sensitivity and specificity in the diagnosis of CFS.

**DESIGN:** Prospective controlled study.

**METHODS:** Patients with CFS (n=40), non-CFS chronic fatigue (n=73), fibromyalgia (n=41), neurally mediated syncope (n=58), generalized anxiety disorder (n=28), familial Mediterranean fever (n=50), arterial hypertension (n=28), and healthy subjects (n=59) were evaluated with a standardized head-up tilt test (HUTT). The HIS was calculated from blood pressure (BP) and heart rate (HR) changes during the HUTT.

**RESULTS:** The tilt was prematurely terminated in 22% of CFS patients when postural symptoms occurred and the HIS could not be calculated. In the remainder, the median(IQR) HIS values were: CFS +2.14(4.67), non-CFS fatigue -3.98(5.35), fibromyalgia -2.81(2.62), syncope -3.7(4.36), generalized anxiety disorder -0.21(6.05), healthy controls -2.66(3.14), FMF -5.09(6.41), hypertensives -5.35(2.74) (p<0.0001 vs. CFS in all groups, except for anxiety disorder, p=NS). The sensitivity for CFS at HIS >-0.98 cut-off was 90.3% and the overall specificity was 84.5%.

DISCUSSION: There is a particular dysautonomia in CFS that differs from dysautonomia in other disorders, characterized by HIS >-0.98. The HIS can reinforce the clinician's diagnosis by providing objective criteria for the assessment of CFS, which until now, could only be subjectively inferred.

PMID: 12589011 [Indexed for MEDLINE]

4581. Am J Med. 2003 Feb 1;114(2):148-52.

A founder effect in the hyperimmunoglobulinemia D and periodic fever syndrome.

Simon A(1), Mariman EC, van der Meer JW, Drenth JP.

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PMID: 12586237 [Indexed for MEDLINE]

4582. J Pediatr. 2003 Feb;142(2):191-3.

A new mutation causing autosomal dominant periodic fever syndrome in a Danish family.

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Comment in

J Pediatr. 2003 Feb;142(2):99-101.

We describe four members in a family of 8 individuals over 3 generations with the autosomal dominant inherited periodic fever syndrome tumor necrosis factor receptor-associated periodic syndrome (TRAPS). The patients had recurrent

episodes of fever, abdominal pain, arthritis, and rash. We examined the gene coding for the tumor necrosis factor receptor TNFRSF1A in all first-degree family members. In all 4 symptomatic members of the family, a hitherto undescribed mutation C98Y (380G-->A) in the TNFRSF1A gene was identified. In contrast, this mutation was not found in the 4 family members reported to be healthy nor in 50 normal control patients. The youngest member of the family, a 2-year-old boy, was treated successfully with etanercept.

DOI: 10.1067/mpd.2003.15

PMID: 12584543 [Indexed for MEDLINE]

4583. J Pediatr. 2003 Feb;142(2):99-101.

The revolution in molecular biology leads to new understanding of the clinical expression of immunodeficiencies.

John CC, Schreiber JR.

Comment on

J Pediatr. 2003 Feb;142(2):191-3.

J Pediatr. 2003 Feb;142(2):194-6.

DOI: 10.1067/mpd.2003.104

PMID: 12584526 [Indexed for MEDLINE]

4584. J Rheumatol. 2003 Feb;30(2):313-5.

Increased soluble FAS suggests delayed apoptosis in familial Mediterranean fever complicated with amyloidosis.

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**OBJECTIVE:** Interactions of the FAS with FAS ligand have been proposed as a major regulatory mechanism of immune homeostasis. Soluble FAS (sFAS) acts as a competitive antagonist to FAS, thereby inhibiting FAS mediated apoptosis. sFAS concentrations have been studied in various autoimmune diseases, with controversial results. In this cross sectional study, we investigated the role of sFAS protein in attack-free patients with familial Mediterranean fever (FMF) with and without amyloidosis.

**METHODS:** Twelve FMF patients without amyloidosis (male/female: 7/5; median age 23.5 yrs, range 17-38), 10 FMF patients with amyloidosis (male/female: 5/5; median age 41.5 yrs, range 33-51), and 14 controls (male/female: 6/8; median age 46 yrs, range 38-57) were enrolled in the study. Serum sFAS concentrations were studied by ELISA.

**RESULTS:** Median serum sFAS concentrations were 4630 (2580-12,270), 1338 (453-3240), and 3430 (2110-5960) pg/ml in FMF patients without amyloidosis, FMF patients with amyloidosis, and controls, respectively. Intergroup differences were all statistically significant ( $p < 0.05$ ).

**CONCLUSION:** Elevated serum sFAS concentrations in attack-free FMF patients might be due to dysregulated apoptosis of polymorphonuclear leukocytes together with the ongoing subclinical inflammatory activity. On the other hand, decreased sFAS concentrations could contribute to the augmented apoptosis together with the alterations in immune response leading to the amyloidosis.

PMID: 12563687 [Indexed for MEDLINE]

4585. J Rheumatol. 2003 Feb;30(2):308-12.

Male sex coupled with articular manifestations cause a 4-fold increase in susceptibility to amyloidosis in patients with familial Mediterranean fever homozygous for the M694V-MEFV mutation.

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**OBJECTIVE:** Familial Mediterranean fever (FMF) is an autosomal recessive disorder

characterized by attacks of fever, serositis, and a predisposition to the development of amyloidosis. The wide clinical variability of the disease has been partly attributed to MEFV allelic heterogeneity and partly to the influence of additional genetic and/or environmental modifiers. Of these, male sex was found to influence disease penetrance and susceptibility to amyloidosis. We investigated the role of sex as an independent contributor to the phenotypic profile in FMF and further defined the factors affecting disease expression and severity.

**METHODS:** A total of 124 patients with FMF who were all homozygous for the M694V mutation, including 47 patients with nephropathic amyloidosis, were identified. A detailed chart review and physical examination were undertaken to determine demographic characteristics, history, clinical manifestations, and treatment, and we calculated the disease severity score from the Tel-Hashomer key.

**RESULTS:** A preponderance of male patients was documented (73:51; 1.4). The overall male:female ratio was significantly higher among patients with amyloidosis (32:15; 2.1) compared to patients without amyloidosis (41:36; 1.1). FMF severity scores, independently calculated for male and female patients, were equally high (9.5 +/- 3.0 and 9.7 +/- 2.8, respectively). The frequency of arthritic attacks, significantly higher in women than men ( $p = 0.015$ ), remained notably higher in male FMF patients with amyloidosis compared to male FMF patients without amyloidosis ( $p = 0.002$ ). Significant correlation between arthritis attacks and amyloidosis was found ( $R > 0.285$ ,  $p < 0.001$ ).

**CONCLUSION:** Susceptibility to renal amyloidosis is influenced both by sex and the occurrence of joint attacks, acting as 2 MEFV independent factors (OR 2.37, 95% CI 1.06-5.26 and OR 3.27, 95% CI 1.23-8.68, respectively).

PMID: 12563686 [Indexed for MEDLINE]

4586. Joint Bone Spine. 2002 Dec;69(6):560-5.

Hip involvement in patients with familial Mediterranean fever. A review of ten cases.

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Hip involvement is uncommon in familial Mediterranean fever (FMF) and can result either from a process specific to this disease or from a coexisting chronic inflammatory joint disease, usually suggestive of ankylosing spondylitis (AS). We report ten cases of FMF with radiologically-documented inflammatory hip disease. Five patients had AS and one had juvenile idiopathic arthritis. There were six men and four women, with a mean age of 34.4 years  $\pm$  17.6 (range, 15-70 years). Onset of the inflammatory hip disease occurred after bouts of acute hip symptoms in one of the patients with isolated FMF and after protracted hip arthritis in another; the two other patients had no history of hip symptoms. The HLA-B27 antigen was looked for in two of the five patients with FMF and AS, with negative results in both; another patient in this subgroup had severe ulcerative colitis. Total hip replacement or replacement of the acetabulum was required in six patients, including two with isolated FMF. Chronic joint disease has been estimated to contribute fewer than 5% of the joint manifestations in FMF. In previous studies, the hips and knees were affected in 75% of patients with chronic joint disease related to FMF. The association of FMF and AS (usually without the HLA-B27 antigen) has been well documented, although the pathogenic mechanisms that link these two conditions remain unknown.

PMID: 12537263 [Indexed for MEDLINE]

4587. Eur J Hum Genet. 2003 Jan;11(1):50-6.

Familial Mediterranean fever is no longer a rare disease in Italy.

La Regina M(1), Nucera G, Diaco M, Procopio A, Gasbarrini G, Notarnicola C, Kone-Paut I, Touitou I, Manna R.

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Comment in

Eur J Hum Genet. 2004 Feb;12(2):85-6.

Familial Mediterranean fever (FMF) is an autosomal recessive disorder,

characterised by short, recurrent attacks of fever with abdominal, chest or joint pain and erysipelas-like erythema. It is an ethnically restricted genetic disease, found commonly among Mediterranean populations, as well as Armenians, Turks, Arabs and Jews. Traditionally, Italians have been considered little affected by FMF, despite the geographical position of Italy (northern Mediterranean basin) and the migratory changes in its population. The objective was to characterise the demographic, clinical and genetic features of FMF in Italy. Patients of Italian origin were recruited from those referred to Italian-French medical centres for FUO (Fever of Unknown Origin) or 'surgical' emergencies; clinical history, genealogy and physical examination were recorded; all other possible infectious, neoplastic, auto-immune and metabolic diseases were excluded. Mutational analysis of the gene responsible for FMF (MEFV on 16p13.3) was performed, after which geno-phenotypical correlations were established. Italian FMF patients, 40 women and 31 men, aged from 3 to 75 years, have shown all the clinical manifestations indicative of FMF described in the literature, but with a lower incidence of amyloidosis. The genetic tests have been contributive in 42% of cases. The frequency of each different mutation has been similar to that found in a series of 'endemic' countries. The geno-phenotypical correlations have suggested the existence of genetic and/or environmental modifier-factors. Among Italians FMF seems to be more frequent than was believed in the past. The data presented are consistent with their geographical location and their history.

DOI: 10.1038/sj.ejhg.5200916

PMID: 12529705 [Indexed for MEDLINE]

4588. Eur J Hum Genet. 2003 Jan;11(1):3-4.

Discovery of old diseases: the molecular approach.

Deltas CC.

DOI: 10.1038/sj.ejhg.5200917

PMID: 12529698 [Indexed for MEDLINE]

4589. Blood. 2003 Feb 1;101(3):1205; author reply 1205-6.

Should patients with FMF undergo BMT?

Touitou I.

Comment on

Blood. 2002 Aug 1;100(3):774-7.

DOI: 10.1182/blood-2002-10-3066

PMID: 12529300 [Indexed for MEDLINE]

4590. Hum Genet. 2003 Feb;112(2):209-16. Epub 2002 Nov 16.

Fine structure mapping of CIAS1: identification of an ancestral haplotype and a common FCAS mutation, L353P.

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Familial cold autoinflammatory syndrome (FCAS) is an autosomal dominant inflammatory disease with a high degree of penetrance that is characterized by episodes of rash, arthralgia, fever, conjunctivitis, and leukocytosis after generalized exposure to cold. FCAS was previously mapped to a 10-cM region on chromosome 1q44, and subsequently the gene ( CIAS1) responsible for FCAS was identified. In this paper, we describe the physical and genetic mapping of the FCAS locus, and we report a large ancestral haplotype and a new disease-causing mutation. A BAC contig of approximately 3 Mb was developed and subsequently used for high throughput sequencing. We identified a critical region of 4 cM using rare crossover events in four large North American FCAS families. An unusually large shared haplotype (40 cM) was identified in three of the four families. We found a single heterozygous missense mutation (T1058C=L353P) in exon 3 of CIAS1 in all four families that is responsible for the large majority of FCAS cases described in the literature. We also report a comprehensive list of intragenic single nucleotide polymorphisms. The data provided here will assist others

researching the 1q44 region and will aid clinicians in the diagnosis of FCAS.

DOI: 10.1007/s00439-002-0860-x

PMID: 12522564 [Indexed for MEDLINE]

4591. Nucleic Acids Res. 2003 Jan 1;31(1):286-90.

The MetaFMF website: a high quality tool for meta-analysis of FMF.

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We present here the MetaFMF database (freely accessible at [http://fmf.igh.cnrs.fr/metaFMF/index\\_us.html](http://fmf.igh.cnrs.fr/metaFMF/index_us.html)) that attempts to gather and unify, in a common resource, data on phenotype-genotype correlation in familial Mediterranean fever (FMF). A single accession form, including a large number of quality controls, has been implemented such that data, collected worldwide, are included in an homogeneous manner. The inclusion criterion has the objective to avoid interpretational bias: patients will be included only if they bear at least two mutations. The clinical form has been set up by an International editorial board (12 FMF expert centres), which guarantees the validity of the data. Data are anonymous and submitted by a secure interface, in which the researcher is logged in with a specific ID and password. A pilot study on 211 patients has shown the feasibility and relevance of this project. We anticipate that the use of MetaFMF will enable reliable assessment of phenotype-genotype correlations in FMF, and define a set of severe versus mild mutations/genotypes. It should also highlight reasons for previous inconsistencies in such correlations.

PMCID: PMC165544

PMID: 12520004 [Indexed for MEDLINE]

4592. Nucleic Acids Res. 2003 Jan 1;31(1):282-5.

INFEVERS: the Registry for FMF and hereditary inflammatory disorders mutations.

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We have established the INFEVERS--Internet periodic FEVERS--website (which is freely accessible at <http://fmf.igh.cnrs.fr/infevers/>). Our objectives were to develop a specialist site to gather updated information on mutations responsible for hereditary inflammatory disorders: i.e. Familial Mediterranean Fever (FMF), TRAPS (TNF Receptor 1A Associated Syndrome), HIDS (HyperIgD Syndrome), MWS (Muckle-Wells Syndrome)/FCU (Familial Cold Urticaria)/CINCA (Chronic Infantile Neurological Cutaneous and Articular Syndrome). Contributors submit their novel mutations through a 3 step form. Depending on the disease concerned, a member of the editorial board is automatically solicited to overview and validate new submissions, via a special secured web interface. If accepted, the new mutation is available on the INFEVERS web site and the discoverer, who is informed by email, is credited by having his/her name and date of the discovery on the site. The INFEVERS gateway provides researchers and clinicians with a common access location for information on similar diseases, allowing a rapid overview of the corresponding genetic defects at a glance. Furthermore, it is interactive and extendable according to the latest genes discovered.

PMCID: PMC165478

PMID: 12520003 [Indexed for MEDLINE]

4593. J Rheumatol. 2003 Jan;30(1):185-90.

Clinical and diagnostic value of genetic testing in 216 Israeli children with Familial Mediterranean fever.

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**OBJECTIVE:** Familial Mediterranean fever (FMF) is an autosomal recessive disease with diverse clinical presentation. The FMF gene (MEFV) has recently been cloned and 30 point mutations causing the disease have been identified. We appraised the value of mutation analysis as a diagnostic test for FMF in symptomatic pediatric patients, and explored the possible correlations between MEFV genotypes and the diverse phenotypic expression of the disease.

**METHODS:** Two hundred sixteen children who met the clinical criteria for FMF underwent molecular genetic studies to detect the 3 most common mutations in the Israeli FMF patient population (M694V, V726A, E148Q). The mutations found were related to clinical presentation and disease severity, using the Tel-Hashomer severity score.

**RESULTS:** Of the 216 children who fulfilled the diagnostic criteria for FMF, 82 (38.0%) had 2 of the tested mutations, 73 (33.8%) had only one mutation, and 61 (28.2%) had none of the mutations studied. The M694V was the most frequent mutation, detected in 174 of 432 MEFV alleles (40.0%). The V726A mutation was found in 39 alleles (9.0%) and the E148Q mutation in 25 (5.8%). The severity score correlated with the number of mutations. Children with no mutations presented at an older age compared to children with one or 2 mutations. Children homozygous for the M694V mutation presented at a younger age, had a higher severity score, and more commonly had arthritis.

**CONCLUSION:** Limited genetic molecular testing for MEFV mutations may explain some of the FMF clinical variability, but is diagnostically ineffective. The use of clinical criteria remains essential in establishing the diagnosis of FMF.

PMID: 12508410 [Indexed for MEDLINE]

4594. Microsc Res Tech. 2003 Jan 1;60(1):30-7.

Genetic abnormalities of the endothelium.

Butany JW(1), Verma S, Leask RL, Mohsen B, Asa SL.

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Endothelial cell dysfunction plays an important role in the development and progression of cardiovascular and other disease. The purpose of this review is to discuss some of the genetic diseases known to adversely affect endothelial function. Although the list is exhaustive, we focus our discussion on primary pulmonary hypertension, diabetes mellitus, Alzheimer's disease, Crohn's disease, Von-Hippel-Lindau disease, familial Mediterranean fever, thrombotic microangiopathy, and key vascular malformations. Endothelial dysfunction results from a complex interplay between genetic and environmental factors. This review highlights some of the growing body of evidence implicating endothelial dysfunction as an important mediator of diverse diseases.

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DOI: 10.1002/jemt.10240

PMID: 12500258 [Indexed for MEDLINE]

4595. Hum Mutat. 2003 Jan;21(1):96-7.

MEFV sequence variants and amyloidosis: still an enigmatic question.

Altioek O, Séguret F, Touitou I.

Comment on

Hum Mutat. 2001;17(1):71.

DOI: 10.1002/humu.10137

PMID: 12497636 [Indexed for MEDLINE]

4596. Curr Opin Rheumatol. 2003 Jan;15(1):61-9.

The expanding spectrum of systemic autoinflammatory disorders and their rheumatic manifestations.

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The authors review the genes, and their respective proteins, responsible for eight autoinflammatory conditions. Familial Mediterranean fever is caused by mutations in pyrin, which is the prototype of a new family of proteins belonging to the death-domain superfamily. This new group of proteins, which regulate apoptosis, inflammation, and cytokine processing, share an approximately 90-amino-acid N-terminal sequence called the PYRIN domain. Mutations in another PYRIN domain protein, termed cryopyrin, are responsible for three clinically defined illnesses, Muckle-Wells syndrome, familial cold autoinflammatory syndrome, and NOMID/CINCA. A related protein encoded by the gene is responsible for the Mendelian disorder, Blau syndrome, and also predisposes to Crohn disease. The gene responsible for PAPA syndrome has recently been identified as, and preliminary results from the authors' laboratory also implicate its protein product in these pathways. Lastly, the authors discuss the broadening genetic and clinical spectrum of TRAPS, an autoinflammatory syndrome resulting from mutations in the 55-kDa receptor for tumor necrosis factor.

PMID: 12496512 [Indexed for MEDLINE]

4597. Arch Dis Child. 2003 Jan;88(1):92.

Differential diagnosis of periodic fevers.

La Regina M, Nucera G, Diaco M, Manna R, Gasbarrini G.

Comment on

Arch Dis Child. 2002 Jun;86(6):434-5.

PMCID: PMC1719261

PMID: 12495986 [Indexed for MEDLINE]

4598. Arthritis Rheum. 2002 Dec;46(12):3340-8.

De novo CIAS1 mutations, cytokine activation, and evidence for genetic heterogeneity in patients with neonatal-onset multisystem inflammatory disease (NOMID): a new member of the expanding family of pyrin-associated autoinflammatory diseases.

Aksentijevich I(1), Nowak M, Mallah M, Chae JJ, Watford WT, Hofmann SR, Stein L, Russo R, Goldsmith D, Dent P, Rosenberg HF, Austin F, Remmers EF, Balow JE Jr, Rosenzweig S, Komarow H, Shoham NG, Wood G, Jones J, Mangra N, Carrero H, Adams BS, Moore TL, Schikler K, Hoffman H, Lovell DJ, Lipnick R, Barron K, O'Shea JJ, Kastner DL, Goldbach-Mansky R.

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**OBJECTIVE:** Neonatal-onset multisystem inflammatory disease (NOMID; also known as chronic infantile neurologic, cutaneous, articular [CINCA] syndrome) is characterized by fever, chronic meningitis, uveitis, sensorineural hearing loss, urticarial skin rash, and a characteristic deforming arthropathy. We investigated whether patients with this disorder have mutations in CIAS1, the gene which causes Muckle-Wells syndrome and familial cold autoinflammatory syndrome, two dominantly inherited disorders with some similarities to NOMID/CINCA syndrome.

**METHODS:** Genomic DNA from 13 patients with classic manifestations of NOMID/CINCA syndrome and their available parents was screened for CIAS1 mutations by automated DNA sequencing. Cytokine messenger RNA (mRNA) levels were assessed by real-time polymerase chain reaction on peripheral blood leukocyte mRNA, and serum cytokine levels were assayed by enzyme-linked immunosorbent assay. Protein expression was assessed by Western blotting of lysates from plastic-adherent peripheral blood mononuclear cells.

**RESULTS:** In 6 of the 13 patients, we found 6 heterozygous missense substitutions in CIAS1. Five of the 6 mutations are novel. None of these sequence changes was observed in a panel of >900 chromosomes from healthy controls. Two distinct nucleotide changes in a single codon in unrelated patients resulted in the same amino acid change. In 4 mutation-positive children whose parental DNA was available, no mutation was found in the parental DNA, supporting the conclusion that the mutations arose de novo. Consistent with the recently discovered role of CIAS1 in the regulation of interleukin-1 (IL-1), we found evidence of increased

IL-1beta, as well as tumor necrosis factor, IL-3, IL-5, and IL-6, but not transforming growth factor beta, in a mutation-positive patient compared with normal controls.

CONCLUSION: Our data increase the total number of known germline mutations in CIAS1 to 20, causing a spectrum of diseases ranging from familial cold autoinflammatory syndrome to Muckle-Wells syndrome to NOMID/CINCA syndrome. Mutations in CIAS1 were only found in approximately 50% of the cases identified clinically as NOMID/CINCA syndrome, which raises the possibility of genetic heterogeneity. IL-1 regulation by CIAS1 suggests that IL-1 receptor blockade may constitute a rational approach to the treatment of NOMID/CINCA syndrome.

DOI: 10.1002/art.10688

PMCID: PMC4556432

PMID: 12483741 [Indexed for MEDLINE]

4599. J Clin Ultrasound. 2003 Jan;31(1):51-4.

Tuberculous ileitis in a renal transplant recipient with familial Mediterranean fever: Gray-scale and power Doppler sonographic findings.

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The ileocecal area is the most common site of involvement of intestinal tuberculosis. We report the case of a 26-year-old renal transplant recipient with familial Mediterranean fever who developed tuberculous ileitis. Gray-scale sonography and CT showed circumferential thickening of the bowel wall and enlargement of the mesenteric lymph nodes. Power Doppler sonography revealed markedly increased vascularity in the wall of the affected ileal segment and in the mesenteric nodes. Some nodes had no flow at the center owing to caseation necrosis, a finding consistent with the diagnosis of tuberculous ileitis.

Colonoscopy was performed, and histopathologic examination of biopsy specimens revealed acute inflammatory changes. Cultures of the specimens confirmed the presence of Mycobacterium tuberculosis. We conclude that findings on power Doppler sonography may support a diagnosis of tuberculous ileitis and avoid

clinical mismanagement.

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DOI: 10.1002/jcu.10122

PMID: 12478654 [Indexed for MEDLINE]

4600. Trends Mol Med. 2002 Dec;8(12):550-4.

Genetic clues to understanding periodic fevers, and possible therapies.

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Significant breakthroughs in our understanding of the molecular basis of the inflammatory response have been achieved in the past five years, with the successive identification of the genetic basis of all known hereditary periodic-fever syndromes. Impaired cytokine recognition and defective signalling molecules have been implicated in the inception of recurrent attacks of fever with acute-phase protein response. Disorders of interleukin-1 processing and of regulation of nuclear factor kappaB transcription factor, and possibly defective apoptosis, might be involved in the pathogenesis of all but one of these disorders. Mutations in genes of both the pyrin and tumour-necrosis-factor-receptor superfamilies are postulated to lead to the survival of leukocytes that would ordinarily undergo apoptosis, and ultimately to a prolonged inflammatory response. Improved therapies have reduced the incidence of systemic amyloidosis, but this complication remains the most frequent cause of death.

PMID: 12470987 [Indexed for MEDLINE]

4601. Dokl Biol Sci. 2002 Jul-Aug;385:329-30.

Protein composition of circulating immune complexes in patients with periodic disease complicated or not complicated by renal amyloidosis.

Mkrtchyan GM(1), Boyajyan AS, Karageuzyan KG, Aivazyan AA, Pashinyan SA, Nazaretyan EE.

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PMID: 12469605 [Indexed for MEDLINE]

4602. Eur J Hum Genet. 2002 Dec;10(12):786-9.

The significance of paired MEFV mutations in individuals without symptoms of familial Mediterranean fever.

Tunca M, Akar S, Hawkins PN, Booth SE, Sengül B, Yavuzşen TU, Oktem S, Soytürk M, Akkoç N, Booth DR.

The majority of patients with familial Mediterranean fever (FMF) have identifiable mutations in both alleles of the MEFV gene, while some individuals with paired MEFV mutations do not have clinical symptoms of the disease. During family studies we identified nine such individuals from six kindreds, most of whom either subsequently developed FMF or had other clinically significant inflammatory disease; one case benefiting substantially from colchicine therapy. Four individuals remained asymptomatic. Two further asymptomatic subjects with paired MEFV mutations were identified among 49 healthy controls from western Turkey, of whom a further 18.4 per cent were simple heterozygotes. This carrier rate was higher than would be expected from prevalence of FMF in this region, suggesting that penetrance of paired recognised pathogenic MEFV mutations may frequently be incomplete. MEFV genotyping results must be interpreted with due caution, and follow-up of apparently asymptomatic subjects with paired mutations is advisable.

DOI: 10.1038/sj.ejhg.5200900

PMID: 12461684 [Indexed for MEDLINE]

4603. Turk J Pediatr. 2002 Oct-Dec;44(4):317-20.

Tubular functions in familial Mediterranean fever.

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In this study, we aimed to evaluate renal tubular function in familial Mediterranean fever (FMF). Urinary N-acetyl-beta-D glucosaminidase (U-NAG, beta2-microglobulin (U-beta2M) and microalbumin (Ua) levels were measured in children with different clinical stages of FMF (58 patients with FMF, 9 patients with amyloidosis secondary to (FMF). Control groups were healthy children (n=21), children with upper respiratory tract infection (URTI) (n=21) and with steroid sensitive nephrotic syndrome (SSNS) (n=18). U-NAG was significantly increased in patients with a recent diagnosis of FMF compared to patients with FMF on colchicine and to healthy controls. In patients with recently diagnosed FMF, a marked decrease in U-NAG, U-beta2M and Ua were determined after three months on colchicine therapy. On the other hand, U-NAG and Ubeta2M levels were increased in patients with FMF during attacks and then decreased in the post-attack period. U-beta2M in patients with FMF during attacks was significantly different from patients with URTI. Finally, U-NAG and U-beta2M were increased significantly in patients with FMF-amyloidosis and SSNS when compared with other FMF groups and healthy controls, respectively. In conclusion, the high U-NAG value in newly diagnosed patients compared to that of patients taking colchicine and the decline of U-NAG and U-beta2M levels after attack to the levels observed in colchicine users (without a significant change in Ua value) suggest that the renal injury early in the course of FMF might be dominantly at the level of the tubuli.

PMID: 12458807 [Indexed for MEDLINE]

4604. Isr Med Assoc J. 2002 Nov;4(11 Suppl):935-9.

# Detrimental effects of cyclosporin A on long-term graft survival in familial Mediterranean fever renal allograft recipients: experience of two transplantation centers.

Shabtai M(1), Ben-Haim M, Zemer D, Malinger-Saavedra P, Rosin D, Kuriansky J, Lustig S, Shabtai EL, Shapira Z, Ayalon A.

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**BACKGROUND:** Cyclosporin A has been associated with severe toxic side effects in patients with familial Mediterranean fever who underwent renal transplantation.

Nevertheless, the impact on graft function and survival is not well documented.

**OBJECTIVE:** To compare long-term graft function and survival, between CsA-based vs. CsA free immunosuppressive protocols in FMF recipients of renal allograft.

**METHODS:** Data of FMF recipients were analyzed retrospectively. Graft survival and function and the incidence of acute rejection were correlated to graft source (living donor vs. cadaveric donor), colchicine dose, presence of proteinuria, and immunosuppression protocol (CsA-based triple drug therapy vs. azathioprine-prednisone alone).

**RESULTS:** There were 35 FMF patients with primary renal grafts (13 from living donors and 22 from cadaveric donors). Mean follow-up was 10.6 +/- 6.05 years. Sixteen patients were on CsA-based triple drug therapy and 19 patients on AZA-Pred alone. Mean overall graft survival was 11.2 +/- 0.6 years and 9.4 +/- 1.36 vs. 11.6 +/- 0.4 years for CsA-treated and AZA-Pred groups respectively (P = 0.05). One-year survival was 94% and 96.6% for CsA-treated vs. non-CsA patients (not significant), but 5 and 10 years survival were 76% and 46%, compared to 94.5% and 86% respectively (P = 0.05 at 5 years and 0.001 at 10 years). Mean serum creatinine at time of data collection was 2.3 +/- 1.5 mg/dl in the CsA group vs. 1.6 +/- 0.7 mg/dl in the AZA-Pred group (P = 0.02). There were 14 and 13 reversible rejection episodes in the AZA-Pred and CsA groups respectively (not significant).

**CONCLUSION:** It is suggested that CsA exerts detrimental effects on long-term renal graft function and survival in FMF patients.



4605. Clin Exp Immunol. 2002 Dec;130(3):484-8.

Hyper IgD syndrome (HIDS) associated with in vitro evidence of defective monocyte TNFRSF1A shedding and partial response to TNF receptor blockade with etanercept.

Arkwright PD(1), McDermott MF, Houten SM, Frenkel J, Waterham HR, Aganna E, Hammond LJ, Mirakian RM, Tomlin PI, Vijaydurai PI, Cant AJ.

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Hereditary periodic fever syndromes comprise a group of distinct disease entities linked by the defining feature of recurrent febrile episodes. Hyper IgD with periodic fever syndrome (HIDS) is caused by mutations in the mevalonate kinase (MVK) gene. The mechanisms by which defects in the MVK gene cause febrile episodes are unclear and there is no uniformly effective treatment. Mutations of the TNFRSF1A gene may also cause periodic fever syndrome (TRAPS). Treatment with the TNFR-Fc fusion protein, etanercept, is effective in some patients with TRAPS, but its clinical usefulness in HIDS has not been reported. We describe a 3-year-old boy in whom genetic screening revealed a rare combination of two MVK mutations producing clinical HIDS as well as a TNFRSF1A P46L variant present in about 1% of the population. In vitro functional assays demonstrated reduced receptor shedding in proband's monocytes. The proband therefore appears to have a novel clinical entity combining Hyper IgD syndrome with defective TNFRSF1A homeostasis, which is partially responsive to etanercept.

PMCID: PMC1906535

PMID: 12452839 [Indexed for MEDLINE]

4606. J Am Acad Dermatol. 2002 Dec;47(6):967.

Familial Mediterranean fever: attacks during isotretinoin treatment.

Alli N, Toy GG.

DOI: 10.1067/mjd.2002.122744

PMID: 12451392 [Indexed for MEDLINE]

4607. Clin Rheumatol. 2002 Nov;21(6):511-5.

Comparison of synovial MMP-1 and TIMP-1 levels in patients with various inflammatory arthritides: is there any difference between rheumatoid arthritis, Behçet's disease and familial Mediterranean fever?

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The purpose of this study was to investigate synovial levels of matrix metalloproteinase-1 (MMP-1), known to break down collagen, and tissue inhibitor of metalloproteinase (TIMP-1), its natural antagonist, in patients with various inflammatory disorders. Eighty-five patients with different inflammatory arthritides (20 Behçet's disease, 20 familial Mediterranean fever, 26 rheumatoid arthritis and 19 osteoarthritis) were enrolled in the study. Synovial MMP-1 and TIMP-1 levels were measured by two-step sandwich ELISA. There were significant differences between study and control groups regarding erythrocyte sedimentation rate, C-reactive protein, MMP-1 and TIMP-1 values. The synovial MMP-1 levels of patients with Behçet's disease and familial Mediterranean fever were no different from those in patients with rheumatoid arthritis, but significantly higher than those of patients with osteoarthritis. The synovial TIMP-1 levels in patients with osteoarthritis were higher than those of patients with the other three diseases, among which the difference was not statistically significant, and the difference between osteoarthritis and the others was statistically significant. Because of the detection of similar levels of synovial MMP-1 in patients with familial Mediterranean fever, Behçet's disease and rheumatoid arthritis, we conclude that the absence of erosions in patients with familial Mediterranean fever and Behçet's disease may be explained by MMP-1 being a marker of cytokine-driven inflammation, or by the short-lived and transient nature of the arthritis observed in these patients.

DOI: 10.1007/s100670200125

PMID: 12447637 [Indexed for MEDLINE]

4608. Clin Rheumatol. 2002 Nov;21(6):497-500.

Amyloid goitre in familial Mediterranean fever: report on three patients and review of the literature.

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Familial Mediterranean fever (FMF) is a hereditary disease, the most threatening complication of which is systemic amyloidosis. The thyroid gland may be asymptotically involved in most patients with systemic amyloidosis secondary to FMF. However, clinically detectable thyroid goitre is quite rare, and until now only nine cases of thyroid goitre secondary to amyloid deposition in FMF have been reported. Of 1,100 FMF patients regularly followed up at our centre, thyroid goitre due to the accumulation of amyloid substance could be detected in only three (0.27%). In this report, we summarise the clinical and laboratory features of these patients. All three patients were euthyroid. Total thyroidectomy was performed for compressive symptoms in one patient and for aesthetic purposes in the other two. In countries with a high prevalence of FMF, such as Turkey, secondary amyloidosis of the thyroid gland should be borne in mind in long-standing FMF patients.

DOI: 10.1007/s100670200122

PMID: 12447634 [Indexed for MEDLINE]

4609. Hum Mol Genet. 2002 Dec 1;11(25):3115-24.

Temperature dependence of mutant mevalonate kinase activity as a pathogenic factor in hyper-IgD and periodic fever syndrome.

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Hyper-IgD and periodic fever syndrome (HIDS) and mevalonic aciduria are autosomal recessive disorders characterized by recurrent episodes of fever and generalized inflammation. Both syndromes are caused by specific mutations in the gene encoding mevalonate kinase (MK), resulting in a depressed enzymatic activity mainly due to reduced protein levels. We studied the effect of temperature on the activity of wild-type and several mutant MKs in fibroblasts. All fibroblast cell lines from HIDS patients and harbouring the common V377I MVK allele displayed substantially higher MK activities at 30 degrees C as compared to 37 degrees C. As shown by temperature inactivation experiments this resulted in a protein nearly as stable as in control cell lines, indicating that primarily the maturation of the protein is affected. Accordingly, when HIDS cell lines were cultured at 39 degrees C, MK activity decreased further. This triggered a compensatory increase in 3-hydroxy-3-methylglutaryl-CoA reductase activity, indicating that MK becomes progressively rate-limiting. A similar phenomenon occurs in vivo. MK activity in peripheral blood mononuclear cells drops 2-8-fold when HIDS patients experience febrile attacks. Our results suggest that minor elevations in temperature can set off a chain of events with MK becoming progressively rate-limiting, leading to a temporary deficiency of isoprenoid end-products, which induces inflammation and fever.

PMID: 12444096 [Indexed for MEDLINE]

4610. Medicine (Baltimore). 2002 Nov;81(6):411-6.

Crohn disease in patients with familial Mediterranean fever.

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Crohn disease and familial Mediterranean fever (FMF) are inflammatory diseases characterized by abdominal pain and fever. The concurrence of the 2 diseases

(FMF-CD) may pose a challenge to diagnosis and treatment. We undertook the present study to determine the prevalence of Crohn disease in FMF and to characterize FMF-CD patients clinically and genetically. Using a computerized search, the patients of our FMF clinic were screened for a concomitant diagnosis of Crohn disease. Patients and their medical records were thoroughly examined, and their DNA was genotyped for mutations in the MEFV gene. Control groups of ethnically and sex-matched patients suffering from each of the diseases alone, either Crohn disease or FMF, were used for comparison. We identified 7 patients with concomitant Crohn disease and FMF, which is more than the expected prevalence in the general population ( $p = 0.03$ ). Crohn disease presented at a significantly later age in the FMF-CD group ( $40.6 \pm 10.0$  yr versus  $26.2 \pm 11.4$  yr;  $p < 0.004$ ). Disease severity and other characteristics of Crohn disease were comparable to the Crohn disease control group. Contrary to the FMF control group patients, FMF in FMF-CD patients was characterized by a higher attack frequency ( $p < 0.05$ ) and increased prevalence of amyloidosis ( $p < 0.02$ ). The overall severity score was similar in both groups. In conclusion, Crohn disease appears to be more prevalent in FMF and presents later than in patients without FMF. FMF in this group of patients shows a higher attack frequency and is more often complicated by amyloidosis.

PMID: 12441897 [Indexed for MEDLINE]

4611. Nephrol Dial Transplant. 2002 Nov;17(11):2003-5.

A retrospective analysis for aetiology and clinical findings of 287 secondary amyloidosis cases in Turkey.

Tuglular S(1), Yalcinkaya F, Paydas S, Oner A, Utas C, Bozfakioglu S, Ataman R, Akpolat T, Ok E, Sen S, Düsünsel R, Evrenkaya R, Akoglu E.

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Comment in

Nephrol Dial Transplant. 2003 May;18(5):1031; author reply 1032.

**BACKGROUND:** Secondary amyloidosis is the most frequent of the various types of systemic amyloidosis, the epidemiology of which is not yet fully known. The aim of our study was to evaluate retrospectively the collective data for the aetiological distribution, clinical findings and approaches to the management of secondary amyloidosis in Turkey.

**METHODS:** Data from a simple questionnaire addressing aetiology, and demographic and clinical characteristics of patients with biopsy-proven secondary amyloidosis was retrospectively analysed. Eleven nephrology clinics contributed data for this study.

**RESULTS:** The 11 contributing centres provided a total of 287 cases (102 female, 185 male). The aetiological distribution was as follows: familial Mediterranean fever (FMF) 64%, tuberculosis 10%, bronchiectasis and chronic obstructive lung disease 6%, rheumatoid arthritis 4%, spondylarthropathy 3%, chronic osteomyelitis 2%, miscellaneous 4%, unknown 7%. Oedema accompanied by proteinuria was present in 88% of the cases, hepatomegaly in 17%, and splenomegaly in 11%. The mean systolic and diastolic blood pressures were 115+/-26 and 73+/-15 mmHg respectively. The family history was positive in 16%; 73% of the cases were on colchicine treatment when the questionnaire was administered. Thirty-eight per cent of the cases had progressed to ESRD and were on renal replacement therapy.

**CONCLUSIONS:** FMF is the leading cause of secondary amyloidosis in Turkey, followed by tuberculosis. Oedema accompanied by proteinuria is the most prominent presenting finding, and hypotension seems to be common among these patients.

PMID: 12401861 [Indexed for MEDLINE]

4612. Nephrol Dial Transplant. 2002 Nov;17(11):1921-3.

MEFV gene mutations in familial Mediterranean fever phenotype II patients with renal amyloidosis in childhood: a retrospective clinicopathological and molecular study.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurring attacks of fever and serositis. The definition of the mutated gene has allowed molecular diagnosis of the disease. The most important complication of FMF is the development of AA type secondary amyloidosis. In a group of patients clinically designated as phenotype II amyloidosis patients, renal amyloidosis develops without being preceded by typical attacks of the disease. In this study, the mutations of the MEFV gene were analysed in a group of patients clinically recognized as phenotype II.

**METHODS:** DNA samples were obtained from tissue samples of the subjects. PCR-RFLP methods were used to analyse the M694V, M680I, V726A and E148Q mutations that have been previously defined by us to be the most common mutations in our Turkish cohort.

**RESULTS:** The distribution of the four most common mutations among phenotype II patients was 38% for M694V, 8% for M680I, 4% for V726A and 4% for E148Q.

**CONCLUSIONS:** In phenotype II amyloidosis patients, the distribution of the four common MEFV mutations was not significantly different from that found in all FMF patients with typical symptoms who do or do not develop amyloidosis. We therefore suggest that secondary genetic or environmental factors are operative in the development of secondary amyloidosis in patients with FMF.

PMID: 12401847 [Indexed for MEDLINE]

4613. An Esp Pediatr. 2002 Oct;57(4):334-44.

[Periodic fever].

[Article in Spanish]

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Periodic fever can be defined as recurrent episodes of fever lasting from a few days to several weeks separated by symptom-free intervals of variable duration, recurring throughout several months. Although these clinical pictures are unusual

in clinical practice, in some instances the differential diagnosis with recurrent infections, malignancies and connective tissue diseases is difficult. The aim of this review is to group together these different clinical pictures, which are dispersed in the literature, to obtain an overall and detailed perspective. We classified these processes in two categories: hereditary (familial Mediterranean fever, hyper-IgD syndrome, tumor necrosis factor-receptor-associated periodic syndrome, Muckle-Wells syndrome and familial cold urticaria) and non-hereditary (periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome [PFAPA syndrome], cyclic neutropenia, chronic infantile neurological cutaneous and articular syndrome [CINCA syndrome], Castleman's disease, early onset sarcoidosis and Blau syndrome). Although diagnosis is essentially clinical, in recent years many advances have been made in the knowledge of the molecular and genetic bases of hereditary diseases, which may be of considerable help in establishing the diagnosis and improving treatment.

PMID: 12392668 [Indexed for MEDLINE]

4614. Isr Med Assoc J. 2002 Oct;4(10):837-42.

Joint pain in children: an algorithmic approach.

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PMID: 12389359 [Indexed for MEDLINE]

4615. Best Pract Res Clin Rheumatol. 2002 Jul;16(3):443-69.

Overt and occult rheumatic diseases: the child with chronic fever.

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Identification of the genes involved in hereditary periodic fever syndromes has led to the recognition of a new pathophysiological category, the autoinflammatory disorders. The main non-hereditary autoinflammatory disease in childhood is systemic juvenile idiopathic arthritis (SJIA), others being the chronic infantile neurological cutaneous arthropathy (CINCA) syndrome and the periodic fever, aphthous stomatitis, pharyngitis and adenopathy (PFAPA) syndrome. Familial Mediterranean fever (FMF) has been traced to mutations in the MEFV gene. Mutations in the MVK gene, encoding the enzyme mevalonate kinase, cause the hyper-IgD periodic fever syndrome (HIDS). The tumour necrosis factor(TNF)-receptor-associated periodic syndromes (TRAPS) have been linked to mutations in the TNFRSF1A gene, encoding a TNF-alpha receptor, and the CIAS1 gene is mutated in familial cold autoinflammatory syndrome. We discuss how this knowledge has influenced diagnosis and treatment of these rare genetic disorders and how it might change our approach to the more common rheumatic diseases.

PMID: 12387810 [Indexed for MEDLINE]

4616. Arthritis Rheum. 2002 Oct;46(10):2794-803.

Lack of isoprenoid products raises ex vivo interleukin-1beta secretion in hyperimmunoglobulinemia D and periodic fever syndrome.

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OBJECTIVE: To investigate whether the increased interleukin-1beta (IL-1beta) secretion in hyperimmunoglobulinemia D and periodic fever syndrome is due to the accumulation of mevalonate kinase (MK), the substrate of the deficient enzyme, or

the lack of its products, the isoprenoid compounds.

**METHODS:** The effects of lovastatin and farnesol (FOH), geranylgeraniol (GGOH), and mevalonate on peripheral blood mononuclear cells (PBMCs) from 8 patients with MK deficiency and from 13 controls were studied. Lovastatin inhibits isoprenoid biosynthesis by reducing the production of mevalonate. FOH and GGOH restore isoprenoid biosynthesis downstream from MK. Culture supernatants were collected for cytokine analysis 48 hours after stimulation with monoclonal antibodies against CD2 + CD28.

**RESULTS:** Lovastatin induced a 15-fold rise in IL-1 $\beta$  secretion by normal anti-CD2 + CD28-stimulated cells ( $P < 0.001$ ). This effect could be countered by mevalonate and, to a lesser extent, by FOH and GGOH. In the absence of lovastatin, mevalonate did not change IL-1 $\beta$  secretion. Stimulated MK-deficient cells secreted 9-fold more IL-1 $\beta$  than control PBMCs ( $P < 0.005$ ), rising 2.4-fold in the presence of lovastatin. The effect of lovastatin on IL-1 $\beta$  secretion was reduced by mevalonate, FOH, and GGOH. Isoprenoid biosynthesis in PBMCs from patients was impaired due to the endogenous MK deficiency. Bypassing this defect with FOH, in the absence of lovastatin, led to a 62% reduction ( $P < 0.02$ ) in IL-1 $\beta$  secretion by these cells.

**CONCLUSION:** In this model, shortage of isoprenoid end products contributes to increased IL-1 $\beta$  secretion by MK-deficient PBMCs, whereas excess mevalonate does not.

DOI: 10.1002/art.10550

PMID: 12384940 [Indexed for MEDLINE]

4617. Arthritis Rheum. 2002 Oct;46(10):2785-93.

Reduced MEFV messenger RNA expression in patients with familial Mediterranean fever.

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**OBJECTIVE:** Familial Mediterranean fever (FMF) is the most common inherited periodic syndrome. The disease phenotype and the almost exclusive expression of

the causative gene, MEFV, in leukocytes suggest that this gene plays an important role in the inflammatory cascade. Since most of the known mutations are conservative, we sought to determine how minor DNA defects can give rise to the dramatic phenotypic features seen in FMF.

**METHODS:** To address whether the molecular basis of the phenotype-genotype correlation could be related to altered MEFV messenger RNA (mRNA) expression, we quantified the relative abundance of MEFV transcripts in peripheral blood leukocytes from patients with FMF, healthy carriers of a single MEFV mutation, and healthy control subjects.

**RESULTS:** We found significantly lower expression of MEFV mRNA in genetically ascertained FMF patients than in healthy controls (0.7 versus 1.1;  $P = 0.00001$ ). In healthy carriers, the mRNA levels were intermediate, suggesting a true dose-response relationship between the number of mutations and the abundance of MEFV transcripts. The difference between healthy controls and healthy carriers was significant (1.1 versus 0.8;  $P = 0.008$ ), demonstrating that the decrease in mRNA expression is related to a molecular defect independent of FMF symptoms. MEFV mRNA expression was also found to be a function of the type of mutations. The lowest MEFV levels were found in healthy carriers and patients with M694V. Moreover, we observed an inverse correlation with the clinical severity score ( $r = -0.6$ ,  $P = 0.04$  and  $r = -0.6$ ,  $P = 0.004$  in patients with 1 and 2 M694V mutations, respectively).

**CONCLUSION:** Our results demonstrate that MEFV message levels are related to both the genotype and the phenotype, and suggest that the pathophysiology of FMF relies on a quantitative defect of MEFV mRNA expression.

DOI: 10.1002/art.10575

PMID: 12384939 [Indexed for MEDLINE]

4618. Clin Exp Rheumatol. 2002 Jul-Aug;20(4 Suppl 26):S8-12.

Early blunted cortisol response to insulin induced hypoglycaemia in familial Mediterranean fever.

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**OBJECTIVE:** To study cortisol, adrenocorticotrophic hormone and C-reactive protein responses to specific stimuli in familial Mediterranean fever (FMF).

**METHODS:** For the purpose of measuring cortisol, ACTH, and CRP responses to insulin induced hypoglycaemia during attack-free periods, 14 FMF patients, 11 patients with ankylosing spondylitis or Behçet's disease as disease controls (DC), and a further 10 healthy control subjects (HC) were involved in this study. None of the subjects had ever received corticosteroids before this study. Cortisol and ACTH levels were measured by chemiluminescence enzyme immunoassay.

**RESULTS:** No attack was observed among FMF patients during the test. No significant difference in the mean cortisol values after insulin induced hypoglycaemia was observed between the groups involved at any stage of the test. The integral cortisol response to hypoglycaemia expressed as the AUC (0-90 min) was found not to differ among the study groups (1827 +/- 115.6 in FMF; 2196 +/- 205.4 in DC,  $p = 0.12$ ; 1771 +/- 98.4 in HC,  $p = 0.9$ ). The delta response of cortisol to insulin induced hypoglycaemia was found to be statistically lower ( $-4 \pm 0.8$  mg/dl vs.  $-1.9 \pm 0.7$  microg/dl;  $p < 0.03$ ) only for the 0 to 30 min interval in patients with FMF compared to HC respectively. Similar results, though of no statistical significance, were also found for the 0 to 45 min interval ( $1.17 \pm 2.2$  microg/dl in FMF patients vs.  $3.3 \pm 2$  microg/dl in HC;  $p = 0.6$ ). The mean basal CRP level of patients with FMF was remarkably higher than that in HC. Although the mean CRP level at 90 min for FMF cases with cortisol levels under 12 microg/dl at 30 min was found to be higher than those with cortisol levels over 12 microg/dl at 30 min, no significant difference was observed.

**CONCLUSION:** An early blunted cortisol response observed in a stressful situation in FMF patients may well account for the curious relationship between stress and an inflammatory reaction and/or attack. Furthermore, the fact that the CRP level was relatively higher in FMF patients with lower cortisol levels might also highlight the importance of endogen cortisol in the inflammatory feature of this disease.

PMID: 12371641 [Indexed for MEDLINE]

4619. Clin Exp Rheumatol. 2002 Jul-Aug;20(4 Suppl 26):S57-8.

Is there a heterozygote advantage for familial Mediterranean fever carriers

against tuberculosis infections: speculations remain?

Ozen S, Balci B, Ozkara S, Ozcan A, Yilmaz E, Besbas N, Ozguc M, Kastner DL, Bakkaloglu A.

Comment in

Clin Exp Rheumatol. 2003 Jul-Aug;21(4 Suppl 30):S53-4; author reply S54.

PMID: 12371639 [Indexed for MEDLINE]

4620. Clin Exp Rheumatol. 2002 Jul-Aug;20(4 Suppl 26):S45-53.

Fire and ICE: the role of pyrin domain-containing proteins in inflammation and apoptosis.

Gumucio DL(1), Diaz A, Schaner P, Richards N, Babcock C, Schaller M, Cesena T.

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The genetic bases for several human autoinflammatory syndromes have recently been identified, and the mutated proteins responsible for these diseases are rapidly being characterized. Here, we examine two of these newly identified proteins, pyrin (also called marenostin, product of the familial Mediterranean fever locus, MEFV) and cryopyrin (product of the CAIS1 locus, and mutated in familial cold urticaria, Muckle Wells syndrome and chronic infantile neurological cutaneous and articular syndrome). Both pyrin and cryopyrin contain an N-terminal domain that encodes a death domain-related structure, now known as the pyrin domain, or PyD. We trace the molecular interactions mediated by these PyDs, examine the evolution of the family of molecules containing this domain, and discuss the function of PyD-containing proteins and their homologues. Synthesis of the available data indicates that both pyrin and cryopyrin interact via their PyDs with a common adaptor protein, ASC. ASC itself participates in at least three important cellular processes: apoptosis, recruitment and activation of pro-caspase-1 (with associated processing and secretion of IL-1beta), and activation of NF-kappaB (a transcription factor involved in both initiation and

resolution of the inflammatory response). Through PyD:PyD interactions, pyrin and cryopyrin, as well as several related, but still uncharacterized PyD containing proteins, appear to modulate the activity of all three of these processes, each of which plays a crucial role in the inflammatory pathways that characterize the innate immune system.

PMID: 12371636 [Indexed for MEDLINE]

4621. Clin Exp Rheumatol. 2002 Jul-Aug;20(4 Suppl 26):S43-4.

Successful treatment of familial Mediterranean fever attacks with thalidomide in a colchicine resistant patient.

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Colchicine is the treatment of choice in familial Mediterranean fever (FMF) both for attacks and for prevention of secondary amyloidosis. The overall non-responder rate varies from 5-10 to 40%. Thalidomide is known to blunt the acute phase response. We report the efficacy of the addition of thalidomide to colchicine in controlling the febrile attacks and acute phase response in a patient with FMF resistant to 2 mg colchicine per day.

PMID: 12371635 [Indexed for MEDLINE]

4622. Clin Exp Rheumatol. 2002 Jul-Aug;20(4 Suppl 26):S25-9.

Molecular diagnosis of FMF: lessons from a study of 446 unrelated individuals.

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**BACKGROUND:** Traditionally, the diagnosis of familial Mediterranean fever (FMF) has been based on clinical manifestations and the physician's experience.

Following the cloning of the gene associated with this disease (MEFV), genetic analysis of its mutations has become available, providing a new tool for the establishment or confirmation of the diagnosis of FMF.

**OBJECTIVES:** We analyzed the results of molecular testing for MEFV mutations in 600 individuals. We wished to determine how many of them bore mutations and what percentage had clinically active FMF. We also compared the rate of genetic confirmation of the FMF diagnosis in referrals with suspected FMF seen by general practitioners with that of persons sent for genetic analysis by FMF experts.

**METHODS:** Of 600 individuals tested for FMF mutations, we analyzed separately 446 unrelated persons for the combination of their mutations, epidemiological data, and clinical manifestations. The five most common mutations in the present cohort were analyzed using the amplification refractory mutation system (ARMS).

**RESULTS:** Of the 446 subjects analyzed, 249 (55%) bore mutations: 147 of these were homozygotes or compound heterozygotes, all of whom had FMF according to clinical criteria. Of the remaining 102 heterozygotes, 72 had FMF according to clinical criteria. Two patients with none of the five mutations also had FMF:

North African Jews bore mainly mutations M694V and E148Q. The M694V mutation was found exclusively in Palestinian Arabs. The rate of confirmation of FMF diagnosis by mutation analysis in subjects sent by FMF experts was significantly higher than that of persons referred by general practitioners. Analysis of the molecular testing of the multicase families (154 individuals) revealed that 141 of them bore MEFV mutations and that 4 persons homozygous for E148Q were asymptomatic.

**CONCLUSIONS:** Molecular analysis of FMF mutations confirmed the diagnosis in about 60% of the referrals with suspected FMF. Some (33%) of the patients were heterozygotes, and there were also FMF patients with none of the 5 mutations analyzed. A second opinion by an FMF expert may decrease the need for mutation analysis in subjects suspected of having FMF.

PMID: 12371631 [Indexed for MEDLINE]

4623. Clin Exp Rheumatol. 2002 Jul-Aug;20(4 Suppl 26):S13-6.

Colchicine neuromyopathy: a report of six cases.

Altıparmak MR(1), Pamuk ON, Pamuk GE, Hamuryudan V, Ataman R, Serdengeçti K.

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Colchicine has been in use for therapeutic purposes for many years. It can, however, cause subacute onset muscle and peripheral nerve toxicity in patients with chronic renal failure. In this report we describe 6 patients who developed neuromyopathy after the administration of colchicine. All patients presented with proximal muscle weakness, elevated serum creatine kinase (CK) levels, and neuropathy and/or myopathy on electromyography (EMG). The diagnosis of colchicine toxicity was confirmed in all cases by the normalization of CK levels and EMG after discontinuation of the drug. Toxicity developed in 4 renal failure patients on therapeutic doses of the drug, while one patient took a massive dose for suicidal reasons, and the other was on high-dose therapy. Patients using colchicine--especially those with renal failure--should be warned about the side effects of the drug and physicians should be careful in the administration of the drug.

PMID: 12371628 [Indexed for MEDLINE]

4624. Clin Exp Rheumatol. 2002 Jul-Aug;20(4 Suppl 26):S1-2.

Thoughts on the proposed links between Behçet's disease and familial Mediterranean fever.

Ben-Chetrit E, Yazici H.

Comment in

Clin Exp Rheumatol. 2003 Mar-Apr;21(2):266; author reply 266.

PMID: 12371627 [Indexed for MEDLINE]



4625. Ann Trop Paediatr. 2002 Sep;22(3):251-6.

The changing aetiological spectrum of pericarditis in children.

Tutar HE(1), Yilmaz E, Atalay S, Ucar T, Uysalel A, Kiziltepe U, Gumus H.

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The aetiologies, clinical features and follow-up data of 62 children with pericarditis admitted to a university hospital during a 6-year period were retrospectively assessed. Uraemic pericarditis was the most frequent and infections the second most frequent cause. In this series, the proportion of children with purulent pericarditis is less than in previous reports from developing countries. Familial Mediterranean fever, neoplasias, acute rheumatic fever and post-pericardiotomy syndrome were other important causes of pericarditis.

DOI: 10.1179/027249302125001534

PMID: 12369490 [Indexed for MEDLINE]

4626. Ugeskr Laeger. 2002 Sep 9;164(37):4269-71.

[Autoinflammatory disease: a new concept].

[Article in Danish]

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PMID: 12362866 [Indexed for MEDLINE]

4627. *Pediatr Rev.* 2002 Oct;23(10):359-64.

Index of suspicion.

[No authors listed]

PMID: 12359870 [Indexed for MEDLINE]

4628. *Clin Auton Res.* 2002 Aug;12(4):264-72.

Fractal analysis and recurrence quantification analysis of heart rate and pulse transit time for diagnosing chronic fatigue syndrome.

Naschitz JE(1), Sabo E, Naschitz S, Rosner I, Rozenbaum M, Priselac RM, Gaitini L, Zukerman E, Yeshurun D.

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Comment in

*Clin Auton Res.* 2002 Aug;12(4):228-30.

This study aimed to develop a method to distinguish between the cardiovascular reactivity in chronic fatigue syndrome (CFS) and other patient populations. Patients with CFS (n = 23), familial Mediterranean fever (n = 15), psoriatic arthritis (n = 10), generalized anxiety disorder (n = 12), neurally mediated syncope (n = 20), and healthy subjects (n = 20) were evaluated with a shortened head-up tilt test (HUTT). A 10-minute supine phase of the HUTT was followed by recording 600 cardiac cycles on tilt, i. e., 5 to 10 minutes. Beat-to-beat heart rate (HR) and pulse transit time (PTT) were acquisitioned. Data were processed by recurrence plot and fractal analysis. Fifty-two variables were calculated in each subject. On multivariate analysis, the best predictors of CFS were HR-tilt-R/L, PTT-tilt-R/L, HR-supine-DET, PTT-tilt-WAVE, and HR-tilt-SD. Based on these predictors, the 'Fractal & Recurrence Analysis-based Score' (FRAS) was calculated:  $FRAS = 76.2 + 0.04 \times HR\text{-supine-DET} - 12.9 \times HR\text{-tilt-R/L} - 0.31 \times HR\text{-tilt-SD} - 19.27 \times PTT\text{-tilt-R/L} - 9.42 \times PTT\text{-tilt-WAVE}$ . The best cut-off differentiating CFS

from the control population was FRAS = + 0.22. FRAS > + 0.22 was associated with CFS (sensitivity 70 % and specificity 88 %). The cardiovascular reactivity received mathematical expression with the aid of the FRAS. The shortened HUTT was well tolerated. The FRAS provides objective criteria which could become valuable in the assessment of CFS.

DOI: 10.1007/s10286-002-0044-8

PMID: 12357280 [Indexed for MEDLINE]

4629. Arthritis Rheum. 2002 Sep;46(9):2445-52.

Association of mutations in the NALP3/CIAS1/PYPAF1 gene with a broad phenotype including recurrent fever, cold sensitivity, sensorineural deafness, and AA amyloidosis.

Aganna E(1), Martinon F, Hawkins PN, Ross JB, Swan DC, Booth DR, Lachmann HJ, Bybee A, Gaudet R, Woo P, Feighery C, Cotter FE, Thome M, Hitman GA, Tschopp J, McDermott MF.

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(1)Barts and the London, Queen Mary's School of Medicine and Dentistry, University of London, London, UK.

Erratum in

Arthritis Rheum 2002 Dec;46(12):3398.

**OBJECTIVE:** Familial cold urticaria (FCU) and Muckle-Wells syndrome (MWS) are dominantly inherited autoinflammatory disorders that cause rashes, fever, arthralgia, and in some subjects, AA amyloidosis, and have been mapped to chromosome 1q44. Sensorineural deafness in MWS, and provocation of symptoms by cold in FCU, are distinctive features. This study was undertaken to characterize the genetic basis of FCU, MWS, and an overlapping disorder in French Canadian, British, and Indian families, respectively.

**METHODS:** Mutations in the candidate gene NALP3, which has also been named CIAS1 and PYPAF1, were sought in the study families, in a British/Spanish patient with apparent sporadic MWS, and in matched population controls. Identified variants were sought in 50 European subjects with uncharacterized, apparently sporadic periodic fever syndromes, 48 subjects with rheumatoid arthritis (RA), and 19

subjects with juvenile idiopathic arthritis (JIA).

RESULTS: Point mutations, encoding putative protein variants R262W and L307P, were present in all affected members of the Indian and French Canadian families, respectively, but not in controls. The R262W variant was also present in the subject with sporadic MWS. The V200M variant was present in all affected members of the British family with MWS, in 2 of the 50 subjects with uncharacterized periodic fevers, and in 1 of 130 Caucasian and 2 of 48 Indian healthy controls. No mutations were identified among the subjects with RA or JIA.

CONCLUSION: These findings confirm that mutations in the NALP3/CIAS1/PYPAF1 gene are associated with FCU and MWS, and that disease severity and clinical features may differ substantially within and between families. Analysis of this gene will improve classification of patients with inherited or apparently sporadic periodic fever syndromes.

DOI: 10.1002/art.10509

PMID: 12355493 [Indexed for MEDLINE]

4630. Medicine (Baltimore). 2002 Sep;81(5):349-68.

The TNF receptor-associated periodic syndrome (TRAPS): emerging concepts of an autoinflammatory disorder.

Hull KM(1), Drewe E, Aksentijevich I, Singh HK, Wong K, McDermott EM, Dean J, Powell RJ, Kastner DL.

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The present report describes and expands the clinical and genetic spectrum of the autoinflammatory disorder, tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS). A total of 20 mutations have been identified since our initial discovery of 6 missense mutations in TNF receptor super family 1A (TNFRSF1A) in 1999. Eighteen of the mutations result in amino acid substitutions within the first 2 cysteine-rich domains (CRDs) of the extracellular portion of the receptor. A single splicing mutation also affects the first CRD by causing the insertion of 4 amino acids. Haplotype analysis of the most commonly occurring

and ethnically heterogeneous mutation, R92Q, demonstrates an ancient founder; however, analysis of the T50M mutation, another commonly occurring mutation in Irish and Scottish families, does not, suggesting that T50M is a recurring mutation. Mutations that result in cysteine substitutions demonstrate a higher penetrance of the clinical phenotype (93% versus 82% for noncysteine residue substitutions), and also increase the probability of developing life-threatening amyloidosis (24% versus 2% for noncysteine residue substitutions). Retrospective and prospective evaluation of more than 50 patients, representing 10 of the 20 known mutations, allows us to expand and better define the clinical spectrum of TRAPS. Recurrent episodes of fever, myalgia, rash, abdominal pain, and conjunctivitis that often last longer than 5 days are the most characteristic clinical features of TRAPS. Defective shedding of TNFRSF1A can only partially explain the pathophysiologic mechanism of TRAPS, since some mutations have normal shedding. Consequently, other mechanisms may be mediating the observed phenotype. We are currently investigating other possible mechanisms using stable and transiently transfected cell systems in vitro, as well as developing a knockin mouse model. Preliminary data suggest that etanercept may be effective in decreasing the severity, duration, and frequency of symptoms in TRAPS patients. Additionally, it provides a viable therapeutic alternative to glucocorticoid therapy, which has numerous serious, long-term adverse effects. Two clinical trials are being conducted to evaluate the efficacy of etanercept in decreasing the frequency and severity of symptoms in TRAPS. Lastly, we have summarized data that R92Q and P46L, and probably as yet undiscovered substitutions, represent very low penetrance mutations that may play a much larger role in more broadly defined inflammatory diseases such as rheumatoid arthritis. Our laboratories are currently undertaking both clinical and basic research studies to define the role of these mutations in more common inflammatory diseases.

PMID: 12352631 [Indexed for MEDLINE]

4631. Clin Rheumatol. 2002 Sep;21(5):378-81.

Antistreptococcal response is exaggerated in children with familial Mediterranean fever.

Yalçinkaya F(1), Ince E, Uçar T, Ozkaya N, Tekin M, Elhan AH, Tutar E, Güriz DH, Aysev D, Gökdemir R, Doğru U, Tümer N.

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Familial Mediterranean fever (FMF) is an autosomal recessive disorder. Although the pathogenesis of the disease is not yet completely understood, enhanced acute-phase responsiveness is considered to be one of the most important mechanisms. The presence of high levels of antistreptolysin O (ASO) antibodies and streptococcus-associated diseases, such as acute poststreptococcal glomerulonephritis (AGN) and acute rheumatic fever (ARF), has been reported in patients with FMF. In order to better understand the effect of FMF on antistreptococcal antibody response, we measured ASO and antideoxyribonuclease B (anti-DNAse B) levels in patients with FMF and compared them with those in healthy controls. The study consisted of two parts. In the first step, antistreptococcal antibody levels were analysed in 44 patients with FMF and 165 healthy children who had no history or clinical evidence of upper respiratory tract infection (URTI) for the last 4 months. In the second step, antistreptococcal antibody levels were measured in 15 patients with FMF and 22 healthy controls in response to documented group A beta-haemolytic streptococcal pharyngitis. In the first part of the study, ASO and anti-DNAse B levels in patients with FMF were found to be significantly higher than those in healthy controls ( $P<0.001$ ). In the second part, ASO and anti-DNAse B titres were found to be significantly higher in patients with FMF than in controls ( $P<0.001$  and  $<0.05$ , respectively) 4 weeks after a positive throat culture. We concluded that patients with FMF have an exaggerated response to streptococcal antigens and might be prone to poststreptococcal non-suppurative complications, such as ARF.

DOI: 10.1007/s100670200101

PMID: 12223985 [Indexed for MEDLINE]

4632. *Pediatr Hematol Oncol.* 2002 Oct-Nov;19(7):467-73.

Plasma levels of the von Willebrand factor-cleaving protease in physiological and pathological conditions in children.

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The hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are rare disorders characterized by thrombocytopenia, hemolytic anemia, and ischemic organ failure due to thrombotic occlusions in arterioles. The recent observation that a von Willebrand factor-cleaving protease (VWF-CP) is low in the plasma of patients with TTP but normal in those with HUS has potentially offered a new specific tool for differential diagnosis. In this study, the authors evaluated the plasma levels of the VWF-CP during the neonatal state and healthy childhood and in some pathological pediatric conditions. The protease was measured in 16 healthy newborns, 20 healthy children aged 5-18 years, patients with diabetes mellitus type 1 (n = 7), acute viral hepatitis (n = 10), chronic viral hepatitis (n = 10), transfusion-dependent beta-thalassemia major (n = 10), acute varicella infection (n = 11), the nephrotic syndrome (n = 11), and familial Mediterranean fever (n = 10). Mean protease levels were significantly lower in newborns than in healthy children (50.5 +/- 16.1% vs. 83.3 +/- 16.3%)(p = .0001). In patients with acute viral hepatitis, protease levels were also significantly reduced (40.2 +/- 27% v s. 83.3 +/- 16.3% in healthy children)(p = .0001). Other patient groups had normal protease levels. In conclusion, low protease levels are far from being a specific beacon for TTP. The current paradigm that a single laboratory test may enable physicians to distinguish TTP from HUS seems to be challenged by these and other findings.

DOI: 10.1080/08880010290097288

PMID: 12217192 [Indexed for MEDLINE]

4633. Vestn Ross Akad Med Nauk. 2001;(10):84-8.

[DNA comet assay for evaluation of genotoxic effects in risk groups].

[Article in Russian]

Arutiunian RM, Oganessian GG, Nersesian AK.

DNA comet assay (CA), gel electrophoresis of single cells, is effective in evaluating the genetic (genotoxic) effects of endogenous and exogenous agents. CA was used to study the extent of spontaneous or UV-induced DNA damages in the

leukocytes in two groups at genetic risk: in Chernobyl accident liquidators and patients with familial Mediterranean fever (FMF). There was a significant increase in the number of UV-induced and excision repair-mediated DNA breaks in both risk groups as compared to control samples. The spontaneous extent of DNA breaks in the cells of the liquidators and FMF patients were similar to those in the controls. The extent of oxidative DNA damages detected during incubation with the endonuclease enzymes formamidopyrimidine glycosylase and endonuclease III were also determined in FMF patients. There were no statistically significant differences in the extent of oxidative DNA damage in the cells of FMF patients as compared to the controls. The findings give grounds to recommend CA for biomonitoring of genotoxic effects.

PMID: 12216465 [Indexed for MEDLINE]

4634. Arthritis Rheum. 2002 Aug;46(8):2189-94.

Monocytic fasciitis: a newly recognized clinical feature of tumor necrosis factor receptor dysfunction.

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Comment in

Arthritis Rheum. 2003 Jun;48(6):1768-9; author reply 1769-70.

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is a dominantly inherited autoinflammatory syndrome that results from mutations in TNFRSF1A, the gene that encodes the 55-kd tumor necrosis factor receptor. Clinically, patients present with recurrent episodes of fever in conjunction with localized inflammation at various sites. Myalgia is one of the most characteristic features of this syndrome and is frequently associated with an overlying erythematous, macular rash that, together with the myalgia, displays centrifugal migration. This has previously been believed to occur as a result of myositis. We describe herein the case of a 60-year-old man with TRAPS, in whom



magnetic resonance imaging of the left thigh demonstrated edematous changes in the muscle compartments and surrounding soft tissues. A full-thickness wedge biopsy was performed, and hematoxylin and eosin staining and immunohistochemistry analysis of the specimen demonstrated normal myofibrils but a severely destructive monocytic fasciitis. These results suggest that the myalgia experienced by individuals with TRAPS is due to a monocytic fasciitis and not to myositis.

DOI: 10.1002/art.10448

PMID: 12209524 [Indexed for MEDLINE]

4635. Arthritis Rheum. 2002 Aug;46(8):2181-8.

The enlarging clinical, genetic, and population spectrum of tumor necrosis factor receptor-associated periodic syndrome.

Dodé C(1), André M, Bienvenu T, Hausfater P, Pêcheux C, Bienvenu J, Lecron JC, Reinert P, Cattani D, Piette JC, Szajnert MF, Delpech M, Grateau G; French Hereditary Recurrent Inflammatory Disorder Study Group.

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(1)Hôpital Cochin, Institut Cochin, and Institut fédératif de recherche, de l'INSERM, Université Paris V, Paris, France.

Comment in

Arthritis Rheum. 2003 Jun;48(6):1768-9; author reply 1769-70.

**OBJECTIVE:** To characterize the frequency, clinical signs, and genotypic features of tumor necrosis factor receptor-associated periodic syndrome (TRAPS) in a series of 394 patients of various ethnic origins who have recurrent inflammatory syndromes.

**METHODS:** Sequencing of the coding region of the TNFRSF1A gene was performed in 128 patients in whom there was a high suspicion of TRAPS, and denatured high-performance liquid chromatography was used to systematically screen for TNFRSF1A in 266 patients with recurrent inflammatory syndrome and no or only 1 Mediterranean fever gene (MEFV) mutation.

**RESULTS:** TNFRSF1A mutations were found in 28 (7.1%) of 394 unrelated patients. Nine (32%) of the 28 patients had a family history of recurrent inflammatory

syndromes. In 13 patients, the length of the attack of inflammation was fewer than 5 days. Three of the mutations (Y20H, L67P, and C96Y) were novel. Two mutations, R92Q and (mainly) P46L, found in 12 and 10 patients, respectively, had lower penetrance compared with other mutations. TNFRSF1A mutations were found in patients of various ethnic origins, including those at risk for familial Mediterranean fever (FMF): Armenians, Sephardic Jews, and especially Arabs from Maghreb. Only 3 (10.7%) of the 28 patients had amyloidosis.

CONCLUSION: TRAPS is an underdiagnosed cause of recurrent inflammatory syndrome. Its presence in the population of persons of Mediterranean ancestry and the short duration of the attacks of inflammation can lead to a fallacious diagnosis of FMF. Because an accurate diagnosis in patients with recurrent inflammatory syndromes is crucial for proper clinical management and treatment, genetic screening for TNFRSF1A is warranted.

DOI: 10.1002/art.10429

PMID: 12209523 [Indexed for MEDLINE]

4636. Acta Neuropathol. 2002 Oct;104(4):385-90. Epub 2002 May 23.

Effects of intravenous immunoglobulins on T cell and oligodendrocyte apoptosis in high-dose antigen therapy in experimental autoimmune encephalomyelitis.

Weishaupt A(1), Kuhlmann T, Schönrock LM, Toyka KV, Brück W, Gold R.

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Intravenous immunoglobulins (IVIg) are purified preparations of immunoglobulins from plasma of healthy human donors containing polyclonal IgG and various immunomodulatory contaminants. IVIg may exert its therapeutic effect at several levels of the immune network. Antigen-specific therapy of adoptive transfer-(AT)-EAE in Lewis rats leads to elevated serum levels of tumor necrosis factor-alpha (TNF-alpha). TNF-alpha release at sites of inflammation increased apoptosis of autoaggressive T cells in spinal cord in situ and oligodendrocyte apoptosis. In addition, autoinflammatory T cells in liver were destroyed and caused liver damage by TNF-alpha release. To explore a possible neutralizing

effect of IVIg on TNF-alpha secreted by antigen-specific T cells, we analyzed T cell and oligodendrocyte apoptosis as well as liver damage in rats that had been injected with myelin basic protein (MBP) and co-treated intravenously with human IVIg. As in our earlier studies, we found that TNF-alpha serum levels were raised by antigen therapy and decreased with concomitant IVIg administration. Using IVIg treatment, antigen-induced T cell apoptosis in inflamed spinal cord and liver of MBP/IVIg-treated animals was significantly reduced compared to control rats treated with MBP/albumin. T cell apoptosis decreased to levels observed in EAE rats receiving albumin only. In addition, serum levels of liver enzymes were raised after MBP/albumin administration and decreased by co-treatment with IVIg, indicating protection of hepatocytes by the neutralization of TNF-alpha. In contrast, oligodendrocyte apoptosis in animals receiving MBP/IVIg was significantly higher than in EAE controls. This indicates that IVIg may have different tissue-specific effects. Besides neutralization of TNF-alpha-mediated cell death, IVIg may also interfere with the network of local immune cells, thus modulating survival of glial cells.

DOI: 10.1007/s00401-002-0568-y

PMID: 12200625 [Indexed for MEDLINE]

4637. An Esp Pediatr. 2002 Sep;57(3):269-70.

[Polyarthritis and Mediterranean spotted fever].

[Article in Spanish]

Murga Sierra ML, Ramírez Fernández J, Vegas Muñoz E, Carrasco Torres A, Beceiro Mosquera J.

PMID: 12199953 [Indexed for MEDLINE]

4638. Clin Rheumatol. 2002 Aug;21(4):317-21.

Cranial nerve lesions and abnormal visually evoked potentials associated with the M694V mutation in familial Mediterranean fever.

Finsterer J(1), Stöllberger C, Shinar Y.

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A 52-year-old Turkish man with familial Mediterranean fever (FMF) due to the homozygous M694V mutation in the MEFV-gene on chromosome 16p13.3, newly developed hemicrania, blurred and double vision, ptosis, ophthalmoparesis and peripheral facial nerve palsy. Except for double vision, all the other abnormalities disappeared spontaneously within 10 days after onset. Markedly prolonged latencies of the visually evoked potentials were also found. At follow-up, 8 months after onset of the neurological abnormalities, right-sided bradydiadochokinesia, right-sided discrete weakness and right-sided hypaesthesia were found. After the exclusion of other hereditary fever syndromes, migraine, stroke, Molaret's meningitis, Behçet's syndrome and mitochondriopathy by clinical, serological, CSF investigations, funduscopy, electroencephalography, and cerebral MRI and MRI angiography, the described neurological abnormalities were regarded as CNS and PNS manifestation of vasculitis or amyloidosis in FMF.

DOI: 10.1007/s100670200083

PMID: 12189462 [Indexed for MEDLINE]

4639. Genet Test. 2002 Spring;6(1):15-21.

Familial Mediterranean fever (FMF) mutations occur frequently in the Greek-Cypriot population of Cyprus.

Deltas CC(1), Mean R, Rossou E, Costi C, Koupepidou P, Hadjiyanni I, Hadjiroussos V, Petrou P, Pierides A, Lamnisou K, Koptides M.

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Familial Mediterranean Fever (FMF) is an autosomal recessive disease of high prevalence within Mediterranean countries and particularly common in four ethnic populations: Arabs, non-Ashkenazi Jews, Armenians, and Turks. The responsible

gene MEFV has been assigned to chromosome 16p13.3. Our aim was to establish the frequencies of the most common mutations in Greek-Cypriots. We found that 1 in 25 is a carrier of one of three mutations. V726A, M694V, and F479L. In 68 Grek-Cypriot FMF chromosomes analyzed, we found V726A (25%), F479L (20.6%), M694V (17.6%), and others (36.8%). Mutation F479L, relatively common in this population, is very rare elsewhere. Our study indicates that FMF is not a rare condition in Cyprus and that, because of the significant morbidity associated with this disorder, which is often diagnosed only after unnecessary surgeries, a newborn screening program to detect affected in this population may be warranted.

DOI: 10.1089/109065702760093861

PMID: 12180071 [Indexed for MEDLINE]

4640. Pathol Biol (Paris). 2002 Jul;50(6):357-60.

[Genetic diagnosis of periodic diseases (familial mediterranean fever or FMF)].

[Article in French]

Touitou I.

Periodic disease is the prototype of a group of hereditary disorders characterised by recurrent inflammatory attacks. Since the discovery of the causing gene (MEFV) in 1997, three hospital laboratories in France, and around 20 throughout the world, propose a specific genetic test, based on the search of the common MEFV mutations on DNA extracted from a simple blood sample. This strategy allows definitive confirmation of periodic disease if one mutation is detected on each of the two chromosomes (around 30 mutations are reported today), but do not exclude the diagnosis in the other cases (one or no mutation detected). A non-contributive test shows the existence of rare MEFV mutations, or the involvement of another gene responsible for inflammatory hereditary syndrome; important differential diagnosis to be done, because their mode of management may be different from that of periodic disease.

PMID: 12168253 [Indexed for MEDLINE]

4641. Rev Med Interne. 2002 Jul;23(7):581-3.

[Hot and cold in periodic fever].

[Article in French]

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PMID: 12162213 [Indexed for MEDLINE]

4642. Int J Clin Pract. 2002 Jun;56(5):342-4.

Clinical and biochemical outcome of renal amyloidosis.

Odabas AR(1), Cetinkaya R, Selcuk Y, Erman Z, Bilen H.

Author information:

(1)Department of Nephrology, Ataturk University, School of Medicine, Erzurum, Turkey.

AA amyloidosis is a relatively rare disease which complicates chronic inflammatory diseases, chronic infections, familial Mediterranean fever (FMF) and malignant diseases. Although amyloid deposition may be found in many organs, renal involvement dominates the clinical picture. We reviewed 63 patients with AA amyloidosis who presented to our nephrology department between 1995 and 2000. Prognostic markers, detailed history, physical examination and laboratory tests were evaluated. The causes of AA amyloidosis were as follows: FMF 42 (66.6%), pulmonary tuberculosis 9 (14.2%), chronic osteomyelitis 4 (6.3%), bronchiectasia 4 (6.3%), rheumatoid arthritis 1 (1.5%), juvenile idiopathic arthritis 1 (1.5%), inflammatory abdominal aortic aneurysm 1 (1.5 %), unknown aetiology 1 (1.5%). The diagnosis was made on renal biopsies in 63.4% of the patients, while the remaining 36.6% were diagnosed as a result of rectal biopsies. Sixteen patients died. A low serum albumin, high creatinine and high 24-hour urine albumin

excretion were associated with high mortality.

PMID: 12137441 [Indexed for MEDLINE]

4643. Ter Arkh. 2002;74(6):80-3.

[Genetic aspects of periodic diseases and associated amyloidosis].

[Article in Russian]

Rameev VV, Kozlovskaja LV, Sarkisova IA, Simonian AKh.

PMID: 12136494 [Indexed for MEDLINE]

4644. Blood. 2002 Aug 1;100(3):774-7.

Allogeneic bone marrow transplantation: cure for familial Mediterranean fever.

Milledge J(1), Shaw PJ, Mansour A, Williamson S, Bennetts B, Roscioli T, Curtin J, Christodoulou J.

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Comment in

Blood. 2003 Jul 1;102(1):409.

Blood. 2003 Feb 1;101(3):1205; author reply 1205-6.

We describe data on a 7-year-old girl with congenital dyserythropoietic anemia (CDA), who also had familial Mediterranean fever (FMF). Repeated transfusions required since the age of 6 months to treat her CDA led to iron overload and a persistently high ferritin level. Her relapsing FMF made effective iron chelation therapy very difficult. Consequently, at the age of 4 years, she underwent allogeneic, sibling bone marrow transplantation (BMT). During conditioning for her BMT, symptoms of FMF, including splenomegaly, arthritis, and recurrent

abdominal pain, began to resolve and she was gradually weaned off colchicine. Now, 2 years after the transplantation, she remains free from FMF symptomatology and is off all immunosuppressants. This case demonstrates that symptoms of FMF can be alleviated by the therapy used during allogeneic BMT. In this patient it is likely that the missing factor in FMF is now being provided by granulocytes derived from the stem cells within transplanted bone marrow.

DOI: 10.1182/blood-2002-02-0651

PMID: 12130485 [Indexed for MEDLINE]

4645. Hum Mutat. 2002 Aug;20(2):148-50.

I591T MEFV mutation in a Spanish kindred: is it a mild mutation, a benign polymorphism, or a variant influenced by another modifier?

Aldea A, Casademont J, Aróstegui JI, Rius J, Masó M, Vives J, Yagüe J.

DOI: 10.1002/humu.10103

PMID: 12124996 [Indexed for MEDLINE]

4646. Ital Heart J Suppl. 2002 Jun;3(6):590-7.

[Fibril-forming proteins: the amyloidosis. New hopes for a disease that cardiologists must know].

[Article in Italian]

Arbustini E(1), Gavazzi A, Merlini G.

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(1)Laboratorio di Diagnostica Molecolare, Area Trapiantologica di Ricerca, IRCCS Policlinico San Matteo, Dipartimento di Biochimica, Università degli Studi, Pavia. e.arbustini@smatteo.pv.it

Several proteins share the property of conforming as antiparallel beta-sheets, and forming insoluble amyloid fibrils that deposit in the interstitium of organs/tissues and cause systemic amyloidosis. Cardiac involvement is frequent



and constitutes a major predictor of poor outcome. Its typical phenotype is that of restrictive cardiomyopathy. The biochemical classification of the amyloidogenic proteins provides the bases for innovative therapeutic approaches. Primary systemic amyloidosis (AL) is a protein conformation disorder in which monoclonal immunoglobulin light chains (kappa or lambda) produced by clonal plasma cells, are deposited as amyloid in kidneys, heart, liver, and other organs. The recent evidence that chemotherapy reduces or even eradicates the amyloidogenic clone with consequent functional improvement of the affected organs raises new hopes for a treatment, whose key of success is early diagnosis. Heart transplantation can be proposed in patients < 60 years of age in association with autologous stem cell transplantation. In serum amyloid A amyloidosis, fibrils are constituted of the acute phase serum amyloid A protein that is produced in excess in chronic inflammatory diseases such as familial mediterranean fever, autoimmune disorders and chronic infections. The strategy is to treat the underlying inflammatory disease, but new molecules inhibiting amyloid formation and promoting amyloid resorption are facing the clinical scenario and trials are in progress. In transthyretin (TTR) amyloidosis, the non-senile forms are autosomal dominant diseases caused by defective proteins synthesized by mutated TTR genes (more than 70 known mutations with different genotype-phenotype correlations). The treatment is based on transplantation of the TTR-producing liver; exceptionally, liver plus heart or kidney are transplanted. Apolipoprotein A1 amyloidosis is an inherited autosomal dominant disease that benefits from the transplantation of the most impaired organs, usually heart, liver or kidney, either single or combined. The diagnosis of apolipoprotein A1 and TTR amyloidosis relies on positive family history, immunocharacterization of the amyloid fibrils in a tissue biopsy, gene defect detection and absence of light chains in serum and urines. Vice versa, non-familial primary amyloidoses are diagnosed when kappa or lambda light chains are identified with immunofixation in serum or urines. Tissue studies provide the gold standard for the diagnosis and immunocharacterization of amyloid protein. Heart involvement is diagnosed with a multiparametric approach that includes clinical, electrocardiographic and echocardiographic evaluation. The fine-needle biopsy of the periumbilical fat is the preferral procedure for amyloid detection and immunocharacterization of amyloid protein. This approach excludes, with a few exceptions, the need of endomyocardial biopsy.

4647. J Investig Allergol Clin Immunol. 2002;12(1):60-1.

Recurrent urticaria as a rare manifestation of familial Mediterranean fever.

Alonso R(1), Cisteró-Bahima A, Enrique E, San Miguel-Moncín MM.

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Familial Mediterranean fever (FMF) is a genetic disorder characterized by acute episodes of fever with some combination of severe abdominal pain, pleurisy, arthritis, and skin rash. The case of a patient with recurrent urticaria referred for study of drug allergy is presented. After allergy had been ruled out, the urticaria was attributed to previously undiagnosed symptoms of an underlying systemic disease: FME. Urticaria is the least frequent cutaneous manifestation of this disease, and genetic analysis was required to confirm the diagnosis.

PMID: 12109534 [Indexed for MEDLINE]

4648. Arch Pediatr. 2002 Jun;9(6):638-43.

[Periodic fevers].

[Article in French]

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Periodic fever is defined as a series of unexplained febrile episodes, most often starting during childhood. The febrile episodes last usually few days, are of fixed or variable duration, and regress spontaneously, the intervals between episodes being asymptomatic. Fever is accompanied by clinical manifestations

affecting peritoneal, pleural and/or mucous membranes, joints and skin. Four different etiologies are presently known. Three are hereditary diseases: familial mediterranean fever and periodic fever with hyperimmunoglobulinemia D which have a recessive autosomal transmission, and TNF receptor associated periodic syndrome or TRAPS which has a dominant autosomal transmission. One is sporadic: periodic fever with aphthous stomatitis, pharyngitis and adenopathy or PFAPA. Other etiologies are yet to be identified as many cases of periodic fever remain unexplained.

PMID: 12108320 [Indexed for MEDLINE]

4649. Rev Med Interne. 2002 Jun;23 Suppl 2:247s-249s.

[A case of periodic fever...].

[Article in French]

Schiller D(1), Gröbner S, Binder L, Mittermayer H.

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PMID: 12108202 [Indexed for MEDLINE]

4650. Rev Med Interne. 2002 Jun;23 Suppl 2:228s-231s.

[Long live springtime! My mother...it is not a trap...].

[Article in French]

Dupond JL(1), Gil H, Navellou JC, Meaux N, Magy N, Mahammedi H.

Author information:

(1)Service de médecine interne, hôpital Jean-Minjoz, 25020 Besançon, France.

PMID: 12108196 [Indexed for MEDLINE]

4651. Rev Med Interne. 2002 May;23 Suppl 1:21s-22s.

[Periodic illness, affecting digestion and amylose].

[Article in French]

Grateau G(1).

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(1)Service de médecine interne, L'Hôtel-Dieu, 1, place du parvis Notre-Dame, 75181 Paris, France.

PMID: 12108188 [Indexed for MEDLINE]

4652. Am J Med. 2002 Jul;113(1):80-1.

Chronic ascites related to encapsulating peritonitis in familial Mediterranean fever.

Lelievre JD, Ranque-Francois B, Aslangul-Castier E, Adle-Biassette H, Papo T.

PMID: 12106628 [Indexed for MEDLINE]

4653. Nephrol Dial Transplant. 2002 Jul;17(7):1212-7.

Mutational spectrum in the MEFV and TNFRSF1A genes in patients suffering from AA amyloidosis and recurrent inflammatory attacks.

Dodé C(1), Hazenberg BP, Pêcheux C, Cattan D, Moulin B, Barthélémy A, Gubler MC, Delpech M, Grateau G.

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**BACKGROUND:** Among hereditary fevers characterized by recurrent attacks of fever and organ localized inflammation, familial Mediterranean fever (FMF), and tumour necrosis factor receptor superfamily 1A (TNFRSF1A) receptor associated periodic syndrome (TRAPS) are diseases with identified genes that can be associated with renal amyloidosis of the AA type. In this study we have characterized FMF and TRAPS genotypes in 38 unrelated patients suffering from amyloidosis AA and recurrent inflammatory attacks.

**METHODS:** Mutations of the MEFV and TNFRSF1A genes, responsible respectively for FMF and TRAPS, were searched for by amplifying, using polymerase chain reaction (PCR), genomic DNA, and direct sequencing.

**RESULTS:** Twenty-seven patients (71%) carried mutations in MEFV (22 patients with two mutations, two patients with a single mutation) or TNFRSF1A genes (three patients). Patients with MEFV mutations belonged to the classical at-risk ethnic group for FMF: Sephardic Jews, Turks, Armenians, and Arabs from the Maghreb. The main genotype encountered was M694V/M694V (19/22), one Turkish patient was M680I/M680I, and two Arab patients from the Maghreb were M694I/M694I. We found three Caucasian patients with the C55S, C70Y, R92Q mutations in the TNFRSF1A gene.

**CONCLUSIONS:** In this series we observed that FMF is the main cause of AA amyloidosis in Sephardic Jews and Turks. MEFV and TNFRSF1A mutations were found in only 6 of 14 Arab patients from the Maghreb. We found three families (one Caucasian and two from Maghreb) with AA amyloidosis without MEFV or TNFRSF1A mutations, suggesting that other genetic cause(s) exist(s). The characterization of mutations in MEFV and TNFRSF1A is important for the therapeutic behaviour of AA amyloidosis associated with inherited recurrent fever.

PMID: 12105243 [Indexed for MEDLINE]

4654. Clin Chest Med. 2002 Jun;23(2):505-11.

Thoracic and lung involvement in familial Mediterranean fever (FMF).

Lidar M(1), Pras M, Langevitz P, Livneh A.

Author information:

(1)Heller Institute of Medical Research, Sheba Medical Center, Tel-Hashomer, Israel.

Lung involvement in FMF is limited mainly to transient pleuritis during acute attacks. Amyloidosis of the lung is rare and is associated with symptomatic involvement of other organs while remaining subclinical in itself. Vasculitis of the lung in FMF is possible because of the strong association between FMF and a variety of vasculitides. With the exception of one case of isolated pulmonary vasculitis, vasculitis of the lung in FMF has not been described. The claim that FMF protects against asthma has not been established, but this inverse association, if present, may be traced to linkage disequilibrium in which MEFV modifies the effect of asthma and atopic-related genes, or to eosinophil function. Mesothelioma has been reported in at least four patients with FMF and is related to chronic or recurrent stimulation of the serous membrane. Three patients had peritoneal mesothelioma, while one developed mesothelioma of the lung. Finally, thromboembolism should be considered, particularly in patients with FMF amyloidosis who present with respiratory distress.

PMID: 12092043 [Indexed for MEDLINE]

4655. Semin Arthritis Rheum. 2002 Jun;31(6):371-6.

Genotype/phenotype correlations in Arab patients with familial Mediterranean fever.

Majeed HA(1), El-Shanti H, Al-Khateeb MS, Rabaiha ZA.

Author information:

(1)Department of Pediatrics, Faculty of Medicine, University of Jordan, Amman. pal@go.com.jo

**OBJECTIVES:** To study the phenotype/genotype correlations in Arab patients with familial Mediterranean fever (FMF).

**PATIENTS AND METHODS:** The study was performed in a 3-year period (February

1998-February 2001). Patients were seen in the pediatric FMF clinic of Jordan University Hospital, and the diagnosis of FMF was made according to published criteria. Screening for mutations was carried out by direct sequencing of the entire coding sequence of exon 10 and its donor splice site and by restriction endonuclease testing for mutations in exon 2. A total of 278 patients with clinically positive FMF were screened.

RESULTS: Of the 278 patients, 50 (18%) had 2 mutations identified, and 76 (27%) other patients had only 1 mutation identified. The 50 patients with 2 mutations are the subject of this report. The M694V/M694V and the M694V/V726A and M694I/M694I genotypes were the most common (30%, 16%, and 14%, respectively). Three homozygous genotypes (M694V/M694V, V726A/V726A, and M694I/M694I) and 2 compound heterozygous genotypes (M694V/V726A and V726A/M680I) accounted for 78% of mutations. The difference in the mean severity score ( $14 \pm 2$ ) of the M694V/M694V group and the V726A/V726A (mean severity score,  $10 \pm 3$ ) and M694I/M694I (mean severity score,  $6 \pm 1$ ) groups was statistically significant ( $P = .003$  and  $0$ , respectively). The difference between the M649V/M694V group and the M694V/V726A (mean severity score,  $15 \pm 2$ ) was not statistically significant ( $P = 0.31$ ).

CONCLUSIONS: The genotypes M694V/M694V and M694V/V726A have a severe clinical course in Arab patients with FMF, whereas the M694I/M694I is associated with mild disease.

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PMID: 12077709 [Indexed for MEDLINE]

4656. J Rheumatol. 2002 Jun;29(6):1324-5.

Familial Mediterranean fever in 2 Japanese families.

Shinozaki K(1), Agematsu K, Yasui K, Nagumo H, Naitoh H, Naganuma K, Komiyama A.

Author information:

(1)Department of Pediatrics, Graduate School of Medicine, Shinshu University, Matsumoto, Japan.

We describe 3 Japanese patients in 2 families with familial Mediterranean fever

(FMF) as determined by gene analysis. FMF is an ethnically related, genetic disease, occurring commonly in some Mediterranean populations. The FMF gene (MEFV) mutation found in our patients is M694I. The patients may be remote from East Asian extraction.

PMID: 12064853 [Indexed for MEDLINE]

4657. J Rheumatol. 2002 Jun;29(6):1227-35.

Parvoviral infection of endothelial cells and its possible role in vasculitis and autoimmune diseases.

Magro CM(1), Crowson AN, Dawood M, Nuovo GJ.

Author information:

(1)Department of Pathology, Ohio State University, Columbus 43210, USA.

**OBJECTIVE:** To analyze a series of biopsies from 16 patients who, on the basis of clinical and dermatopathologic findings, had a spectrum of connective tissue diseases (CTD), autoinflammatory or CTD-like syndromes for parvoviral DNA, RNA, and protein.

**METHODS:** Most of the patients were initially screened for parvoviral-related IgG and IgM antibodies. Parvoviral DNA was analyzed by solution phase polymerase chain reaction (PCR). In situ localization of viral VP1 RNA was accomplished by in situ reverse transcriptase (RT) PCR; viral protein (VP2) was detected by immunohistochemistry and these results correlated with the histologic findings. (J Rheumatol 2002;29:xxxx)

**RESULTS:** Of 11 people tested, 10 had either IgG or IgM specific antibodies against parvovirus. Common histologic features of the 16 cases included an interface dermatitis, interstitial histiocytic infiltration with variable collagen necrobiosis, a mononuclear cell dominant vasculitis, and interstitial neutrophilia. Detection of parvoviral RNA by in situ RT-PCR in 14 of 16 cases corroborated solution phase PCR data and demonstrated that the endothelial cells and surrounding mononuclear cells were the viral target. Viral protein as revealed by immunohistochemistry showed an equivalent histologic distribution. Anti-tumor necrosis factor-alpha (TNF-alpha) therapy (etanercept) yielded dramatic improvement after worsening of symptoms with traditional



immunosuppressive therapy in the 3 patients in whom this drug was administered; TNF-alpha mRNA was detected by in situ RT-PCR in the area of parvoviral infected cells.

CONCLUSION: Parvoviral induced endothelialitis may be responsible for cases of "idiopathic" CTD.

PMID: 12064841 [Indexed for MEDLINE]

4658. Intern Med. 2002 May;41(5):329-30.

Reactive amyloidosis and familial Mediterranean fever (FMF).

Takahashi N, Suzuki E, Gejyo F.

PMID: 12058876 [Indexed for MEDLINE]

4659. Biochem Biophys Res Commun. 2002 May 24;293(5):1314-8.

ASC, which is composed of a PYD and a CARD, is up-regulated by inflammation and apoptosis in human neutrophils.

Shiohara M(1), Taniguchi S, Masumoto J, Yasui K, Koike K, Komiyama A, Sagara J.

Author information:

(1)Department of Pediatrics, Shinshu University School of Medicine, Asahi 3-1-1, Matsumoto 390-8621, Japan.

ASC is an adaptor protein that is composed of two protein-protein interaction domains, a PYRIN domain (PYD), and a caspase-recruitment domain (CARD). Recently, ASC was identified as a binding partner of pyrin, which is the product of MEFV, a gene causing familial Mediterranean fever (FMF). Mutations in MEFV result in defects in control of neutrophil-mediated inflammation. Thus we focused on the expression of ASC in neutrophils. Immunohistochemical study showed that ASC is increased in neutrophils in severe inflammatory sites of gangrenous appendicitis. We, then, tested whether proinflammatory mediators induce ASC using peripheral

blood neutrophils in vitro. ASC expression was transiently up-regulated by IL-1alpha, IL-1beta, IFN-alpha, IFN-gamma, TNFalpha, and LPS. ASC was also increased by incubation with either anti-Fas antibody or recombinant soluble Fas ligand. The Fas-mediated induction of ASC was inhibited by a general caspase inhibitor, z-VAD-fmk, and an immunocytochemical study showed that ASC was increased in neutrophils exhibiting characteristic phenotypes for apoptosis. These findings suggest that up-regulation of ASC is closely associated with inflammation and apoptosis in neutrophils.

DOI: 10.1016/S0006-291X(02)00384-4

PMID: 12054656 [Indexed for MEDLINE]

4660. Rheumatol Int. 2002 Apr;21(6):213-7.

Arthritis in children with familial Mediterranean fever.

Ince E(1), Cakar N, Tekin M, Kendirli T, Ozkaya N, Akar N, Yalçinkaya F.

Author information:

(1)Department of Pediatrics, Ankara University School of Medicine, Turkey.  
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The clinical spectrum of arthritis in 124 children with well-documented familial Mediterranean fever (FMF) was investigated in a retrospective study. Seven mutations in the FMF gene (MEFV) were also screened using restriction enzyme digestion and amplification refractory mutation system techniques in 110 patients. Mean age at the onset of FMF arthritis was 5.93+/-3.50 years, 75% of the patients being under 10 years of age. Arthritis in the lower extremities, upper extremities, and small joints of the hands and feet was noted in 122 (98%), 17 (14%), and 15 (12%) patients, respectively. Three patients had atypical arthritis involving temporomandibular, sacroiliac, and sternoclavicular joints. Although most of the arthritic attacks resolved within a few weeks, 12 (10%) patients developed protracted arthritis persisting for months. Amyloidosis was demonstrated in 17 (14%) patients who had not received colchicine treatment. Mutation analysis confirmed the diagnosis of FMF in 77 (62%) children. The clinical presentations of arthritis in FMF may be an important source of diagnostic confusion in FMF. Mutation analysis is of value in situations of diagnostic uncertainty.

PMID: 12036206 [Indexed for MEDLINE]

4661. J Rheumatol. 2002 May;29(5):987-9.

Cardiovascular autonomic dysfunction in familial Mediterranean fever.

Rozenbaum M(1), Naschitz JE, Yudashkin M, Rosner I, Sabo E, Shaviv N, Gaitini L, Zuckerman E, Yeshurun D.

Author information:

(1)Department of Rheumatology and Zevulun Clinic, Bnai Zion Medical Center, Haifa, Israel.

**OBJECTIVE:** To compare the hemodynamic responses to autonomic challenge evoked by upright tilt table testing in patients with familial Mediterranean fever (FMF).

**METHODS:** Forty consecutive patients with FMF and 25 age and sex matched healthy controls were evaluated using the head-up tilt test (HUTT). The main outcome measures were the values of blood pressure (BP) and heart rate (HR) recorded during recumbence and tilt. The endpoints of vasodepressor and cardioinhibitory reactions, orthostatic tachycardia, and postural tachycardia syndrome were recorded.

**RESULTS:** Patients with FMF exhibited significantly higher diastolic BP during supine and tilt measurements ( $p = 0.003$  and  $0.04$ , respectively). In response to tilt, patients showed significant increases in HR compared to healthy subjects ( $p = 0.02$ ). Pathological endpoints on tilt were observed in the FMF group in 7 patients (17%) and in no controls. FMF severity, genotype, duration of illness, response to therapy, and associated amyloidosis did not correlate with pathological reactions on HUTT.

**CONCLUSION:** FMF patients exhibit an abnormal cardiovascular reactivity, which is clinically occult, but can be detected on autonomic challenge. The abnormal autonomic activity in FMF is similar to dysautonomia described in a variety of rheumatic disorders.

PMID: 12022362 [Indexed for MEDLINE]

4662. J Rheumatol. 2002 May;29(5):1084-7.

An unknown autoinflammatory syndrome associated with short stature and dysmorphic features in a young boy.

Mégarbané A(1), Sanders A, Chouery E, Delague V, Medlej-Hashim M, Torbey PH.

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A young boy from nonconsanguineous Palestinian parents presented with short stature, motor developmental delay, wide nasal bridge, bilateral periorbital edema, everted lower lip, brachydactyly, large interphalangeal articulations, drumstick extremities of the fingers, bilateral simian crease, clinodactyly of the 5th fingers, painful joints, subcutaneous nodules all over his body and recurrent episodes of fever of unknown origin. Differential diagnoses such as the hyperimmunoglobulinemia D syndrome, tumor necrosis factor receptor associated periodic syndrome (TRAPS), the chronic infantile neurological cutaneous and articular (CINCA) syndrome, and the newly recognized nodulosis, arthropathy, and osteolysis (NAO) syndrome are discussed. This syndrome may not have been previously reported.

PMID: 12022327 [Indexed for MEDLINE]

4663. Rheumatology (Oxford). 2002 May;41(5):592-3.

Amyloidosis in Behçet's disease and familial Mediterranean fever.

Akpolat T, Yilmaz E, Akpolat I, Dilek M, Karagoz F, Balci B, Ozen S.

PMID: 12011390 [Indexed for MEDLINE]

4664. Heart. 2002 Jun;87(6):568-9.

Familial Mediterranean fever gene (MEFV) mutations in patients with rheumatic heart disease.

Tutar E, Akar N, Atalay S, Yilmaz E, Akar E, Yalçinkaya F.

PMCID: PMC1767132

PMID: 12010946 [Indexed for MEDLINE]

4665. Curr Rheumatol Rep. 2002 Jun;4(3):252-6.

Update on colchicine and its mechanism of action.

Molad Y(1).

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(1)Rabin Medical Center, Beilinson Campus, Rheumatology Unit, Petah Tikva 49100, Israel. ymolad@clalit.org.il

Colchicine is a unique anti-inflammatory drug with respect to its limited clinical usefulness and its mode of action. Colchicine is mainly indicated for the treatment and prophylaxis of gout and familial Mediterranean fever. Its mode of action includes modulation of chemokine and prostanoid production and inhibition of neutrophil and endothelial cell adhesion molecules by which it interferes with the initiation and amplification of the joint inflammation. This paper discusses its adverse effects and indications.

PMID: 12010611 [Indexed for MEDLINE]

4666. Ann Dermatol Venereol. 2002 Mar;129(3):338-42.

[Periodic Fever].

[Article in French]

Dereure O(1).

Author information:

(1)Service de Dermatologie, Phlébologie, CHRU Montpellier, Hôpital Saint-Eloi,  
80, avenue Augustin Fliche, 34295 Montpellier Cedex 5, France.  
o-dereure@chu-monpellier.fr

PMID: 11988699 [Indexed for MEDLINE]

4667. N Engl J Med. 2002 May 2;346(18):1415-6; author reply 1415-6.

Hereditary periodic fever.

Kelley RI, Takada I.

Comment on

N Engl J Med. 2001 Dec 13;345(24):1748-57.

PMID: 11987326 [Indexed for MEDLINE]

4668. N Engl J Med. 2002 May 2;346(18):1415-6; author reply 1415-6.

Hereditary periodic fever.

Goldfinger SE.

Comment on

N Engl J Med. 2001 Dec 13;345(24):1748-57.

PMID: 11987325 [Indexed for MEDLINE]

4669. Pediatrics. 2002 May;109(5):971-3.

Late diagnosis of severe colchicine intoxication.

Güven AG(1), Bahat E, Akman S, Artan R, Erol M.

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(1)Department of Pediatrics, Akdeniz University Medical Faculty, 07070 Antalya, Turkey. gur@med.akdeniz.edu.tr

A 4-year-old Turkish girl was referred to our hospital with the findings of encephalopathy and pancytopenia. She had a history of severe abdominal cramps and gastrointestinal bleeding. A confused state, muscle pain and weakness, erythema-bullous and erythema-nodosum-like skin lesions, and alopecia were observed at her hospitalization. All of these symptoms resolved on follow-up. On laboratory investigation severe thrombocytopenia and leukopenia, mild anemia, a moderate increase in aspartate aminotransferase and alanine aminotransferase levels were detected. After reevaluating her medical history, it was learned that she had accidentally taken 1.3 to 1.5 mg/kg of colchicine 3 to 4 days before her first hospitalization. The possibility of misdiagnosis of colchicine intoxication should be borne in mind, and pediatricians must be aware of its toxic effects, especially in areas where patients with familial Mediterranean fever are present.

PMID: 11986465 [Indexed for MEDLINE]

4670. N Engl J Med. 2002 May 2;346(18):1415-6; author reply 1415-6.

Hereditary periodic fever.

Hull KM, Kastner DL, Balow JE.

Comment on

N Engl J Med. 2001 Dec 13;345(24):1748-57.

DOI: 10.1056/NEJM200205023461819

PMID: 11986423 [Indexed for MEDLINE]

4671. Pediatr Int. 2002 Jun;44(3):326-7.

Hyperimmunoglobulinemia D syndrome successfully treated with a corticosteroid.

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(1)Department of Pediatrics, Tosa Municipal Hospital, Tosa, Kochi, Japan.  
qwt11230@nifty.ne.jp

PMID: 11982908 [Indexed for MEDLINE]

4672. QJM. 2002 May;95(5):332-3.

Pyrin Q148 mutation and familial Mediterranean fever.

Ozen S, Besbas N, Bakkaloglu A, Yilmaz E.

Comment on

QJM. 2001 Oct;94(10):527-31.

PMID: 11978906 [Indexed for MEDLINE]

4673. Am J Med Genet. 2002 May 1;109(3):198-201.

Familial Mediterranean fever: the segregation of four different mutations in 13 individuals from one inbred family: genotype-phenotype correlation and intrafamilial variability.

Gershoni-Baruch R(1), Shinawi M, Shamaly H, Katsinetz L, Brik R.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease



characterized by recurring attacks of fever and serositis. Six sequence alterations (M694V, V726A, K695R, M680I, M694I, and E148Q), in the MEFV gene, account for the majority of FMF chromosomes. Differences in the clinical expression have been mainly attributed to MEFV allelic heterogeneity. Homozygotes for the M694V mutation have a more severe form of the disease and more frequently demonstrate articular and renal complications. The clinical manifestations associated with mutation M680I are considered less severe. Mutations E148Q, K695R and V726A have reduced penetrance, and many individual homozygotes or compound heterozygotes for these mutations remain asymptomatic. Here we report on one inbred family with 13 individuals (one grandparent, three parents, and nine grandchildren), either homozygotes or compound heterozygotes, for one or two of four mutations (V726A, M694V, M680I, and K695R). Three parents and one grandparent who each carried two mutated alleles remained asymptomatic. Of nine grandchildren who were compound heterozygotes for two mutations in the MEFV gene, only those with either the M694V/V726A or the M694V/M680I genotypes manifested the disease, bearing further evidence to the severity of mutation M694V in individuals sharing a similar genetic and environmental background. Nevertheless, one father and one grandmother who carried the M694V/V726A compound heterozygous genotype were symptom-free, while the four grandchildren with the same genotype manifested the disease from early age, providing further evidence for the role of additional environmental and genetic modifiers. The occurrence of four different mutations in two sets of consanguineous parents merits consideration per se.

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DOI: 10.1002/ajmg.10352

PMID: 11977178 [Indexed for MEDLINE]

4674. Hum Mol Genet. 2002 Apr 15;11(8):961-9.

Mutations in CD2BP1 disrupt binding to PTP PEST and are responsible for PAPA syndrome, an autoinflammatory disorder.

Wise CA(1), Gillum JD, Seidman CE, Lindor NM, Veile R, Bashiardes S, Lovett M.

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PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, and acne, OMIM #604416) and familial recurrent arthritis (FRA) are rare inherited disorders of early onset, primarily affecting skin and joint tissues. Recurring inflammatory episodes lead to accumulation of sterile, pyogenic, neutrophil-rich material within the affected joints, ultimately resulting in significant destruction. We recently localized the genes for PAPA syndrome and FRA to chromosome 15q and suggested that they are the same disorder. We have now established this by the identification of co-segregating disease-causing mutations in the CD2-binding protein 1 (CD2BP1; GenBank accession no XM 044569) gene in the two reported families with this disorder. E250Q or A230T amino acid substitutions occur within a domain highly homologous to yeast cleavage furrow-associated protein CDC15. CD2BP1 and its murine ortholog, proline-serine-threonine phosphatase interacting protein (PSTPIP1), are adaptor proteins known to interact with PEST-type protein tyrosine phosphatases (PTP). Yeast two-hybrid assays demonstrate severely reduced binding between PTP PEST and both the E250Q and A230T mutant proteins. Previous evidence supports the integral role of CD2BP1 and its interacting proteins in actin reorganization during cytoskeletal-mediated events. We hypothesize that the disease-causing mutations that we have identified compromise physiologic signaling necessary for the maintenance of proper inflammatory response. Accordingly we suggest classification of PAPA syndrome as an autoinflammatory disease. This CD2BP1-mediated biochemical pathway(s) may function in common inflammatory disorders with apparent etiological overlap, such as rheumatoid arthritis and inflammatory bowel disease.

PMID: 11971877 [Indexed for MEDLINE]

4675. Arthritis Rheum. 2002 Apr;46(4):1061-6.

A novel mutation in the third extracellular domain of the tumor necrosis factor receptor 1 in a Finnish family with autosomal-dominant recurrent fever.

Nevala H(1), Karenko L, Stjernberg S, Raatikainen M, Suomalainen H, Lagerstedt A, Rauta J, McDermott MF, Peterson P, Pettersson T, Ranki A.

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**OBJECTIVE:** To investigate the presence of TRAPS (tumor necrosis factor receptor-associated periodic syndrome), which is a recently defined, dominantly inherited autoinflammatory syndrome caused by mutations in the tumor necrosis factor receptor superfamily 1A gene (TNFRSF1A, CD120a), in a Finnish family with recurrent fever.

**METHODS:** The TNFRSF1A gene was sequenced in both affected and unaffected family members. Flow cytometry and enzyme-linked immunosorbent assay analyses were used to assess membrane expression and serum levels of the TNFRSF1A protein, respectively.

**RESULTS:** A missense mutation in exon 4, located in the third extracellular domain of TNFRSF1A and resulting in an amino acid substitution (F112I) close to a conserved cysteine, was found in all 4 affected family members and in 1 asymptomatic individual. The mutation was clearly associated with low levels of soluble TNFRSF1A as well as with the clinical symptoms of recurrent fever and abdominal pain. Impaired shedding of TNFRSF1A after phorbol myristate acetate stimulation was detected in blood granulocytes and monocytes from the 3 adult family members with the mutation, but in the child bearing the mutation and showing clinical symptoms of recent onset, the shedding defect was less marked.

**CONCLUSION:** TRAPS should be suspected in any patient who presents with a history of intermittent fever accompanied by unexplained abdominal pain, arthritis, or skin rash, particularly in the presence of a family history of such symptoms. Screening for low serum levels of soluble TNFRSF1A identifies individuals who are likely to have TNFRSF1A mutations.

PMID: 11953985 [Indexed for MEDLINE]

4676. Duodecim. 1999;115(18):1951-3.

[Mutation of the cytokine receptor behind periodical fever syndrome].

[Article in Finnish]

Pettersson T, Karenko L, Ranki A.

PMID: 11941812 [Indexed for MEDLINE]

4677. Eur J Hum Genet. 2002 Feb;10(2):145-9.

The differential contribution of MEFV mutant alleles to the clinical profile of familial Mediterranean fever.

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Author information:

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Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterised by recurring attacks of fever and serositis. Five sequence alterations (M694V, V726A, M680I, M694I and E148Q), in the MEFV gene, account for the majority of FMF chromosomes. The wide clinical variability of the disease has been related to MEFV allelic heterogeneity. M694V homozygotes have a severe form of the disease. Mutations E148Q and V726A have reduced penetrance. The clinical features, associated with the M680I and the complex V726A-E148Q allele, are not well defined. This study aims to further characterise the phenotypic profile associated with the major MEFV mutations. We investigated 220 FMF patients, in whom both FMF alleles have been identified, and found that different genotypes are characterised by a specific allelic related clinical profile and penetrance. Homozygotes for the M694V mutation and the complex V726A-E148Q allele are the most severely affected and often endure renal amyloidosis. Homozygotes for the M680I and V726A alleles and compound heterozygotes for either the M694V or the V726A-E148Q alleles in combination with either the E148Q, the V726A or the M680I alleles are significantly less severely affected. The morbidity associated with the complex V726A-E148Q allele by far outweighs that associated with the V726A allele, bearing evidence to the fact that the E148Q mutation is not a benign polymorphism. These findings increase our understanding of the role of allelic variability in disease expression.

DOI: 10.1038/sj.ejhg.5200776

PMID: 11938447 [Indexed for MEDLINE]

4678. Intern Med. 2002 Mar;41(3):221-4.

End-stage renal disease associated with familial Mediterranean fever.

Tomiyama N(1), Oshiro S, Higashiuesato Y, Yamazato M, Sakima A, Tana T, Tozawa M, Muratani H, Iseki K, Takishita S.

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A 39-year-old man had been suffering from periodic fever since childhood. He was started on hemodialysis due to secondary amyloidosis on December 2000. The patient was believed to have Familial Mediterranean fever (FMF) because of recurrent fever with peritonitis, arthritis and inflammatory changes and secondary amyloidosis in his kidneys, heart and colon. No other family member had recurrent fever. IL-6, TNF, and dopamine beta-hydroxylase were not increased in the febrile phase. The patient was homozygous for the M694I mutation. We report the first Japanese case of FMF associated with amyloidosis and confirmed by a gene mutation.

PMID: 11929185 [Indexed for MEDLINE]

4679. Vestn Ross Akad Med Nauk. 2002;(2):41-5.

[The spectrum and level of low-weight molecular compounds of microbial origin in familial Mediterranean fever].

[Article in Russian]

Ktsoian ZhA, Beloborodova NV, Osipov GA, Sarkisian NN, Karagezian KG.

Familial Mediterranean fever (FMF) is a disease whose etiopathogenesis is not clarified yet. The infectious theory of FMF has not been confirmed either. Nevertheless, the involvement of microbes in the trigger of an inflammatory process cannot be excluded since today's well-known pathogenetic processes in FMF are to be directly related to the key cells of an inflammatory response. According to the existing concept, homeostasis of small molecules originating from microbes (SMOM) in healthy individuals is achieved due to adequate immune

system function with the preserved biocenosis of a macroorganism whose disturbance with resultant immune shifts triggers a cascade of inflammatory reactions in the body. An attempt was taken to reveal the participation of microorganisms at the onset of an inflammation in case of FMF by using chromatographic mass spectrometry to detect chemical components of microorganisms and their vital activity products. The method allows one to screen a large number of microbial markers in a clinical sample. Pronounced impairments in the homeostasis of non-protein SMOM were found in the blood of examined patients with FMF (n = 16). There was a uniformity of deviations from the normal values in all the examinees in the episodes and episode-free periods. These qualitative and quantitative deviations basically differ from the direction of changes with other diseases (n 59) or healthy individuals (n = 18). All significant deviations affect non-traditional participants of an inflammatory process in the host. The similar microecological breakages in the human body and their consequences have not been earlier detected and investigated. The findings show it necessary to continue studies to receive an answer to the question as to whether the detected homeostatic features of SMOM in patients with FMF are primary or what is their role in the etiopathogenesis.

PMID: 11924128 [Indexed for MEDLINE]

4680. Rev Prat. 2002 Jan 15;52(2):172-5.

[Management of intermittent fever in the child].

[Article in French]

Reinert P(1).

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Recurrent fevers in children are common, mainly due to viral (particularly in day care centers), or to bacterial (urinary tract upper and lower respiratory) infections. The diagnosis of recurrent hereditary fever is now possible on the basis of clinical features, biochemical and genetic tests. Familial Mediterranean

Fever (FMF) remains the most frequent disorder of this group, which includes now three other entities: TNF receptor associated periodic syndrome (TRAPS), the hyperIgD syndrome (HIDS) and the Muckle-Wells syndrome.

PMID: 11915562 [Indexed for MEDLINE]

4681. Rev Prat. 2002 Jan 15;52(2):155-9.

[Hereditary intermittent fevers, other than familial Mediterranean fevers].

[Article in French]

Grateau G(1), Cuisset L, Dodé C, Delpech M.

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Familial Mediterranean fever is no more the sole hereditary disease characterized by recurrent inflammatory attacks. Three other main entities have now been defined, both at clinical and genetic levels: a dominant disease due to mutations of one of the tumour necrosis factor receptor, called TRAPS for tumour necrosis factor receptor associated periodic syndrome, the hyper-immuno-globulinaemia D and periodic fever syndrome (HIDS), which is a metabolic disorder and the Muckle-Wells syndrome. A thorough diagnosis of these diseases is crucial for appropriate management and treatment.

PMID: 11915559 [Indexed for MEDLINE]

4682. Rev Prat. 2002 Jan 15;52(2):149-54.

[Familial Mediterranean fever].

[Article in French]

Cattan D(1), Dervichian M.

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Familial mediterranean fever is a hereditary inflammatory disease, with autosomal recessive transmission, due to mutations in the MEFV gene. The MEFV gene, located on the short arm of chromosome 16, codes an anti-inflammatory protein, marenostine or pyrin. The disease is characterised by paroxysmal bouts of fever with acute and painful serositis. Appearance of renal amyloidosis indicates severe prognosis. The disease appeared several thousands of years ago in an ancestor common to Sephardic Jews, Turks, Armenians and Arabs. The full clinical description, including renal complications and familial forms, was made by two French investigators and dates from the 1950s. That this description is relatively recent is due to the scarcity of medical treatment and the poor living conditions in the regions concerned, which also explains the occurrence of endemic diseases (in particular tuberculosis), the frequency of acute rheumatic fever, malaria and pyogenic infections. Prophylactic treatment by colchicine, suggested by Turkish authors and one American author, has been demonstrated to avoid not only inflammatory episodes but also the development of amyloidosis.

PMID: 11915558 [Indexed for MEDLINE]

4683. J Rheumatol. 2002 Mar;29(3):530-4.

Familial mediterranean fever and Behçet's disease--are they associated?

Ben-Chetrit E(1), Cohen R, Chajek-Shaul T.

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(1)Department of Medicine, Hadassah University Hospital, Jerusalem, Israel. eldad@hadassah.org.il

**OBJECTIVE:** To test whether the coexistence of familial Mediterranean fever (FMF) and Behçet's disease (BD) is more frequent than expected and whether each disease affects the severity of the other.



**METHODS:** We screened 353 charts of patients with FMF to detect individuals with concomitant BD. Of these, 152 patients with FMF over the age of 18 years were also interviewed and examined specifically. We also studied 53 patients with BD, looking for FMF and for their MEFV mutations. We compared BD patients with MEFV mutations to those without them.

**RESULTS:** None of 353 patients with FMF was found to have concomitant BD. Sixteen patients with BD bore MEFV mutations, 2 of whom were symptomatic homozygotes and had concomitant FMF. No patient with BD with a single MEFV mutation had FMF. Both BD groups (with or without MEFV mutations) were similar in their clinical manifestations and disease course.

**CONCLUSION:** BD and FMF are 2 separate entities that have a mild trend toward a higher than expected association. However, there was no mutual effect of FMF on BD or vice versa.

PMID: 11908568 [Indexed for MEDLINE]

4684. Clin Genet. 2002 Jan;61(1):71-3.

Familial Mediterranean fever: the potential for misdiagnosis of E148V using the E148Q usual RFLP detection method.

Medlej-Hashim M, Salem N, Chouery E, Rawashdeh M, Delague V, Haffar M, Mansour I, Naman R, Lefranc G, Loiselet J, Mégarbané A.

PMID: 11903360 [Indexed for MEDLINE]

4685. Z Arztl Fortbild Qualitatssich. 2002 Jan;96(1):59-63.

[Aspects of colchicine therapy. 1: Pharmacology, toxicology, classic indications].

[Article in German]

Lange U(1), Schumann C, Schmidt KL.

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Colchicine has been traditionally used for the treatment of gout. Many observations discuss the prophylactic and/or therapeutic action of colchicine upon a whole range of other diseases. The first part of the overview deals with the pharmacology, and toxicology and the classical indications.

PMID: 11876051 [Indexed for MEDLINE]

4686. Genes Immun. 2002 Feb;3(1):43-5.

Enhanced cytokine mRNA levels in attack-free patients with familial Mediterranean fever.

Notarnicola C(1), Didelot MN, Seguret F, Demaille J, Touitou I.

Author information:

(1)Laboratory of Genetics, Arnaud de Villeneuve Hospital, Montpellier, France.

Familial Mediterranean fever (FMF) is a recessively inherited inflammatory disorder, characterized by recurrent attacks of fever and serositis. Screening of mutations in the causing gene (MEFV) now allows accurate diagnosis of FMF among other inflammatory conditions. It is well documented that secreted levels of some pro-inflammatory cytokines are elevated in FMF. Here, we investigated cytokine expression at the transcriptional level, in patients that could be genetically ascertained. We have measured the transcript abundance of tumor necrosis factor alpha, interleukin-1beta, interleukin-6 and interleukin-8, in circulating leukocytes and shown that these were more elevated in attack-free FMF patients than in controls ( $P=0.01$ ,  $P=0.008$ ,  $P=0.02$ ,  $P=0.001$  respectively). There was no significant difference according to MEFV genotype or colchicine treatment. Our results suggest that cytokine transcriptional pathways are misregulated in attack-free FMF patients, and further supports the hypothesis that these patients have subclinical inflammation between attacks.

DOI: 10.1038/sj.gene.6363813

PMID: 11857061 [Indexed for MEDLINE]

4687. Urology. 2002 Feb;59(2):201-5.

Value of testis biopsy in the diagnosis of systemic amyloidosis.

Ozdemir BH(1), Ozdemir OG, Ozdemir FN, Ozdemir AI.

Author information:

(1)Department of Pathology, Başkent University Faculty of Medicine, Ankara, Turkey.

**OBJECTIVES:** To evaluate testis biopsy as a diagnostic tool in systemic amyloidosis, to assess how amyloidosis affects testicular tissue, and to examine the relationship between testicular amyloidosis and infertility.

**METHODS:** Testicular biopsies from 72 patients with confirmed systemic amyloidosis were examined for amyloid deposition after Congo red and crystal violet staining. A rectal biopsy was also done in each case, and the results were compared with the testicular biopsy findings.

**RESULTS:** Testicular amyloid deposition was detected in 62 (86.1%) of 72 patients. Fifty-one (85%) of 60 patients with secondary amyloidosis, 11 (91.7%) of 12 patients with primary amyloidosis, and 28 (87.5%) of 32 patients with familial Mediterranean fever showed amyloid deposition in the testis. Rectal biopsies were positive in 40 cases (55.6%). Only 4 of the 62 patients with testicular amyloid showed normal spermatogenesis. The remaining 58 exhibited abnormal spermatogenesis, and 77.7% of patients had seconder infertility. Of 62 patients with positive testis biopsies, 30 had serum creatinine levels less than 1.5 mg/dL, and 29 patients with testicular amyloid manifested nephrotic syndrome.

**CONCLUSIONS:** The testis biopsy is a valuable and more sensitive method than rectal biopsy for diagnosing systemic amyloidosis. The results also showed that testicular amyloidosis causes infertility at a higher rate than expected.

PMID: 11834385 [Indexed for MEDLINE]

4688. Arthritis Rheum. 2002 Jan;46(1):245-9.

An Israeli Arab patient with a de novo TNFRSF1A mutation causing tumor necrosis factor receptor-associated periodic syndrome.

Aganna E(1), Zeharia A, Hitman GA, Basel-Vanagaite L, Allotey RA, Booth DR, Hawkins PN, Thacker C, Syndercombe-Court D, McDermott MF.

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(1)MRCPI: Barts and the London, Queen Mary's School of Medicine and Dentistry, University of London, UK.

**OBJECTIVE:** To investigate genetic susceptibility to recurrent fevers, generalized severe myalgia, and migratory erythema in an Israeli Arab child with no family history of similar disease.

**METHODS:** DNA sequencing of exons 1-6 of the TNFRSF1A gene (formerly TNFR1) was performed in the patient and his parents to determine the presence of the autosomal-dominant tumor necrosis factor receptor-associated periodic syndrome (TRAPS); informative markers spanning the TNFRSF1A locus were used to genotype all available members of the patient's family. The TNFRSF1A gene was subsequently screened in 69 healthy Arab controls and 96 Caucasian controls. Formal forensic paternity testing was performed on the child.

**RESULTS:** We found a de novo missense mutation in exon 3 of the TNFRSF1A gene, involving a novel C-->T transition encoding a Cys70Arg (C70R) variant, in the Israeli Arab patient. Eight of the common familial Mediterranean fever (FMF) gene MEFV mutations were excluded. This mutation was not present in the parents or siblings, or among the 69 healthy Arab controls. However, another TNFRSF1A variant, Pro46Lys (P46L), was present in 1 of the Arab controls.

**CONCLUSION:** We have identified a TNFRSF1A mutation associated with periodic fever in an Arab patient, and a TNFRSF1A variant, which is variably pathogenic in Caucasians, in an Arab control. This is the first report of a de novo mutation in periodic fevers in general, and also of TRAPS in the Arab population. These findings demonstrate the need to include TRAPS in the differential diagnosis of recurrent fevers in this population.

DOI: 10.1002/1529-0131(200201)46:1<245::AID-ART10038>3.0.CO;2-6  
PMID: 11817598 [Indexed for MEDLINE]

4689. Isr Med Assoc J. 2002 Jan;4(1):7-12.

# Effect of colchicine and cytokines on MEFV expression and C5a inhibitor activity in human primary fibroblast cultures.

Abedat S(1), Urieli-Shoval S, Shapira E, Calko S, Ben-Chetrit E, Matzner Y.

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(1)Hematology Unit, Hadassah Hospitals, Mount Scopus, Israel.

**BACKGROUND:** Familial Mediterranean fever is an autosomal recessive disease characterized by sporadic attacks of inflammation affecting the serosal spaces. The gene associated with FMF (MEFV), mainly expressed in neutrophils, was recently found to be expressed also in primary cultures of serosal origin (peritoneal and synovial fibroblasts). A C5a inhibitor, previously detected in normal serosal fluids, was recently identified in serosal cultures as well, and was found to be deficient in serosal fluids and cultures obtained from FMF patients.

**OBJECTIVE:** To investigate the effect of colchicine (the main therapeutic agent for FMF patients) and certain inflammatory cytokines (IL-1 beta, TNF-alpha, IFN-alpha, IFN-gamma) on MEFV expression and C5a inhibitor activity in neutrophils and primary peritoneal fibroblast cultures.

**METHODS:** Human primary peritoneal fibroblast cultures and neutrophils were studied for MEFV expression and C5a inhibitor activity, using reverse transcription-polymerase chain reaction and C5a-induced myeloperoxidase assay, respectively, in the presence and absence of colchicine and cytokines.

**RESULTS:** MEFV expression in neutrophils was high and could not be induced further. Its expression in the peritoneal fibroblasts was lower than in neutrophils and could be induced using colchicine and cytokines parallel with induction of C5a inhibitor activity. Semi-quantitative RT-PCR assays enabled estimation of MEFV induction by the cytokines at 10-100-fold and could not be further increased by concomitant addition of colchicine.

**CONCLUSION:** Serosal tissues, which are afflicted in FMF, express colchicine and cytokine-inducible MEFV and contain inducible C5a inhibitor activity. The relation between the ability of colchicine to induce MEFV and C5a inhibitor activity, and its efficacy in FMF treatment, require further investigation.

PMID: 11802319 [Indexed for MEDLINE]

4690. Eur J Hum Genet. 2001 Nov;9(11):849-54.

Familial Mediterranean Fever: association of elevated IgD plasma levels with specific MEFV mutations.

Medlej-Hashim M(1), Petit I, Adib S, Chouery E, Salem N, Delague V, Rawashdeh M, Mansour I, Lefranc G, Naman R, Loiselet J, Lecron JC, Serre JL, Mégarbané A.

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(1)Unité de Génétique Médicale, Faculté de Médecine, Université Saint Joseph, Beirut, Lebanon.

Familial Mediterranean Fever (FMF) is a recessively inherited disorder, characterized by episodic fever, abdominal and arthritic pain, as well as other forms of inflammation. Some FMF patients present higher IgD serum levels, and it is not yet known whether such an elevation is related to specific genotypes or correlated with a specific phenotype. In order to evaluate the association between known FMF-related mutations and IgD levels in confirmed patients, as well as the correlation between those levels and the presence of specific clinical signs, genotypic analysis and IgD plasma measurements were performed for 148 Lebanese and Jordanian FMF patients. Most common mutational patterns were M694V heterozygotes (19%) and homozygotes (17%), and V726A heterozygotes (18%) and homozygotes (5%), with an additional 11% combining both mutations. Twenty-one patients had higher IgD levels (superior to 100 microg/ml). The risk for higher IgD levels was significantly associated with M694V homozygote status (OR = 6.25) but not with heterozygotic one (OR = 1). Similarly, the risk for higher IgD was also found with V726A homozygotes (OR = 2.2) but not with heterozygotes (OR = 1.05). The use of colchicine was not statistically associated with IgD levels. Clinically, hyper IgD was also found significantly associated with arthritis (OR = 18). Thus, homozygotic status for M694V, and to a lesser extent V726A, is associated with increased risk for higher IgD plasma levels, regardless of colchicine use. Elevated IgD plasma levels are also correlated with the severity of FMF manifestations, and especially with arthritis.

DOI: 10.1038/sj.ejhg.5200725

PMID: 11781702 [Indexed for MEDLINE]

4691. Ann Rheum Dis. 2002 Jan;61(1):79-81.

Acute phase response in familial Mediterranean fever.

Korkmaz C(1), Ozdogan H, Kasapçopur O, Yazici H.

Author information:

(1)Department of Rheumatology, Medical School of Osmangazi University, Eskisehir, Turkey.

**OBJECTIVE:** To test the hypothesis that not all acute phase reactants respond in the same way during attacks of familial Mediterranean fever (FMF) and that there is a subclinical acute phase response (APR) in a proportion of patients during the interval between attacks.

**METHODS:** Blood and urine samples were obtained from 49 patients with FMF during an attack and the attack-free period that followed, to test for erythrocyte sedimentation rate, C reactive protein (CRP), fibrinogen, white blood cell count, platelet count, factor VIII related antigen, haptoglobin, protein electrophoresis, ferritin, proteinuria, and haematuria. Control groups comprised 29 patients with juvenile idiopathic arthritis, 10 patients with various infectious diseases, and 19 healthy subjects.

**RESULTS:** A marked APR was seen during the FMF attacks which was comparable with that obtained in the diseased control groups. CRP was the only acute phase protein that was raised during all attacks. Neither thrombocytosis nor an increase in ferritin levels (except one) was noted in any attack. Serum albumin levels remained unchanged. In two thirds of the patients with FMF a continuing APR was seen in between the attacks.

**CONCLUSION:** Platelet, ferritin, and albumin responses are not part of the significant APR seen during short lived attacks of FMF, and inflammation continues in about two thirds of the patients during an attack-free period.

PMCID: PMC1753891

PMID: 11779767 [Indexed for MEDLINE]

4692. Clin Exp Rheumatol. 2001 Sep-Oct;19(5 Suppl 24):S80-1.

Bilateral uveitis in a 7-year-old patient with familial Mediterranean fever. An extremely rare complication.

Ozaltin F, Bakkaloglu A, Orhon M, Duzova A, Irkec M.

PMID: 11760412 [Indexed for MEDLINE]

4693. Clin Exp Rheumatol. 2001 Sep-Oct;19(5 Suppl 24):S79.

Reporting a desensitization protocol for colchicine treatment.

Levinger U, Monselise A.

PMID: 11760410 [Indexed for MEDLINE]

4694. Clin Exp Rheumatol. 2001 Sep-Oct;19(5 Suppl 24):S78-9.

A case of familial Mediterranean fever, Behçet's disease and polyarteritis nodosa complicated by perirenal haematoma.

Korkmaz C, Zubaroglu I, Kaya T, Akçar N, Gürbüz E, Ozen S.

PMID: 11760409 [Indexed for MEDLINE]

4695. Clin Exp Rheumatol. 2001 Sep-Oct;19(5 Suppl 24):S76.

Colchicine treatment in familial Mediterranean fever: an indirect effect on in vitro serum amyloid A secretion via leukocyte derived factors.

Barash J, Pirogovski A, Livneh A, Brezniak N, Dror Y, Hahn T.

PMID: 11760407 [Indexed for MEDLINE]



4696. Clin Exp Rheumatol. 2001 Sep-Oct;19(5 Suppl 24):S72-5.

Growth and IGF-1 levels of children with familial Mediterranean fever on colchicine treatment.

Savgan-Gürol E(1), Kasapçopur O, Hatemi S, Ercan O, Caliskan S, Sever L, Ozdogan H, Arisoy N.

Author information:

(1)Departments of Pediatrics and Rheumatology, Cerrahpasa Medical Faculty, Istanbul University, Istanbul, Turkey.

**OBJECTIVE:** To evaluate growth process and insulin like growth factor-1 (IGF-1) levels in children with familial Mediterranean fever (FMF).

**METHODS:** This prospective study group consisted of 51 children with FMF under colchicine therapy (20 boys, 31 girls) and 42 healthy children (22 boys, 20 girls). All children were prepubertal. Bone ages and IGF-1 levels were determined in all cases. Height velocity (HV), height standard deviation score (SDS), target height and target height SDS were calculated.

**RESULTS:** There was no statistical difference in age, HSDS, target height SDS and bone ages between healthy and diseased subjects. HV of children with FMF did not differ significantly from the control group. There was no statistical difference in age, HSDS, target height SDS and bone ages between healthy and FMF subjects. HV of children with FMF did not differ significantly from the control group. There was no significant correlation between disease duration, number of attacks, erythrocyte sedimentation rate and HV, HSDS and IGF-1 levels of FMF patients. There was positive correlation between cumulative colchicine dose and HV ( $r = 0.29$ ).

**CONCLUSION:** Growth and IGF-1 levels of children with FMF do not differ from their healthy peers. However, there was positive correlation between HV and cumulative colchicine dose. This study suggests that colchicine not only has no adverse influence on growth, but more by suppressing disease activity and inflammation it has an enhancing role.

PMID: 11760406 [Indexed for MEDLINE]

4697. Clin Exp Rheumatol. 2001 Sep-Oct;19(5 Suppl 24):S68-71.

Increased neutrophil apoptosis during attacks of familial Mediterranean fever.

Ozen S(1), Uckan D, Baskin E, Besbas N, Okur H, Saatci U, Bakkaloglu A.

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(1)Department of Pediatric Nephrology and Rheumatology, Hacettepe University Faculty of Medicine, Sıhhiye 06100 Ankara, Turkey.

**AIM:** Apoptosis is a programmed form of cell death. Recently much attention has been devoted to the role of apoptosis in rheumatological diseases. We have aimed to analyze apoptosis in the inflammatory pathway of familial Mediterranean fever (FMF).

**METHODS:** 26 FMF patients and 12 age and sex matched controls were the subject of the study. Twelve of the patients were analyzed during an FMF attack whereas samples were obtained at least a week after an attack in 14. Four of the patients had renal amyloidosis. Whole blood was treated with ammonium chloride for RBC lysis. Subsequently the cells were stained with propidium iodide and annexin. Neutrophils and lymphocytes were gated separately for analysis by flow cytometry. We have also analyzed cellular Fas and Fas-ligand expression in these cells.

**RESULTS:** The mean age of the patients was  $12.00 \pm 3.17$ , and was not different than the control subjects. Erythrocyte sedimentation rate and CRP levels were significantly elevated in the attack group as compared to the attack-free group. The mean levels of neutrophil apoptosis in the FMF patients with an attack, attack-free and controls were  $12.94 \pm 11.78$ ,  $6.60 \pm 7.83$  and  $3.98 \pm 4.27$ , respectively. Lymphocyte apoptosis in the same groups were  $7.84 \pm 8.63$ ,  $2.75 \pm 2.33$ , and  $1.22 \pm 0.93$ , respectively. Neutrophil and monocyte apoptosis was significantly increased during the attack as compared to the controls ( $p < 0.05$ ). However lymphocyte apoptosis was not different between the aforementioned groups. On the other hand, lymphocyte apoptosis was significantly increased in the SLE patients ( $p < 0.05$ ), whereas neutrophil apoptosis was not. Fas staining of neutrophils were not different between the groups ( $p > 0.05$ ). On the other hand the difference between the groups for FasL was significant ( $p < 0.05$ ).

**CONCLUSION:** Neutrophil and monocyte but not lymphocyte apoptosis was significantly increased during FMF attacks reminding us that FMF is an autoinflammation of certain peripheral cells. The increased apoptosis in these patients maybe regarded as a response to clear the unwanted inflammatory cells. On the other hand the increased apoptosis maybe the explanation of the self-limited nature of the FMF attacks. Future studies will enlighten us on the

significance of this increased apoptosis in the process of inflammation.

PMID: 11760405 [Indexed for MEDLINE]

4698. Clin Exp Rheumatol. 2001 Sep-Oct;19(5 Suppl 24):S63-7.

Familial Mediterranean fever (FMF)-associated amyloidosis in childhood. Clinical features, course and outcome.

Cakar N(1), Yalçinkaya F, Ozkaya N, Tekin M, Akar N, Koçak H, Misirlioğlu M, Akar E, Tümer N.

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(1)Department of Pediatric Nephrology, Ankara Social Security Children's Hospital, Ankara, Turkey. nilguncakar@hotmail.com

**OBJECTIVE:** Familial Mediterranean fever (FMF) is an autosomal recessive disorder of childhood characterized by attacks of fever and serositis. Renal amyloidosis is the most important complication of the disease that determines the prognosis.

**METHODS:** Forty-eight Turkish FMF patients with amyloidosis who have been followed at the two hospitals in Ankara were included in this study.

**RESULTS:** All patients with amyloidosis had been symptomatic for FMF at the time of the diagnosis (Phenotype I), none had received regular colchicine therapy and all presented with proteinuria. Ten of them had asymptomatic proteinuria; 38 had nephrotic syndrome and 8 of them had renal insufficiency (CRI) as well, at the time of the diagnosis. Regular colchicine therapy was commenced to all of the patients. At the end of observation period of 4.5 +/- 2.23 years (range 2-12 yrs) on treatment, nephrotic syndrome resolved in 13 patients and proteinuria was lost in 5 of them. None but 2 of the patients who were diagnosed at proteinuric stage progressed to end stage renal failure (ESRF). Seven MEFV mutations (M694V, M680I, V726A, M694I, K695R, R761H, E148Q) were systematically investigated in 32 patients. Six of the seven studied mutations were found in these patients and clinical diagnosis was confirmed by mutation analysis in 24 patients. Eight patients were found to have mutations on one of the alleles.

**CONCLUSION:** Amyloidosis is the most serious complication of FMF. Colchicine treatment ameliorates the progression of renal disease in the patients who presented with proteinuria and even with nephrotic syndrome. No correlation

between the outcome of the patients with nephrotic syndrome and the degree of proteinuria and/or serum albumin levels at the initiation of treatment were noted. Progression to ESRF seems inevitable despite colchicine therapy after the development of CRI in patients with FMF associated amyloidosis.

PMID: 11760404 [Indexed for MEDLINE]

4699. Clin Exp Rheumatol. 2001 Sep-Oct;19(5 Suppl 24):S45-7.

A reassessment of the International Study Group criteria for the diagnosis (classification) of Behçet's syndrome.

Tunç R(1), Uluhan A, Melikoğlu M, Ozyazgan Y, Ozdoğan H, Yazici H.

Author information:

(1)Department of Internal Medicine, Faculty of Medicine, Selcuk University, Konya, Turkey.

**OBJECTIVE:** Patients with ulcerative colitis (UC) and Crohn's disease (CD) were not represented in the diseased controls group that had been utilised in the development of the International Study Group (ISG) criteria for the diagnosis of Behçet's syndrome (BS). Having similar features, both of these conditions can pose problems in the differential diagnosis of BS. Moreover, there has been a recent awareness of coexistence of BS and familial Mediterranean fever (FMF). The aim of this study was to reassess the performance of ISG criteria among patients with BS and other rheumatological conditions, specifically including those with CD, UC, and FMF.

**METHODS:** 302 consecutive patients with BS and 438 patients with other rheumatological conditions were surveyed for the presence or absence of the features of BS by means of a standard form which had been prepared according to ISG criteria. All control patients with a history of oral ulcer had a pathergy test and an eye examination by an experienced ophthalmologist with a slit lamp. The sensitivity and specificity of the ISG criteria were calculated.

**RESULTS:** Seven of 302 patients with BS (2%) did not fulfill the ISG criteria while 5 of 438 controls (1%) fulfilled the ISG criteria.

**CONCLUSION:** In this study ISG criteria performed well in correctly classifying BS. Further specificity studies might be considered in CD.

PMID: 11760398 [Indexed for MEDLINE]

4700. Clin Exp Rheumatol. 2001 Sep-Oct;19(5 Suppl 24):S42-4.

Nailfold capillary abnormalities in patients with familial Mediterranean fever.

Dinç A(1), Melikoğlu M, Korkmaz C, Fresko I, Ozdoğan H, Yazici H.

Author information:

(1)Division of Rheumatology, Department of Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Turkey.

**OBJECTIVE:** To determine the frequency and the degree of the nailfold capillary abnormalities in patients with familial Mediterranean fever (FMF).

**METHODS:** We studied 67 (M/F: 28/39) patients with FMF. Thirty-seven healthy subjects (16/21), 19 patients (0/19) with systemic lupus erythematosus (SLE), and 8 patients (0/8) with scleroderma (PSS) were also studied. All participants were questioned for the presence of Raynaud's phenomenon (RP). Capillary loops of eight fingers were evaluated and scored with respect to avascular areas, tortuosity, enlargement and extravasations by the conventional capillary microscopy. Both FMF patients and healthy controls were examined in a blind manner.

**RESULTS:** FMF patients differed from healthy controls by the presence of increased tortuosity and enlargement of capillary loops, but not by microhemorrhages. Being female and the presence of RP were the factors that correlated with the capillaroscopic findings.

**CONCLUSION:** Capillary abnormalities are seen in patients with FMF.

PMID: 11760397 [Indexed for MEDLINE]

4701. Clin Exp Rheumatol. 2001 Sep-Oct;19(5 Suppl 24):S13-4.

The other physician behind the use of colchicine for the treatment of familial Mediterranean fever.

Aral O(1), Ozdogan H, Yazici H.

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(1)Division of Rheumatology, Department of Medicine, Istanbul Medical Faculty, University of Istanbul, Turkey.

PMID: 11760392 [Indexed for MEDLINE]

4702. Clin Exp Rheumatol. 2001 Sep-Oct;19(5 Suppl 24):S1-5.

Enigmas in familial Mediterranean fever (FMF).

Ben-Chetrit E, Levy M.

PMID: 11760391 [Indexed for MEDLINE]

4703. Transplant Proc. 2001 Nov-Dec;33(7-8):3392-3.

Renal transplantation in amyloidosis secondary to familial Mediterranean fever.

Sever MS(1), Turkmen A, Sahin S, Yildiz A, Ecder T, Kayacan MS, Nane I, Aydin AE, Eldegez U.

Author information:

(1)Istanbul School of Medicine, Istanbul, Turkey.

PMID: 11750451 [Indexed for MEDLINE]

4704. Ann Intern Med. 2001 Dec 18;135(12):1096.

Late occurrence of chronic renal failure in familial mediterranean fever after 20 years of colchicine treatment.

Vigneau C, Petrover D, Sraer JD.

PMID: 11747405 [Indexed for MEDLINE]

4705. N Engl J Med. 2001 Dec 13;345(24):1748-57.

Hereditary periodic fever.

Drenth JP(1), van der Meer JW.

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Comment in

N Engl J Med. 2002 May 2;346(18):1415-6; author reply 1415-6.

N Engl J Med. 2002 May 2;346(18):1415-6; author reply 1415-6.

N Engl J Med. 2002 May 2;346(18):1415-6; author reply 1415-6.

DOI: 10.1056/NEJMra010200

PMID: 11742050 [Indexed for MEDLINE]

4706. Minerva Med. 2001 Dec;92(6):421-30.

Familial mediterranean fever - a review and update.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease, which primarily affects populations surrounding the Mediterranean basin. The disease occurs predominantly in Turks, Armenians, Arabs, and Sephardic Jews. FMF is

characterized by recurrent attacks of fever and peritonitis, pleuritis, arthritis or erysipelas-like erythema. Amyloidosis causing renal failure is one of the most severe complications of the disease. In 1997, the gene associated with FMF (MEFV) was isolated. It encodes a protein consisting of 781 amino acids and is expressed mainly in leukocytes. It was named "pyrin" indicating its relation to fever or "marenostrin" (our sea), referring to the Mediterranean focus of the disease. The exact pathogenesis of FMF is not known. Since the MEFV gene encodes a protein that resembles cytokines, which can down-regulate inflammation, it was suggested that pyrin may also have a similar effect. Thus, in FMF patients lacking this protein (or its activity) due to hereditary defects, there is no suppression or inhibition of the inflammatory process, thereby leading to a full-blown attack. Current studies suggest a limited phenotype-genotype correlation. It seems that other genetic and environmental modifiers influence the expression of FMF. Colchicine has been the drug of choice for FMF. It controls the FMF attacks and prevents the development of amyloidosis. Nevertheless, about 5-10% are non-responders and new therapies and approaches for these cases are currently under investigation. The prognosis of FMF patients is favorable, provided they are treated continuously with colchicine. Under this treatment most of the patients are free of acute inflammatory attacks and they will not develop amyloidosis.

PMID: 11740430 [Indexed for MEDLINE]

4707. Isr Med Assoc J. 2001 Nov;3(11):862-3.

Familial Mediterranean fever phenotype II in Greece.

Konstantopoulos K(1), Kanta A, Tzoulianos M, Dimou S, Sotsiou F, Politou M, Loukopoulos D.

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(1)First Department of Medicine, Athens University Medical School, Athens, Greece. kkonstan@med.uoa.gr

PMID: 11729588 [Indexed for MEDLINE]



4708. Isr Med Assoc J. 2001 Nov;3(11):838-40.

Genotype-phenotype relation and correlation in familial mediterranean fever.

Ben-Chetrit E.

Comment on

Isr Med Assoc J. 2001 Nov;3(11):803-4.

PMID: 11729581 [Indexed for MEDLINE]

4709. Isr Med Assoc J. 2001 Nov;3(11):803-4.

MEFV mutations and phenotype-genotype correlations in North African Jews and Armenians with familial Mediterranean fever.

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Comment in

Isr Med Assoc J. 2001 Nov;3(11):838-40.

**BACKGROUND:** Familial Mediterranean fever is a genetic disease in which some characteristic gene mutations have been found.

**OBJECTIVES:** To analyze the phenotype-genotype correlations in North African Jews and Armenians with FMF.

**METHODS:** We studied MEFV gene mutations and phenotype-genotype correlations in North African Jews and Armenians with Familial Mediterranean Fever living in France.

**RESULTS:** M694V mutation was the most common mutation in Jews and in Armenians. Patients with M680I homozygosity or M680I/M694V compound heterozygosity had a phenotype as severe as patients with M694V homozygosity.

**CONCLUSIONS:** This study characterizes the phenotype-genotype in specific ethnic

groups of patients with FMF.

PMID: 11729572 [Indexed for MEDLINE]

4710. Am J Kidney Dis. 2001 Dec;38(6):E39.

Polyglandular endocrine failure in a patient with amyloidosis secondary to familial Mediterranean fever.

Keven K(1), Oztas E, Aksoy H, Duman N, Erbay B, Ertürk S.

Author information:

(1)Departments of Nephrology and Urology, Ankara University Medical School, Ibni Sina Hospital, Ankara, Turkey. kenankeven@hotmail.com

Familial Mediterranean fever (FMF) is 1 of the major causes of secondary amyloidosis. Renal involvement is the main clinical complication and it mostly presents with nephrotic syndrome and chronic renal failure. Although deposition of amyloid has been reported in several endocrine glands such as the adrenal, thyroid, and testes, clinically significant functional impairment is uncommon. Herein, we describe a patient in whom the diagnosis of FMF was based on molecular screening and who presented with recurrent hypoglycemic attacks and extensive amyloid deposition affecting various organ function including adrenal, thyroid, parathyroid, testes, intestinal system, and the heart.

PMID: 11728999 [Indexed for MEDLINE]

4711. Am J Kidney Dis. 2001 Dec;38(6):E34.

A case of familial Mediterranean fever with amyloidosis as the first manifestation.

Kutlay S(1), Yilmaz E, Koytak ES, Tulunay O O, Keven K, Ozcan M, Ertürk S.

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(1)Departments of Nephrology, Pathology, and Hematology, Ankara University Medical School, Turkey. skutlay@hotmail.com

We describe a 22-year-old Turkish woman with nephrotic syndrome who had a history of acute myelocytic leukemia. After careful clinical evaluation, the patient underwent a renal biopsy. Light microscopic examination showed deposition of Congo-positive material both in the mesangium and around the small vessels. By histochemical analyses, the deposited material was proved to be amyloid A (AA). Because the patient's history did not reveal any event that might explain the development of secondary amyloidosis, she was screened for mutations causing familial Mediterranean fever (FMF) and was found to be homozygous for the M694V mutation by denaturing gradient gel electrophoresis. We recommend that FMF-Phenotype II and the development of amyloid nephropathy, before or without other symptoms of FMF, should be kept in mind in the face of unexplained proteinuria/amyloidosis, especially in high-risk ethnic groups.

PMID: 11728994 [Indexed for MEDLINE]

4712. Ren Fail. 2001 Sep;23(5):659-67.

Amyloid goiter in Familial Mediterranean Fever (FMF): a clinicopathologic study of 10 cases.

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Author information:

(1)Department of Pathology, Baskent University Faculty of Medicine, Ankara, Turkey.

FMF Amyloidosis is an important etiological factor of end stage renal disease (ESRD) in Mediterranean Countries. Apart from major target organs as cardiovascular, respiratory and gastrointestinal system, endocrine organs can also be involved. We planned to investigate the thyroid involvement in our amyloidosis group. The aim of this study was to determine clinical characteristics of amyloid goiter in FMF patients and the abnormalities of thyroid function, as well as to identify pathologic characteristics. Twenty-two hemodialysis patients (mean age 34.1 +/- 14 years, range 17-68) whose ESRD

secondary to FMF amyloidosis were evaluated with physical examination, serum levels of thyroid hormones, ultrasound examination of thyroid glands, thyroid syntigraphic studies. Goiter was found in 10 patients (4 male, 6 female) having enlarged neck mass (mean age 35 +/- 14 years, range 23-64). The serum levels of thyroid hormones and TSH were normal in 4 patients. Other four cases had euthyroid sick syndrome. Only one patient developed tender enlarged neck mass with subacute thyroiditis symptoms and one had primary hyperthyroidism. Ultrasound examination showed; hypoechoic nodules in 6 patients diffuse multinodular enlargement in 4 patients. Thyroid syntigraphic studies revealed hypoactive nodules in 7 patients and hyperactive nodules in 3 patients. After the laboratory tests were completed, in 10 patients diagnosis were made with fine needle aspiration biopsy. Of 10 patients 5 underwent subtotal thyroidectomy. Immunohistochemical evaluation demonstrated the presence of amyloid AA immunoreactivity in all cases. In conclusion fine needle aspiration from the thyroid when enlarged is useful in the diagnosis of suspected amyloidosis, especially since it is a safe, easily performed procedure. With the help of amyloid goiter diagnosis the patient's prognosis on hemodialysis and with renal transplantation can be predicted. Amyloid goiter must be searched in hemodialysis patients especially in Mediterranean Countries.

PMID: 11725912 [Indexed for MEDLINE]

4713. Arch Intern Med. 2001 Nov 12;161(20):2491-3.

Genetic analysis as a valuable key to diagnosis and treatment of periodic Fever.

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Comment in

Arch Intern Med. 2001 Nov 12;161(20):2406-8.

We describe 2 Dutch patients with recurrent fever attacks undiagnosed for more than 40 years. The diagnosis of periodic fever was made when molecular analysis

revealed novel mutations in the tumor necrosis factor (TNF) receptor gene (TNFRSF1A), establishing the diagnosis of TNF receptor-associated periodic syndrome. This syndrome is an autosomal dominant disorder characterized by recurring episodes of fever, arthralgia, and skin lesions that is caused by mutations in the 55-kd TNFRSF1A gene. This finding has facilitated treatment for TNF receptor-associated periodic syndrome because blocking of TNF signaling seems to alleviate the symptoms. Use of a short course of recombinant p75TNFR:Fc fusion protein (etanercept) induced prolonged remission in one patient.

PMID: 11700162 [Indexed for MEDLINE]

4714. Eur J Haematol. 2001 Aug;67(2):105-9.

Periodic fever (TRAPS) caused by mutations in the TNFalpha receptor 1 (TNFRSF1A) gene of three German patients.

Rösen-Wolff A(1), Kreth HW, Hofmann S, Höhne K, Heubner G, Möbius D, Zintl F, Gahr M, Roesler J.

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TNF-receptor-associated periodic syndrome (TRAPS) is a recently recognized disorder characterized by prolonged attacks of high fever and severe localized inflammation. TRAPS is caused by dominant mutations in the 55 kDa TNF receptor gene (TNFRSF1A). We here describe three German TRAPS patients of two families with Cys30-->Arg and Thr50-->Met mutations, respectively. Both mutations have already been observed before in other nonrelated families. The Thr50-->Met amino acid exchange, caused by an ACG-->ATG transition, has been reported in two other families of different ethnic background. The possibility that the ACG-->ATG sequence alteration is a mutational hot spot causing TRAPS is discussed. Furthermore, we describe and discuss the symptoms of our patients, possible inducers of febrile attacks, and treatments which the patients had received when their diagnoses were still unknown.

PMID: 11722598 [Indexed for MEDLINE]

4715. Chest. 2001 Nov;120(5):1735-8.

Pulmonary hypertension in patients with amyloidosis.

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Author information:

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Pulmonary hypertension (PH) with right-sided cardiac failure is a rare complication of amyloidosis, and its natural history is not well-defined. The aim of our study was to evaluate patients who were seen at our institution who had PH and amyloidosis and to describe the natural history of this complication. The study was a retrospective chart review of patients seen at the Mayo Clinic with both PH and amyloidosis listed as major diagnoses between January 1, 1980, and December 31, 1999. Patients with known causes of PH were excluded. Five patients met our criteria (four women and one man). Four patients had light-chain amyloidosis and one had amyloid A deposition secondary to familial Mediterranean fever. All patients had symptoms related to PH without echocardiographic evidence of left ventricular dysfunction. The median survival time after the diagnosis of amyloidosis was 2.8 years, and PH was found a median of 73 days before death. Five patients died of cardiac complications, including one with sudden cardiac death. PH is an unusual complication of amyloidosis. Patients develop PH late in the disease process and do not have a worse prognosis compared to other patients with cardiac amyloidosis. PH is a marker of advanced amyloidosis.

PMID: 11713162 [Indexed for MEDLINE]

4716. Nat Genet. 2001 Nov;29(3):301-5.

Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome.

Hoffman HM(1), Mueller JL, Broide DH, Wanderer AA, Kolodner RD.

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Comment in

Nat Genet. 2001 Nov;29(3):241-2.

Familial cold autoinflammatory syndrome (FCAS, MIM 120100), commonly known as familial cold urticaria (FCU), is an autosomal-dominant systemic inflammatory disease characterized by intermittent episodes of rash, arthralgia, fever and conjunctivitis after generalized exposure to cold. FCAS was previously mapped to a 10-cM region on chromosome 1q44 (refs. 5,6). Muckle-Wells syndrome (MWS; MIM 191900), which also maps to chromosome 1q44, is an autosomal-dominant periodic fever syndrome with a similar phenotype except that symptoms are not precipitated by cold exposure and that sensorineural hearing loss is frequently also present. To identify the genes for FCAS and MWS, we screened exons in the 1q44 region for mutations by direct sequencing of genomic DNA from affected individuals and controls. This resulted in the identification of four distinct mutations in a gene that segregated with the disorder in three families with FCAS and one family with MWS. This gene, called CIAS1, is expressed in peripheral blood leukocytes and encodes a protein with a pyrin domain, a nucleotide-binding site (NBS, NACHT subfamily) domain and a leucine-rich repeat (LRR) motif region, suggesting a role in the regulation of inflammation and apoptosis.

DOI: 10.1038/ng756

PMCID: PMC4322000

PMID: 11687797 [Indexed for MEDLINE]

4717. Nat Genet. 2001 Nov;29(3):241-2.

A fever gene comes in from the cold.

Kastner DL, O'Shea JJ.

Comment on

Nat Genet. 2001 Nov;29(3):301-5.

DOI: 10.1038/ng1101-241

PMID: 11687785 [Indexed for MEDLINE]

4718. J Allergy Clin Immunol. 2001 Oct;108(4):615-20.

Familial cold autoinflammatory syndrome: phenotype and genotype of an autosomal dominant periodic fever.

Hoffman HM(1), Wanderer AA, Broide DH.

Author information:

(1)Department of Medicine, University of California at San Diego, La Jolla, 92093-0635, USA.

**BACKGROUND:** Familial cold autoinflammatory syndrome (FCAS), commonly known as familial cold urticaria, is a rare autosomal dominant inflammatory disorder with episodic symptoms precipitated by exposure to cold.

**OBJECTIVE:** The goal of this study was to formulate clinical diagnostic criteria for FCAS in a large cohort in whom the diagnosis of FCAS was supported by genetic linkage to chromosome 1q44.

**METHODS:** We assessed 45 affected and 68 unaffected members from 6 American families. DNA analysis was performed to confirm linkage to chromosome 1q44. Clinical characteristics were determined by means of analysis of detailed questionnaires and medical histories.

**RESULTS:** Pedigree and genetic analyses confirmed autosomal dominant transmission and linkage to chromosome 1q44 in all families. The most consistent symptoms during attacks were rash (100%), fever (93%), arthralgia (96%), and conjunctivitis (84%). Age of onset was within the first 6 months of life in 95% of affected subjects. The average delay between cold exposure and onset of symptoms was 2.5 hours, and the average duration of an episode was 12 hours. Renal disease with amyloidosis occurs infrequently in FCAS (2%).

**CONCLUSION:** The most consistent clinical characteristics of FCAS that discriminate it from other periodic fevers are association with cold exposure, conjunctivitis, age of onset, duration of episodes, and an autosomal dominant inheritance pattern. On the basis of the analysis of genotype and phenotype of FCAS, we formulated clinical diagnostic criteria that can be used to distinguish FCAS from other hereditary periodic fever syndromes.



DOI: 10.1067/mai.2001.118790

PMCID: PMC4321996

PMID: 11590390 [Indexed for MEDLINE]

4719. QJM. 2001 Oct;94(10):527-31.

Prevalence and significance of the familial Mediterranean fever gene mutation encoding pyrin Q148.

Booth DR(1), Lachmann HJ, Gillmore JD, Booth SE, Hawkins PN.

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Comment in

QJM. 2002 May;95(5):332-3.

Familial Mediterranean fever (FMF) is caused by more than 25 mutations in the gene MEFV, which encodes pyrin (marennostatin), a protein implicated in the regulation of neutrophil activity. Pyrin Q148, is one of the five most common variants in populations in which FMF typically occurs. Our identification of the pyrin Q148 allele in several patients from ethnic groups in which FMF is not classically recognized who had longstanding fevers or AA amyloidosis prompted us to study the prevalence of pyrin Q148 in healthy British, Indian and Chinese subjects. The gene frequency was also sought in 50 British Caucasian patients with inflammatory arthritis, 25 of whom had AA amyloidosis, five Punjabi Indians with AA amyloidosis complicating inflammatory arthritis, and seven British Caucasian patients with uncharacterized longstanding fever syndromes. The allele frequency for pyrin Q148 was 21%, 15% and 0%, respectively, among Punjabi Indian, Chinese and Caucasian British controls, and was significantly increased among the patients with AA amyloidosis and the patients with obscure fever syndromes ( $p < 0.01$ ). Pyrin Q148 is a polymorphism and occurs widely in global terms, and, although it may cause FMF when associated with certain other MEFV mutations, homozygosity for Q148 alone must usually be insufficient to produce FMF in the populations studied. The association of pyrin Q148 with AA amyloidosis and with obscure chronic inflammatory diseases suggests the variant may augment

inflammation non-specifically, which might have been beneficial during evolution, but could potentially exacerbate many chronic inflammatory disorders.

PMID: 11588211 [Indexed for MEDLINE]

4720. Neth J Med. 2001 Sep;59(3):118-25.

Hereditary periodic fever syndromes.

McDermott MF(1), Frenkel J.

Author information:

(1)Unit of Molecular Medicine, Department of Diabetes and Metabolic Medicine, Barts and the London, Queen Mary's School of Medicine and Dentistry, University of London, UK.

Hereditary periodic fever syndromes are defined by recurrent attacks of generalised inflammation for which no infectious or auto-immune cause can be identified. For most of these disorders, the molecular basis has recently been elucidated. This has opened the prospect of novel therapeutic approaches. Familial Mediterranean fever (FMF) is caused by mutations in the MEFV gene. Pathogenesis is poorly understood. The clinical severity is in part related to the mutations involved. Tumour necrosis factor receptor-1-associated periodic syndrome (TRAPS) is caused by mutations in the TNFRSF1A gene. This results in decreased serum levels soluble TNF-receptor leading to inflammation due to unopposed TNF-alpha action. Results of treatment with recombinant TNF-receptor analogues are promising. The hyper IgD periodic fever syndrome (HIDS) is caused by mutations in the MVK gene, leading to mevalonate kinase deficiency. The pathogenesis remains unclear. Muckle-Wells syndrome (MWS) and familial cold urticaria (FCU) are probably allelic disorders. The gene has been located, but not identified.

PMID: 11583827 [Indexed for MEDLINE]

4721. Rheumatol Int. 2001 Aug;20(6):217-20.

Plasma fibronectin- and thrombospondin-adhesive molecules during acute attacks and attack-free periods of familial Mediterranean fever.

Ertenli I(1), Kiraz S, Oztürk MA, Haznedaroglu IC, Celik I, Kirazli S, Calgüneri M.

Author information:

(1)Department of Rheumatology, Hacettepe University School of Medicine, Ankara, Turkey.

We assessed plasma concentrations of fibronectin (FN) and thrombospondin (TSP) during acute attacks and attack-free periods of patients with familial Mediterranean fever (FMF). Seven female and three male FMF patients (mean age 34+/-7 years) were enrolled in the study. Plasma samples were obtained during acute FMF attacks and after 3 months of freedom from attacks. Erythrocyte sedimentation rate, C-reactive protein, and white blood cell count were evaluated concurrently. Plasma levels of FN and TSP were assayed by enzyme-linked immunosorbent assay (ELISA). Both FN and TSP concentrations were found to increase during acute attacks. Levels of adhesive molecules decreased during attack-free periods ( $P < 0.05$ ). Significant correlations were found between FN and TSP levels and the concentrations of acute-phase response indicators ( $P < 0.05$ ). This study disclosed for the first time significantly higher increments in the plasma levels of FN and TSP during acute FMF attacks than in attack-free periods. Therefore, the two matrix glycoproteins may play precipitating and/or regulatory roles in the inflammatory processes of these attacks.

PMID: 11563578 [Indexed for MEDLINE]

4722. Ann Intern Med. 2001 Sep 4;135(5):S-36.

Summaries for patients. Can genetics help diagnose the hyper-IgD and periodic fever syndrome.

[No authors listed]

PMID: 11556290 [Indexed for MEDLINE]

4723. Internist (Berl). 2001 Aug;42(8):1156-60.

[19-year old Turkish female patient with recurrent abdominal pains and fever.  
Molecular genetics investigation yields a definitive diagnosis ].

[Article in German]

Ascherl J(1), Schmidbaur W, Wienbeck M, Lohse P.

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(1)Zentralklinikum Augsburg, III. Medizinische Klinik, Stenglinstrasse 2, 86156  
Augsburg.

PMID: 11556111 [Indexed for MEDLINE]

4724. Curr Opin Immunol. 2001 Oct;13(5):539-42.

Genetically determined recurrent fevers.

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The usefulness of molecular diagnosis is now well established for genetically  
determined recurrent fevers. In familial Mediterranean fever, the severity of the  
disease and the risk of renal amyloidosis are correlated with mutations in MEFV,  
and the serum amyloid-associated protein (SAA)1 alpha/alpha allele is a modifying  
factor for amyloidosis. Study of the genes in various species shows that the  
human mutations represent a reappearance of the ancestral amino acid state and  
the B30-2 domain, where most human mutations are localized, is absent in the rat

and mouse proteins. Since the discovery of the responsible gene, TNF-receptor-associated periodic syndrome seems to be more frequent than previously considered. Among the new mutations described, some are associated with an incomplete penetrance.

PMID: 11544000 [Indexed for MEDLINE]

4725. Turk J Haematol. 2001 Sep 5;18(3):195-7.

Homozygous  $\beta$ -Thalassemia Associated with Familial Mediterranean Fever in a Turkish Patient.

Canatan D, Coşan R, Taştan H, Bilenoglu O, Başak AN.

We report here a  $\beta$ -thalassemia major case (homozygous IVS-1-110 G-A) associated with Familial Mediterranean Fever (FMF) (homozygous 694 Met-Val). Our patient's clinical course revealed a possible synergistic effect between colchicine and desferrioxamine (DFO). However, this could be only a coincidence, as under colchicine therapy, fever attacks may appear, this may be the topic of a further investigation.

PMID: 27264257

4726. Ann Intern Med. 2001 Sep 4;135(5):338-43.

Molecular analysis of the mevalonate kinase gene in a cohort of patients with the hyper-igd and periodic fever syndrome: its application as a diagnostic tool.

Simon A(1), Cuisset L, Vincent MF, van Der Velde-Visser SD, Delpech M, van Der Meer JW, Drenth JP.

Author information:

(1)University Medical Center St. Radboud, Box 9101, 6500 HB Nijmegen, the Netherlands.

**BACKGROUND:** The hyper-IgD and periodic fever syndrome (HIDS) is characterized by recurrent attacks of fever, abdominal distress, and arthralgia and is caused by mevalonate kinase mutations.

**OBJECTIVE:** To ascertain the role of mevalonate kinase and the usefulness of molecular diagnosis in HIDS.

**DESIGN:** Cross-sectional study.

**SETTING:** The international Nijmegen HIDS registry.

**PATIENTS:** 54 patients from 41 families who met the clinical criteria for HIDS.

**MEASUREMENTS:** Clinical symptoms and signs, immunoglobulin concentration, leukocyte count, erythrocyte sedimentation rate, mutation analysis, and mevalonate kinase enzyme activity assay.

**RESULTS:** There were two groups of patients: 41 patients with mevalonate kinase mutations (classic-type HIDS) and 13 patients without mutations (variant-type HIDS). Patients with classic-type HIDS had a lower mevalonate kinase enzyme activity, a higher IgD level, and more additional symptoms with attacks. The IgD level did not correlate with disease severity, mevalonate kinase enzyme activity, or genotype.

**CONCLUSION:** Genetic heterogeneity exists among patients with a clinical diagnosis of HIDS.

PMID: 11529697 [Indexed for MEDLINE]

4727. Eur J Hum Genet. 2001 Aug;9(8):634-7.

Familial Mediterranean fever: prevalence, penetrance and genetic drift.

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FMF is widely distributed in populations inhabiting the Mediterranean basin. It is mainly attributed to five founder mutations (M680I, M694V, M694I, V726A, E148Q) in the MEFV gene. The frequencies and distribution of these mutations in 146 FMF patients, of Arab and Jewish descent, were compared to that observed in 1173 healthy individuals of pertinent ethnic groups. Five mutations accounted for

91% of FMF chromosomes in our patients. Mutation M694V, predominant in North African Jews, was observed in all patients other than Ashkenazi Jews; mutation V726A was prevalent among all patients other than North African Jews; mutations M694I and M680I were mainly confined to Arab patients. Overall carrier rates, for four mutations (M680I, M694V, V726A, E148Q), were extremely high in our healthy cohort composed of Ashkenazi (n=407); Moroccan (n=243); Iraqi Jews (n=205); and Muslim Arabs (n=318); calculated at 1 : 4.5; 1 : 4.7; 1 : 3.5 and 1 : 4.3 respectively. The V726A allele prevalent among Ashkenazi and Iraqi Jews and Muslim Arabs (carrier rates: 7.4, 12.8 and 7.3%, respectively) was not found among Moroccan Jews. The M694V allele detected among Moroccan and Iraqi Jews and Muslim Arabs (carrier rates 11.1, 2.9 and 0.6%, respectively) was not observed among Ashkenazim. The overall frequency of mutations V726A and E148Q in Ashkenazim, Iraqi Jews and Arabs indicates that the bulk of individuals that comply with the genetic definition of FMF remain asymptomatic.

DOI: 10.1038/sj.ejhg.5200672

PMID: 11528510 [Indexed for MEDLINE]

4728. Klin Med (Mosk). 2001;79(7):21-4.

[The role of systemic and regional immunological reactions in pathogenesis of periodic disease].

[Article in Russian]

Arutiunian VM, Grigorian EG.

PMID: 11523342 [Indexed for MEDLINE]

4729. J Bone Joint Surg Br. 2001 Aug;83(6):912-5.

The inhibitory effects of colchicine on cell proliferation and mineralisation in culture.

Salai M(1), Segal E, Cohen I, Dudkiewicz I, Farzame N, Pitaru S, Savion N.

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(1)Department of Orthopaedic Surgery, Chaim Sheba Medical Centre, Tel Hashomer, Israel.

Colchicine is often used in the treatment of diseases such as familial Mediterranean fever (FMF) and gout. We have previously reported that patients with FMF who had colchicine on a daily basis and who had a total hip arthroplasty showed no heterotopic ossification after surgery. The mechanism by which colchicine causes this clinical phenomenon has never been elucidated. We therefore evaluated the effect of various concentrations of colchicine on cell proliferation and mineralisation in tissue culture, using rat and human cells with and without osteogenic potential. Cell proliferation was assessed by direct cell counts and uptake of (3H)thymidine, and mineralisation by measuring the amount of staining by Alizarin Red. Our findings indicate that concentrations of colchicine of up to 3 ng/ml did not affect cell proliferation but inhibition was observed at 10 to 30 ng/ml. Mineralisation decreased to almost 50%, which was the maximum inhibition observed, at concentrations of colchicine of 2.5 ng/ml. These results indicate that colchicine at low concentrations, of up to 3 ng/ml, has the capacity to inhibit selectively bone-like cell mineralisation in culture, without affecting cell proliferation. Further clinical and laboratory studies are necessary to evaluate the effects of colchicine on biological processes involving the proliferation of osteoblasts and tissue mineralisation in vivo, such as the healing of fractures, the formation of heterotopic bone and neoplastic bone growth.

PMID: 11521938 [Indexed for MEDLINE]

4730. Am J Gastroenterol. 2001 Aug;96(8):2512-3.

Watermelon stomach and familial Mediterranean fever.

Michopoulos S, Tsibouris P, Sotiropoulou M, Petraki K, Vassilopoulos D, Kralios N.

DOI: 10.1111/j.1572-0241.2001.04072.x

PMID: 11513209 [Indexed for MEDLINE]



4731. Cell Mol Biol (Noisy-le-grand). 2001 Jun;47(4):619-35.

TNF and TNFR biology in health and disease.

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Many insights have been gained into cytokine-regulated control of inflammatory processes and host defence in recent years. Evidence has also gradually accumulated that cytokine cascades play a central role in events regulating cell death and differentiation. Further developments include an understanding that the biological effects of the tumor necrosis factor-alpha (TNF-alpha or TNFSF) cytokine may be regulated by soluble TNF receptor binding and that modulation of receptor levels may permit physiological inhibition of TNF action. There has been a gradual realisation of the value of TNF/TNFR ratios as predictors of disease outcome, and the discovery of functional regulatory polymorphisms of the TNF gene and mutations of TNFRSF1A (TNFR1 receptor) have led to conceptual breakthroughs in our understanding of the genetic control of inflammation. However the exact mechanisms by which TNFRSF1A mutations give rise to disease susceptibility are not yet well understood. Over the past 10 years these concepts have been used as the basis for successful anti-TNF therapy of autoimmune diseases like rheumatoid arthritis (RA) and Crohn's disease.

PMID: 11502070 [Indexed for MEDLINE]

4732. J Biol Chem. 2001 Oct 19;276(42):39320-9. Epub 2001 Aug 9.

Interaction between pyrin and the apoptotic speck protein (ASC) modulates ASC-induced apoptosis.

Richards N(1), Schaner P, Diaz A, Stuckey J, Shelden E, Wadhwa A, Gumucio DL.

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Patients with familial Mediterranean fever suffer sporadic inflammatory attacks characterized by fever and intense pain (in joints, abdomen, or chest). Pyrin, the product of the MEFV locus, is a cytosolic protein whose function is unknown. Using pyrin as a "bait" to probe a yeast two-hybrid library made from neutrophil cDNA, we isolated apoptotic speck protein containing a caspase recruitment domain (CARD) (ASC), a proapoptotic protein that induces the formation of large cytosolic "specks" in transfected cells. We found that when HeLa cells are transfected with ASC, specks are formed. After co-transfection of cells with ASC plus wild type pyrin, an increase in speck-positive cells is found, and speck-positive cells show increased survival. Immunofluorescence studies show that pyrin co-localizes with ASC in specks. Speck localization requires exon 1 of pyrin, but exon 1 alone of pyrin does not result in an increase in the number of specks. Exon 1 of pyrin and exon 1 of ASC show 42% sequence similarity and resemble death domain-related structures in modeling studies. These findings link pyrin to apoptosis pathways and suggest that the modulation of cell survival may be a component of the pathophysiology of familial Mediterranean fever.

DOI: 10.1074/jbc.M104730200

PMID: 11498534 [Indexed for MEDLINE]

4733. An Med Interna. 2001 May;18(5):285-6.

[Etiopathogenesis of hereditary periodic fever syndromes].

[Article in Spanish]

de Dios García-Díaz J.

Comment on

An Med Interna. 2000 Apr;17(4):213-6.

PMID: 11496571 [Indexed for MEDLINE]

4734. Am J Med Genet. 2001 Aug 15;102(3):272-6.

Common MEFV mutations among Jewish ethnic groups in Israel: high frequency of carrier and phenotype III states and absence of a perceptible biological advantage for the carrier state.

Kogan A(1), Shinar Y, Lidar M, Revivo A, Langevitz P, Padeh S, Pras M, Livneh A.

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(1)Heller Institute of Medical Research, Sheba Medical Center, Tel Hashomer, and Sackler Faculty of Medicine Tel Aviv University, Tel Aviv, Israel.

Familial Mediterranean fever (FMF) is an autosomal recessive disease, characterized by recurrent attacks of fever and inflammation of serosal membranes and gradual development of nephropathic amyloidosis. The recent cloning of the FMF gene (MEFV) and identification of disease-associated mutations in most patients made the direct determination of FMF carrier frequency feasible. The aim of the present study was to investigate the carrier rate of the most common MEFV mutations among different Jewish ethnic groups in Israel. Further, an attempt was made to elucidate the possible biological advantage that the heterozygote state may confer. Three hundred Ashkenazi, 101 Iraqi, and 120 Moroccan Jews were screened for the E148Q, V726A, and M694V mutations (at least two most common mutations per group), with a resulting overall carrier frequency in the respective ethnic group of 14%, 29%, and 21%. No difference in morbidity between Ashkenazi carriers and non-carriers of MEFV mutations was discerned, although an excess of febrile episodes in carriers of the V726A and in carriers of either V726A or E148Q was evident ( $P < 0.02$  and  $P < 0.05$ , respectively). The frequency of subjects with two MEFV mutations but not expressing FMF (phenotype III) was 1:300 in Ashkenazi Jews and 1:25 in Iraqi Jews, exceeding the reported rate of overt FMF in these ethnic groups by 40-240 fold. These results affirm the high carrier rate among the studied Jewish ethnic groups in Israel and suggest that most subjects with FMF mutations are unaffected.

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PMID: 11484206 [Indexed for MEDLINE]

4735. Kaohsiung J Med Sci. 2001 Apr;17(4):212-5.

Familial Mediterranean fever in a Taiwanese patient.

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Familial Mediterranean fever is a rare disease characterized by cyclic attacks of fever, serositis and strong family background. Here we report a 22-year-old man who suffered from recurrent fever accompanied by chest and abdominal pain for more than 10 years. The attack frequency was about once per 2-3 weeks. Although he consulted many clinics and even received appendectomy at the age of 15, no definite diagnosis was given. During the admission, many laboratory examinations failed to show any abnormality except mild leukocytosis and elevated C-reaction protein. Image studies including chest X ray and abdominal CT scan showed negative result but, interestingly, Gallium-67 scan showed a hot spot in right lower chest and right lower abdomen. After prophylaxis with colchicine 1.0 mg per day, he has enjoyed more than 2 years without the above symptoms.

PMID: 11482133 [Indexed for MEDLINE]

4736. J Lab Clin Med. 2001 Aug;138(2):107-11.

Inhibition of the second phase of amyloidogenesis in a mouse model by a single-dose colchicine regimen.

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Amyloidogenesis consists of two stages. In the first, amyloid enhancing factor

(AEF) is generated, and in the second, deposition of amyloid fibrils occurs. Colchicine is a known inhibitor of amyloidosis of familial Mediterranean fever (FMF) and of mouse experimental amyloidosis, but the timing and mechanism of its effect are still unclear. The aim of this study is to determine whether colchicine inhibits the second phase of amyloidogenesis and to study the time correlate of such an effect. To that end, amyloid was induced in Swiss male mice with AEF and AgNO(3) (an inflammatory stimulus), a method that skips the first phase of amyloidogenesis. Two amyloid induction protocols were used: a standard protocol, in which AEF and AgNO(3) were administered concurrently, and a prolonged protocol, in which the administration of AgNO(3) was delayed by 24 hours or 7 days. To study the inhibitory effect of colchicine on the second phase of amyloidogenesis, a single dose of colchicine (30 microg) was injected intravenously before, during, or after administration of AgNO(3) in both the standard and prolonged amyloid induction protocols. The amount of amyloid deposition in the spleens was determined with the crush-and-smear technique and a 5-grade scale. Colchicine was found to inhibit the second phase of amyloidogenesis. Its best effect was achieved when administered 48 hours after initiation of AgNO(3) injections. The pattern of colchicine-inhibition-in-time in the standard and the prolonged amyloid induction protocols was similar, indicating that colchicine exerts inhibition through its effect on the inflammatory stimulus (AgNO(3)). These findings suggest that (1) colchicine suppresses amyloidogenesis in the late (second) stage and that (2) this suppression is possibly related to the anti-inflammatory effect of colchicine.

DOI: 10.1067/mlc.2001.116488

PMID: 11477377 [Indexed for MEDLINE]

4737. Med Clin (Barc). 2001 Jun 30;117(4):142-6.

[Familial Mediterranean fever].

[Article in Spanish]

Buades Reinés J(1), Aguirre Errasti C.

Author information:

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PMID: 11472687 [Indexed for MEDLINE]

4738. Mutat Res. 2001 Aug 8;479(1-2):235-9.

Two novel mutations R653H and E230K in the Mediterranean fever gene associated with disease.

Timmann C(1), Muntau B, Kuhne K, Gelhaus A, Horstmann RD.

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Familial Mediterranean fever (FMF) is an autosomal recessive disorder caused by mutations in the Mediterranean fever gene (MEFV). We describe two novel missense mutations in MEFV, R653H and E230K. Both were found in compound heterozygosity with the mutation M694V in single Turkish patients with clinical syndromes characteristic for FMF. DNA sequencing and PCR-RFLP typing of the families confirmed the mutations and verified recessive modes of inheritance.

PMID: 11470495 [Indexed for MEDLINE]

4739. Blood. 2001 Aug 1;98(3):851-9.

The familial Mediterranean fever protein, pyrin, associates with microtubules and colocalizes with actin filaments.

Mansfield E(1), Chae JJ, Komarow HD, Brotz TM, Frucht DM, Aksentijevich I, Kastner DL.

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Familial Mediterranean fever (FMF) is a recessive disorder characterized by episodes of fever and intense inflammation. FMF attacks are unique in their sensitivity to the microtubule inhibitor colchicine, contrasted with their refractoriness to the anti-inflammatory effects of glucocorticoids. The FMF gene, MEFV, was recently identified by positional cloning; it is expressed at high levels in granulocytes and monocytes. The present study investigated the subcellular localization of the normal gene product, pyrin. These experiments did not support previously proposed nuclear or Golgi localizations. Instead fluorescence microscopy demonstrated colocalization of full-length GFP- and epitope-tagged pyrin with microtubules; this was markedly accentuated in paclitaxel-treated cells. Moreover, immunoblot analysis of precipitates of stabilized microtubules with recombinant pyrin demonstrated a direct interaction in vitro. Pyrin expression did not affect the stability of microtubules. Deletion constructs showed that the unique N-terminal domain of pyrin is necessary and sufficient for colocalization, whereas disease-associated mutations in the C-terminal B30.2 (rfp) domain did not disrupt this interaction. By phalloidin staining, a colocalization of pyrin with actin was also observed in perinuclear filaments and in peripheral lamellar ruffles. The proposal is made that pyrin regulates inflammatory responses at the level of leukocyte cytoskeletal organization and that the unique therapeutic effect of colchicine in FMF may be dependent on this interaction. (Blood. 2001;98:851-859)

PMID: 11468188 [Indexed for MEDLINE]

4740. Arch Dis Child. 2001 Aug;85(2):158-9.

Increased urinary leukotriene E(4) during febrile attacks in the hyperimmunoglobulinaemia D and periodic fever syndrome.

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**BACKGROUND:** The hyperimmunoglobulinaemia D and periodic fever syndrome is a hereditary periodic fever, caused by deficiency of the enzyme mevalonate kinase. It is unclear how this defect leads to recurrent fever episodes.

**AIM:** To assess the involvement of cysteinyl leukotrienes in the pathogenesis of fever attacks as reflected by urinary leukotriene E(4) (LTE(4)) excretion.

**METHODS:** Urinary LTE(4) was measured in seven patients while febrile and afebrile.

**RESULTS:** LTE(4) was raised during fever in all subjects (46-199 nmol/mol creatinine, mean 92; normal <40). Urinary LTE(4) was normal between attacks, as well as in normal children with fever as a result of miscellaneous causes.

**CONCLUSION:** Our results suggest that cysteinyl leukotrienes play a role in the pathophysiology of this disorder. As no effective treatment is yet available, leukotriene receptor antagonists might offer a new therapeutic approach for patients with the hyperimmunoglobulinaemia D and periodic fever syndrome.

PMCID: PMC1718877

PMID: 11466192 [Indexed for MEDLINE]

4741. Eur J Hum Genet. 2001 Jul;9(7):553-5.

Mutation frequency of Familial Mediterranean Fever and evidence for a high carrier rate in the Turkish population.

Yilmaz E(1), Ozen S, Balci B, Duzova A, Topaloglu R, Besbas N, Saatci U, Bakkaloglu A, Ozguc M.

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Familial Mediterranean Fever (FMF) is a recessive disorder characterised by episodes of fever and neutrophil-mediated serosal inflammation. The FMF gene (MEFV) was recently identified and four common mutations characterised. The aim of this study was to determine the carrier rate in the Turkish population and the mutation frequency in the clinically diagnosed FMF patients. We found a high frequency of carriers in the healthy Turkish population (20%). The distribution of the five most common MEFV mutations among healthy individuals (M694V 3%, M680I



5%, V726A 2%, M694I 0% and E148Q 12%) was significantly different ( $P<0.005$ ) from that found in patients (M694V 51.55%, M680I 9.22%, V726A 2.88%, M694I 0.44% and E148Q 3.55%).

DOI: 10.1038/sj.ejhg.5200674

PMID: 11464248 [Indexed for MEDLINE]

4742. Eur J Hum Genet. 2001 Jul;9(7):473-83.

The spectrum of Familial Mediterranean Fever (FMF) mutations.

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Familial Mediterranean Fever (FMF) is the prototype of a group of inherited inflammatory disorders. The gene (MEFV) responsible for this disease, comprises 10 exons and 781 codons. Twenty-nine mutations, most located in the last exon, have been identified so far. It is unclear whether all are true disease-causing mutations. Five founder mutations, V726A, M694V, M694I, M680I and E148Q account for 74% of FMF chromosomes from typical cases (Armenians, Arabs, Jews, and Turks). Rare mutations are preferentially found in populations not usually affected by FMF (eg Europeans not from the above ancestries). The various combinations of MEFV mutations define severe to mild genotypes. The trend is that genotypes including two mutations located within mutational 'hot-spots' (codons 680 or 694) of the gene are associated with severe phenotypes, whereas mild phenotypes are associated with some other mutations, E148Q being the mildest and least penetrant. Understanding the correlation between the FMF phenotype and genotype is further obscured by the existence of complex alleles, modifier loci, genetic heterogeneity and possible epigenetic factors. Additionally, mutations in the MEFV gene are thought to be involved in non FMF disorders. Carrier rates for FMF mutations may be as high as 1:3 in some populations, suggesting that the disease is underdiagnosed. This review update emphasises that both clinical and genetic features are to be taken into account for patient diagnosis, colchicine treatment and prognosis.

DOI: 10.1038/sj.ejhg.5200658

PMID: 11464238 [Indexed for MEDLINE]

4743. Ryoikibetsu Shokogun Shirizu. 2001;(33):708-9.

[Fever, familial Mediterranean].

[Article in Japanese]

Nagai T(1).

Author information:

(1)Department of Pediatrics, Dokkyo University School of Medicine, Koshigaya Hospital.

PMID: 11462646 [Indexed for MEDLINE]

4744. Ann Rheum Dis. 2001 Aug;60(8):777-80.

Specific glycosylation of alpha(1)-acid glycoprotein characterises patients with familial Mediterranean fever and obligatory carriers of MEFV.

Poland DC(1), Drenth JP, Rabinovitz E, Livneh A, Bijzet J, van het Hof B, van Dijk W.

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(1)Department of Medical Chemistry, Institute for Inflammation and Inflammatory Diseases, Faculty of Medicine, Vrije Universiteit, Amsterdam, The Netherlands.

**BACKGROUND:** Familial Mediterranean fever (FMF) is a periodic febrile disorder, characterised by fever and serositis. The acute phase response during attacks of FMF results from the release of cytokines, which in turn induce increased expression and changed glycosylation of acute phase proteins. A recent study indicated that attacks in FMF are accompanied by a rise of plasma concentrations of serum amyloid A (SAA) and C reactive protein (CRP), which remain significantly raised during remission relative to healthy controls. Another study suggested that obligatory heterozygotes also display an inflammatory acute phase response.

**OBJECTIVE:** To determine the state of inflammation in homozygotic and heterozygotic MEFV genotypes.

**METHODS:** CRP and SAA were studied by enzyme linked immunosorbent assay (ELISA). The glycosylation of the acute phase protein, alpha(1)-acid glycoprotein (AGP), was visualised with crossed affinoimmuno-electrophoresis with concanavalin A as diantennary glycan-specific component and Aleuria aurantia lectin as fucose-specific affinity component.

**RESULTS:** FMF attacks were associated with an increase ( $p<0.05$ ) in the serum inflammation parameters CRP, SAA, and AGP. The glycosylation of AGP showed an increase ( $p<0.05$ ) in fucosylated AGP glycoforms, whereas the branching of the glycans remained unaffected. The glycosylation of AGP in the MEFV carrier group, compared with that in a healthy control group, was characterised by a significant increase ( $p<0.05$ ) in branching of the glycans, whereas the fucosylation remained unaffected.

**CONCLUSION:** The findings suggest an FMF-specific release of cytokines, resulting in a different glycosylation of AGP between a homozygotic and heterozygotic MEFV genotype.

PMCID: PMC1753799

PMID: 11454642 [Indexed for MEDLINE]

4745. Pediatrics. 2001 Jul;108(1):215.

E148Q of the MEFV gene causes amyloidosis in familial Mediterranean fever patients.

Akar N, Akar E, Yalçinkaya F.

PMID: 11452963 [Indexed for MEDLINE]

4746. Am J Hum Genet. 2001 Aug;69(2):301-14. Epub 2001 Jul 6.

The tumor-necrosis-factor receptor-associated periodic syndrome: new mutations in TNFRSF1A, ancestral origins, genotype-phenotype studies, and evidence for further genetic heterogeneity of periodic fevers.

Aksentijevich I(1), Galon J, Soares M, Mansfield E, Hull K, Oh HH, Goldbach-Mansky R, Dean J, Athreya B, Reginato AJ, Henrickson M, Pons-Estel B, O'Shea JJ, Kastner DL.

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Erratum in

Am J Hum Genet 2001 Nov;69(5):1160.

Mutations in the extracellular domain of the 55-kD tumor-necrosis factor (TNF) receptor (TNFRSF1A), a key regulator of inflammation, define a periodic-fever syndrome, TRAPS (TNF receptor-associated periodic syndrome [MIM 142680]), which is characterized by attacks of fever, sterile peritonitis, arthralgia, myalgia, skin rash, and/or conjunctivitis; some patients also develop systemic amyloidosis. Elsewhere we have described six disease-associated TNFRSF1A mutations, five of which disrupt extracellular cysteines involved in disulfide bonds; four other mutations have subsequently been reported. Among 150 additional patients with unexplained periodic fevers, we have identified four novel TNFRSF1A mutations (H22Y, C33G, S86P, and c.193-14 G-->A), one mutation (C30S) described by another group, and two substitutions (P46L and R92Q) present in approximately 1% of control chromosomes. The increased frequency of P46L and R92Q among patients with periodic fever, as well as functional studies of TNFRSF1A, argue that these are low-penetrance mutations rather than benign polymorphisms. The c.193-14 G-->A mutation creates a splice-acceptor site upstream of exon 3, resulting in a transcript encoding four additional extracellular amino acids. T50M and c.193-14 G-->A occur at CpG hotspots, and haplotype analysis is consistent with recurrent mutations at these sites. In contrast, although R92Q also arises at a CpG motif, we identified a common founder chromosome in unrelated individuals with this substitution. Genotype-phenotype studies identified, as carriers of cysteine mutations, 13 of 14 patients with TRAPS and amyloidosis and indicated a lower penetrance of TRAPS symptoms in individuals with noncysteine mutations. In two families with dominantly inherited disease and in 90 sporadic cases that presented with a compatible clinical history, we have not identified any TNFRSF1A mutation, despite comprehensive genomic sequencing of all of the exons, therefore suggesting further genetic heterogeneity of the periodic-fever syndromes.

DOI: 10.1086/321976

PMCID: PMC1235304

PMID: 11443543 [Indexed for MEDLINE]

4747. Clin Microbiol Infect. 2001 Jun;7(6):337-8, 343-4.

Diagnosis at first glance: septic shock in a patient with multiple episodes of fever, abdominal pain and leg inflammation.

González-Beato MJ(1), García-Lechuz JM, Villanueva MJ.

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PMID: 11442568 [Indexed for MEDLINE]

4748. Differentiation. 2001 Mar;67(3):63-71.

Two B or not two B? Overview of the rapidly expanding B-box family of proteins.

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The B-box gene family represents a large number of genes involved in functions such as axial patterning, growth control, differentiation, and transcriptional regulation. These genes possess several conserved motifs that always include a B-box zinc binding motif associated with various other motifs such as the RING zinc finger, an alpha-helical coiled-coil, the rfp or B30.2 motif, propeller domain, and the NHL motif in various combinations. Mutations or rearrangements in several B-box family members are associated with human diseases and cancers such as familial Mediterranean fever (FMF), Optiz/BBB syndrome, acute promyelocytic

leukemia, mulibrey nanism, and thyroid carcinomas. This suggests that members of this gene family play important roles in fundamental biological processes. Here we discuss the known members of this rapidly expanding protein family.

DOI: 10.1046/j.1432-0436.2001.067003063.x

PMID: 11428128 [Indexed for MEDLINE]

4749. Rheumatology (Oxford). 2001 Jun;40(6):606-9.

Genetic counselling in familial Mediterranean fever: has the time come?

Ben-Chetrit E, Sagi M.

PMID: 11426015 [Indexed for MEDLINE]

4750. Aten Primaria. 2001 Jun 15;28(1):85-6.

[PFAPA syndrome: periodic fever, aphthous stomatitis, pharyngitis and adenitis].

[Article in Spanish]

Carretero Ares J, Sánchez Jacob M, Alvarez Hurtado A, de Teresa Romero G.

PMID: 11412587 [Indexed for MEDLINE]

4751. Rheumatol Int. 2001 May;20(4):145-8.

Arthritis in familial Mediterranean fever.

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We studied the rheumatic and various clinical manifestations of familial Mediterranean fever (FMF) in Lebanon. A retrospective review was performed of the medical records of 74 FMF patients seen at the American University of Beirut Medical Centre (AUB-MC) from 1979 to 1996. We also reviewed the medical literature from 1968 to 2000 using MEDLINE and the key words "familial Mediterranean fever" and "arthritis". Arthritis was the presenting symptom in 12 cases (16.2%). Twenty-three patients (31%) had definite arthritis during the course of the disease that was monoarticular in 16 (70%), oligoarticular in six (26%), and polyarticular (rheumatoid-like) in one (4%). Arthritis of the large joints of the knees and ankles was the most frequent articular involvement. The arthritis was transient, monoarticular, nonerosive, and nondeforming in the majority of cases. Four patients (5.4%) had chronic arthritis, with one requiring total hip replacement. As in previous reports on arthritis of FMF, the majority of FMF patients studied in Lebanon had a transient monoarticular nonerosive and nondeforming type of arthritis affecting predominantly the large joints of the lower extremities.

PMID: 11411958 [Indexed for MEDLINE]

4752. J Nephrol. 2001 Mar-Apr;14(2):125-7.

Cardiac and intestinal amyloidosis in a renal transplant recipient with familial Mediterranean fever.

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In Turkey, familial Mediterranean fever (FMF) is an important cause of nephrotic syndrome and endstage renal disease due to renal deposition of AA type amyloid. We report a case of living-related donor renal transplant recipient with FMF and renal AA type amyloidosis, who died of progressive heart failure due to cardiac involvement. The patient also had intractable diarrhea caused by biopsy-proven intestinal amyloidosis. The patient was on 1 mg/day colchicine. Although he was attack-free throughout the post-transplant period, intestinal and clinically

significant cardiac amyloidosis, which implied the presence of sustained inflammation and continuing amyloid deposition, appeared three years after renal transplantation. Cardiac deposition of AA amyloid may cause clinically significant heart disease, leading to cardiovascular mortality after renal transplantation for end-stage renal disease in FMF patients.

PMID: 11411014 [Indexed for MEDLINE]

4753. Arthritis Rheum. 2001 Jun;44(6):1416-9.

The musculoskeletal manifestations of familial Mediterranean fever in children genetically diagnosed with the disease.

Brik R(1), Shinawi M, Kasinetz L, Gershoni-Baruch R.

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**OBJECTIVE:** Familial Mediterranean fever (FMF) is characterized by recurrent episodes of peritonitis, pleuritis, and synovitis. Its most common musculoskeletal manifestation is acute recurrent monarthritis, but other manifestations have also been described. We describe the articular and musculoskeletal manifestations in a group of patients who were found by genetic screening to be homozygous for the FMF gene.

**METHODS:** We surveyed 136 pediatric patients of Mediterranean extraction who were evaluated for a variety of musculoskeletal symptoms, and in whom genetic studies confirmed a diagnosis of FMF. Two groups of patients emerged: group 1 contained 107 patients who displayed a classic picture of FMF, and group 2 comprised 29 patients whose symptoms did not fulfill the criteria for a clinical diagnosis of FMF. Fifty-nine patients were Sephardic Jews and 77 were Arabs. The Jewish patients were all homozygous or compound heterozygous for the M694V mutation, while the Arab patients were homozygous or compound heterozygous for any 1 of the 5 mutations tested (M694V, V726A, M680I, M694I, and E148Q).

**RESULTS:** Acute episodes of monarthritis occurred in 42 (71%) of the Jewish children and 31 (40%) of the Arab children; 70% of these patients had the M694V mutation. Acute monarthritis occurred in 73 (68%) of the patients of group 1, but



in none of the patients from group 2. Ten (34%) of the 29 patients from group 2 exhibited diverse musculoskeletal manifestations. Thirteen patients in our series (10%) presented with a variety of musculoskeletal symptoms, including febrile myalgia syndrome in 6 patients.

CONCLUSION: Acute episodes of monoarthritis are the most common musculoskeletal manifestation of FMF in children bearing the M964V mutation, which predominates among Sephardic Jews, although children with the M694V mutation may also present with diverse nonspecific musculoskeletal manifestations. Genetic screening for FMF appears indicated in the evaluation of unexplained musculoskeletal symptoms in children of Mediterranean extraction.

DOI: 10.1002/1529-0131(200106)44:6<1416::AID-ART236>3.0.CO;2-6

PMID: 11407703 [Indexed for MEDLINE]

4754. Hum Reprod. 2001 Jun;16(6):1218-20.

Azoospermia due to testicular amyloidosis in a patient with familial Mediterranean fever.

Haimov-Kochman R(1), Prus D, Ben-Chetrit E.

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We describe a patient suffering from familial Mediterranean fever (FMF) who presented to our clinic with secondary infertility of 2 years due to amyloid A amyloidosis. His spermiogram disclosed azoospermia. A testicular biopsy revealed hyalinized tubules devoid of full spermatogenesis and containing abundant amyloid, confirmed by Congo red stain. We suggest that testicular amyloidosis be taken into consideration when dealing with azoospermic FMF patients. In view of the progressive nature of amyloid accumulation in the testis we propose to follow routinely the spermiogram of FMF patients with renal amyloidosis. Furthermore, consideration of sperm cryopreservation is suggested in these cases. In FMF patients with azoospermia consideration of testicular biopsy is recommended as early as possible in order to increase the chance of sperm retrieval.

PMID: 11387295 [Indexed for MEDLINE]

4755. Acta Orthop Belg. 2001 Apr;67(2):173-7.

Subtalar arthritis as a presenting symptom of Familial Mediterranean fever: case report and literature review.

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Familial Mediterranean fever (FMF) is an autosomal, recessive disease affecting mainly people of Mediterranean origin. The primary pattern of FMF is acute, self-resolving periodic attacks of high-grade fever, accompanied by either peritonitis, pleuritis, or arthritis and sometimes typical ankle rash that simulates erysipelas. Rare manifestations, such as pericarditis or massive knee effusion, have been reported in the literature as a presenting symptom of FMF. The final diagnosis has recently become more accurate by identification of the gene for FMF. We describe a unique presenting symptom of subtalar arthritis with no former personal or family history of FMF. A genetic evaluation revealed a 694/726 genetic variant that confirmed the diagnosis of FMF. Treatment with daily colchicine, 1 mg/day, resulted in complete resolution of all complaints.

PMID: 11383297 [Indexed for MEDLINE]

4756. Rheumatology (Oxford). 2001 May;40(5):579-84.

Clinical and molecular variability in childhood periodic fever with hyperimmunoglobulinaemia D.

Frenkel J(1), Houten SM, Waterham HR, Wanders RJ, Rijkers GT, Duran M, Kuijpers TW, van Luijk W, Poll-The BT, Kuis W.

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**OBJECTIVES:** The hyperimmunoglobulinaemia D and periodic fever syndrome (HIDS) was found recently to be caused by a deficiency of mevalonate kinase (MK). The aim of this study was to examine whether a relationship exists between the clinical expression of HIDS and the extent of MK deficiency.

**METHODS:** The medical records of children diagnosed with HIDS were reviewed for clinical features and serum immunoglobulin values. The mevalonic acid excretion in urine and MK enzyme activity in patients' cells were measured and the cDNA of the MVK gene was sequenced.

**RESULTS:** Fifteen patients with recurrent fever and raised serum immunoglobulin (Ig) D were included. Their clinical features varied. Eleven patients had a deficiency of MK, caused by mutations in the MVK gene. One mutation (V377I) was common to all 11 patients. Nine patients were compound heterozygotes for V377I and various other MVK mutations. There was no apparent relationship between the observed mutations and the clinical features. Surprisingly, four boys had normal MK activity and no MVK mutations.

**CONCLUSIONS:** Most HIDS patients have mutations in the MVK gene. The clinical variability observed cannot be explained by genotypic differences. Periodic fever and elevated IgD can result from other, still unknown, causes. Hence, testing for MK deficiency is necessary in patients with unexplained periodic fever.

PMID: 11371670 [Indexed for MEDLINE]

4757. Isr Med Assoc J. 1999 Sep;1(1):31-6.

Familial Mediterranean fever: new aspects and prospects at the end of the millenium.

Langevitz P(1), Livneh A, Padeh S, Zaks N, Shinar Y, Zemer D, Pras E, Pras M.

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(1)Heller Institute of Medical Research, Sheba Medical Center, Tel-Hashomer, Israel.

PMID: 11370119 [Indexed for MEDLINE]

4758. Thyroid. 2001 Apr;11(4):397-400.

Amyloid goiter as the initial manifestation of systemic amyloidosis due to familial mediterranean fever with homozygous MEFV mutation.

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We describe a case of amyloid goiter revealing a systemic amyloidosis secondary to familial Mediterranean fever (FMF) with homozygous MEFV mutation, and we review the literature. A 45-year-old euthyroid Sephardic man, known to suffer from FMF, developed a goiter with cold nodule, after which a subtotal thyroidectomy was performed. Histologic evaluation revealed diffuse AA amyloid deposition without any associated thyroid neoplasia. At that time, no other organ was found to be affected by amyloidosis. Colchicine and levothyroxine were prescribed. Eight years later, the patient presented with a rapidly growing neck enlargement. He reported that he had discontinued colchicine therapy 2 years earlier. The serum thyrotropin (TSH) and calcitonin levels were normal. Renal, digestive, and salivary gland biopsies confirmed the presence of systemic AA amyloidosis. Despite the reintroduction of colchicine, the onset of compressive symptoms led to the completion of the total thyroidectomy. The histopathology again demonstrated amyloid deposition, and excluded a malignant neoplasm. Nine cases of amyloid goiter associated with FMF have been reported in the literature; none of them had an amyloid goiter as the first manifestation of systemic amyloidosis. To our knowledge, this is the first case of FMF in which an amyloid goiter preceded the development of secondary systemic amyloidosis. The cessation of colchicine therapy may have played a role in local relapse and the secondary spread of amyloid deposits.

DOI: 10.1089/10507250152039163

PMID: 11349841 [Indexed for MEDLINE]

4759. Isr Med Assoc J. 2001 Jan;3(1):9-12.

Prevalence of ischemic heart disease in patients with familial Mediterranean fever.

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**BACKGROUND:** Familial Mediterranean fever is a genetic disorder manifested by recurrent attacks of peritonitis, pleuritis and arthritis, and characterized by clinical, histological and laboratory evidence for localized and systemic inflammation. Colchicine treatment usually prevents the attacks and the associated inflammation. Inflammation may play an important role in the initiation and progression of atherosclerosis and ischemic heart disease.

**OBJECTIVE:** To study the effect of inflammation and its prevention on the occurrence of IHD, using FMF as a model.

**METHODS AND PATIENTS:** We studied the presence of IHD and its risk factors in 290 FMF patients aged 40 years or more, and in two control groups--233 spouses of the FMF patients, and 126 patients with inflammatory diseases obtained from other outpatient clinics, FMF patients were also compared with age and gender-matched individuals from the population reference data of the Israel Ministry of Health.

**RESULTS:** The prevalence of IHD in FMF patients was significantly lower than in the group of controls from other outpatient clinics (15.5% vs. 30.2%,  $P < 0.05$ ) and comparable with their spouses (11.2%) and with the matched general population in Israel (16%).

**CONCLUSIONS:** These findings suggest that despite the evidence of recurrent inflammation, colchicine-treated FMF patients are not more predisposed to IHD than the normal population.

PMID: 11344818 [Indexed for MEDLINE]

4760. J Pediatr. 2001 May;138(5):759-62.

Incidence of familial Mediterranean fever (FMF) mutations among children of

Mediterranean extraction with functional abdominal pain.

Brik R(1), Litmanovich D, Berkowitz D, Shamir R, Rosenthal E, Shinawi M, Gershoni-Baruch R.

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Erratum in

J Pediatr. 2012 Mar;160(3):533. Litmanovitz, D [corrected to Litmanovich, D].

Of 59 Sephardic Jewish and Arab children in whom functional abdominal pain was diagnosed, we found that 20% were homozygote for the familial Mediterranean fever gene. Inclusion of genetic screening for familial Mediterranean fever may be advisable in the investigation of recurrent abdominal pain among children of Mediterranean extraction.

DOI: 10.1067/mpd.2001.113357

PMID: 11343058 [Indexed for MEDLINE]

4761. Genet Test. 2001 Spring;5(1):53-6.

Study of the mutation M694V of familial Mediterranean fever in Jews.

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Familial Mediterranean fever (FMF) is a recessively inherited disorder characterized by episodes of fever with abdominal pain, pleurisy, or arthritis. The familial Mediterranean fever gene, designated MEFV, was recently cloned, and the missense mutation M694V accounting for most of the patients with this disease was identified. The objective of the present study was to establish frequencies of the M694V mutation in three groups of Jews. The subjects studied were 381 Sephardi, 256 Ashkenazi, and 65 Oriental Jews, all male subjects, previously

collected for an anthropological study, independent of their FMF status. The M694V mutation in the 702 samples was assessed by amplifying genomic DNA with the use of primers that selectively amplify the normal or altered DNA sequence of the M694V mutation, by the amplification refractory mutation system (ARMS). In our sample of Sephardi Jews, the frequency of the M694V mutation is elevated (10.9%), and this is also the case for Oriental Jews (9.2%). In our sample of Ashkenazis, the M694V allele frequency is very low (0.8%).

DOI: 10.1089/109065701750168743

PMID: 11336402 [Indexed for MEDLINE]

4762. J Rheumatol. 2001 Apr;28(4):925-6.

Glucocorticoids but not NSAID abort attacks in hyper-IgD and periodic fever syndrome.

de Dios García-Díaz J, Alvarez-Blanco MJ.

PMID: 11327283 [Indexed for MEDLINE]

4763. Biochim Biophys Acta. 2001 Apr 30;1531(3):165-8.

Characterization of mevalonate kinase V377I, a mutant implicated in defective isoprenoid biosynthesis and HIDS/periodic fever syndrome.

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The list of diseases linked to defects in lipid metabolism has recently been augmented by the addition of hyperimmunoglobulinemia D and periodic fever syndrome (HIDS: MIM 260920), which are correlated with depressed levels of mevalonate kinase activity [1,2] and protein [1]. More specifically, a V377I substitution has been proposed to account for this disease. We observed that V377

appears to be far from invariant in eukaryotic mevalonate kinases. Prokaryotic mevalonate kinases are lower in molecular weight and several terminate prior to residue 377 of the eukaryotic proteins. These observations prompted our direct test of the impact of V377 on activity and protein stability by engineering a V377I mutation in a recombinant human mevalonate kinase. The mutant protein has been isolated and kinetically characterized. In comparison with wild-type enzyme, V377I exhibits only modest differences (notably  $\geq$  6-fold inflation of  $K(m(MVA))$ ) that do not account for the diminished mevalonate kinase activity assayed in HIDS cell extracts. Moreover, thermal inactivation (50 degrees C) of isolated wild-type and V377I enzymes demonstrates little difference in stability between these proteins. We conclude that a single V377I substitution is unlikely to explain the observation of depressed mevalonate kinase stability and catalytic activity in HIDS.

PMID: 11325608 [Indexed for MEDLINE]

4764. Ann Dermatol Venereol. 2001 Mar;128(3 Pt 2):326-33.

[Diagnostic criteria for erysipelas].

[Article in French]

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Diagnosis of erysipelas is based upon the association of an acute inflammatory plaque with fever, lymphagitis, adenopathy and hyperleukocytosis. These associated symptoms are variable (20-70 p. 100 of cases). Bacteriology is not helpful for the diagnosis of erysipelas because of a low sensitivity (hemoculture 5 p. 100, standard examinations 5-41 p. 100), or delayed positivity (serology). Moreover cutaneous bacteriology is difficult to assess when other bacteria than streptococci are isolated. Erysipelas have to be distinguished from non-necrotizing cellulitis by peculiar clinical features (such as erysipeloid, facial staphylococcal infection, Pasteurella, Haemophilus influenzae) and from necrotizing fasciitis. Some non-infectious diseases may mimic erysipelas such as



venous thrombosis, familial Mediterranean fever, prosthesis intolerance, and compartment syndrome. Because the diagnostic value of clinical symptoms is not known and no diagnostic gold standard has been established, it is impossible to be sure that non-streptococcal erysipelas (especially staphylococcal) really exists. Thus, the first line treatment for all erysipelas must be an antistreptococcal antibiotic. Before prescribing a treatment, hemoculture and blood cell count could be useful. If antistreptococcal antibiotherapy is inefficient, all the differential diagnoses must be reviewed.

PMID: 11319359 [Indexed for MEDLINE]

4765. Kidney Int. 2001 May;59(5):1677-82.

Autosomal-dominant periodic fever with AA amyloidosis: Novel mutation in tumor necrosis factor receptor 1 gene Rapid Communication.

Jadoul M(1), Dodé C, Cosyns JP, Abramowicz D, Georges B, Delpech M, Pirson Y.

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**BACKGROUND:** The recent identification of genes responsible for syndromes of periodic fever with amyloidosis has opened the way to a molecular diagnosis of hereditary AA amyloidosis.

**METHODS:** A Belgian woman presented for genetic counseling. Three first-degree relatives had a diagnosis of renal amyloidosis with a history of recurrent fever and inflammatory episodes. Medical records and pathological specimens were obtained from all physicians who had been in charge of her three relatives. Immunohistochemical staining was performed on paraffin-embedded material. A mutation search was performed in the MEFV (Mediterranean fever) and tumor necrosis factor receptor 1 (TNFR1 or TNFRSF1A) genes causing familial Mediterranean fever (FMF) and tumor necrosis factor receptor-associated periodic syndrome (TRAPS), respectively.

**RESULTS:** The family history was consistent with autosomal-dominant transmission of periodic fever with arthralgias, abdominal pain, and eventual AA amyloidosis involving the kidneys, digestive tract, and thyroid. Recurrent amyloidosis in

kidney graft was demonstrated in one patient and was suspected in the other. A novel heterozygous mutation (C55S) in TNFRSF1A was identified in the affected patient available for genetic testing but not in the asymptomatic woman requiring counseling. No mutation was detected in MEFV.

CONCLUSIONS: We report a novel mutation (C55S) in TNFRSF1A, resulting in autosomal-dominant periodic fever and AA amyloidosis. This condition, known as TRAPS, should be added to the differential diagnosis of hereditary renal amyloidosis, with obvious implications for management and genetic counseling.

DOI: 10.1046/j.1523-1755.2001.0590051677.x

PMID: 11318938 [Indexed for MEDLINE]

4766. Eur J Pediatr. 2001 Apr;160(4):264-5.

Isolated recurrent pericarditis in a patient with familial Mediterranean fever.

Tutar HE, Imamoglu A, Kendirli T, Akar E, Atalay S, Akar N.

Familial Mediterranean fever (FMF) should be kept in mind in the differential diagnosis of recurrent pericarditis and mutation analysis should be considered, especially in patients of Mediterranean origin.

PMID: 11317655 [Indexed for MEDLINE]

4767. Eur J Hum Genet. 2001 Apr;9(4):260-6.

Molecular analysis of MVK mutations and enzymatic activity in hyper-IgD and periodic fever syndrome.

Cuisset L(1), Drenth JP, Simon A, Vincent MF, van der Velde Visser S, van der Meer JW, Grateau G, Delpech M; International Hyper-IgD Study Group.

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Hyperimmunoglobulinaemia D and periodic fever syndrome (HIDS) is an autosomal recessive inflammatory disorder characterised by recurrent episode of fever associated with lymphadenopathy, abdominal distress, joint involvement and skin lesions. We recently demonstrated that mutations in the mevalonate kinase gene (MVK) are associated with HIDS. Direct DNA sequencing was done to screen the entire coding region of MVK in 25 unrelated patients with HIDS. Mutations were detected in the coding region of the gene including 11 missense mutations, one deletion, the absence of expression of one allele, as well as three novel polymorphisms. Seven of these mutations are novel. The large majority of the patients were compound heterozygotes for two mutations. Of these, V377I (G-->A) is the most common mutation occurring in 20 unrelated patients and was found to be associated with I268T in six patients. Mutations were associated with a decrease of mevalonate kinase (MK) (ATP:mevalonate 5-phosphotransferase, EC 2.7.1.36) enzymatic activity but not as profound as in mevalonic aciduria, a syndrome also caused by a deficient activity of MK. In HIDS the mutations are located all along the protein which is different from mevalonic aciduria where MK mutations are mainly clustered to a same region of the protein. On the basis of this study, we propose that the diagnostic screen of MVK in HIDS should be first directed on V377I and I268T mutations. Three patients are also described to illustrate the genotypic and phenotypic overlap with mevalonic aciduria.

DOI: 10.1038/sj.ejhg.5200614

PMID: 11313769 [Indexed for MEDLINE]

4768. Eur J Hum Genet. 2001 Apr;9(4):253-9.

Organization of the mevalonate kinase (MVK) gene and identification of novel mutations causing mevalonic aciduria and hyperimmunoglobulinaemia D and periodic fever syndrome.

Houten SM(1), Koster J, Romeijn GJ, Frenkel J, Di Rocco M, Caruso U, Landrieu P, Kelley RI, Kuis W, Poll-The BT, Gibson KM, Wanders RJ, Waterham HR.

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Erratum in

Eur J Hum Genet 2001 Aug;9(8):651.

Mevalonic aciduria (MA) and hyperimmunoglobulinaemia D and periodic fever syndrome (HIDS) are two autosomal recessive inherited disorders both caused by a deficient activity of the enzyme mevalonate kinase (MK) resulting from mutations in the encoding MVK gene. Thus far, disease-causing mutations only could be detected by analysis of MVK cDNA. We now describe the genomic organization of the human MVK gene. It is 22 kb long and contains 11 exons of 46 to 837 bp and 10 introns of 379 bp to 4.2 kb. Three intron-exon boundaries were confirmed from natural splice variants, indicating the occurrence of exon skipping. Sequence analysis of 27 HIDS and MA patients confirmed all previously reported genotypes based on cDNA analysis and identified six novel nucleotide substitutions resulting in missense or nonsense mutations, providing new insights in the genotype/phenotype relation between HIDS and MA.

DOI: 10.1038/sj.ejhg.5200595

PMID: 11313768 [Indexed for MEDLINE]

4769. Eur J Hum Genet. 2001 Mar;9(3):191-6.

A single mutated MEFV allele in Israeli patients suffering from familial Mediterranean fever and Behçet's disease (FMF-BD).

Livneh A(1), Aksentijevich I, Langevitz P, Torosyan Y, G-Shoham N, Shinar Y, Pras E, Zaks N, Padeh S, Kastner DL, Pras M.

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Although familial Mediterranean fever (FMF) is an autosomal recessive disorder, preliminary partial mutation analysis suggested that about 60% of FMF patients, who also suffer from Behçet's disease (FMF-BD), have only a single mutated FMF gene (MEFV). In this study, the possibility that patients with FMF-BD may indeed be carriers of a single mutated MEFV is further analysed. The presence of mutations in the coding region of MEFV of eight patients with FMF-BD, representing six families with 47 members, was determined by sequencing. A

possible role for the non-carrier chromosome and for BD in the expression of FMF in patients with a single mutated MEFV allele was determined by analysing the association between these variables and the presence of FMF in heterozygous kin. Sequence analysis revealed that all eight patients had indeed only one mutation in the coding region of MEFV. The patients' non-carrier chromosomes converged into three different MEFV haplotypes and were shared by heterozygous unaffected kin in five of six families. BD was found in 10 of 11 carriers with FMF vs one of 16 carriers without FMF ( $P < 0.001$ ). These results suggest that FMF may be expressed in individuals harbouring only one coding mutation in MEFV. The findings argue against a role for the non-carrier chromosome in the induction of FMF, and suggest that the FMF phenotype in this cohort was associated with the simultaneous presence of BD. These findings may mirror a more generalised rule, that FMF may be precipitated in carriers of a single mutated FMF gene by factors unrelated to the other MEFV allele.

DOI: 10.1038/sj.ejhg.5200608

PMID: 11313758 [Indexed for MEDLINE]

4770. J Pediatr Ophthalmol Strabismus. 2001 Mar-Apr;38(2):114-6.

Ocular involvement in siblings with familial mediterranean fever.

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Author information:

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PMID: 11310705 [Indexed for MEDLINE]

4771. Eur J Med Res. 2001 Apr 20;6(4):150-60.

Current aspects of colchicine therapy -- classical indications and new therapeutic uses.

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Colchicine has been traditionally used for the treatment of gout. At present there is no generally accepted alternative to colchicine for the treatment of acute attacks or for the prevention of further attacks. The complex actions of this substance, which are mainly attributable to its stabilising action on the cytoskeleton and cell membranes, and its special pattern of distribution form the basis for the results presented here regarding the prophylactic or therapeutic actions of colchicine in a whole range of other diseases. This is all the more significant in that in several instances it concerns diseases that have so far been unsatisfactorily controlled by other treatments. Because of its astonishing absence of side effects, some authors consider that low dose colchicine may be considered as an alternative to previous therapies or even a means of first choice. It is therefore incorrect to think that medical research has shown little interest in this long-known potential and has not sought to confirm promising options by means of controlled studies. Fibrotic and inflammatory systemic diseases and those in which leucocytic chemotaxis play a role seem to be particularly predestined for this.

PMID: 11309227 [Indexed for MEDLINE]

4772. Acta Clin Belg. 2001 Jan-Feb;56(1):46-50.

Progressive bouts of acute abdomen: pet the peritoneum.

Laleman W(1), Vanderschueren S, Mortelmans L, Knockaert DC.

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The recent discovery of the mutated gene responsible for Familial Mediterranean Fever (FMF) is supposed to facilitate its diagnosis which up till now is a

clinical one because there are no specific laboratory tests. The sensitivity of genetic testing is limited because these tests search only for known mutations. In this case report we describe a patient with periodic abdominal pain in whom the diagnosis of FMF was wrongly discarded because of lack of a durable effect of colchicine and negative genetic testing. Diffuse peritoneal inflammation was nicely demonstrated by a FDG-PET (fluoro-deoxy-glucose positron-emission tomography) performed during a typical crisis. We discuss the possible diagnostic pitfalls and conclude that a crisis-PET might upgrade the level of diagnostic certainty in equivocal cases.

DOI: 10.1179/acb.2001.008

PMID: 11307483 [Indexed for MEDLINE]

4773. BJOG. 2001 Apr;108(4):403-7.

Familial Mediterranean fever and menstruation.

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**OBJECTIVE:** To study the prevalence, the nature and the genotype correlation of menstruation associated familial Mediterranean fever attacks.

**METHODS:** One hundred and forty-one female patients with familial Mediterranean fever were studied. A questionnaire regarding the presence and nature of menstruation associated with familial Mediterranean fever was designed and filled in by the authors during the patients' visits to the familial Mediterranean fever clinic. The patients who had a positive history for this manifestation were analysed for their familial Mediterranean fever mutations.

**RESULTS:** Ten out of 141 familial Mediterranean fever female patients (7%) had menstruation-associated familial Mediterranean fever attacks. These patients varied in their disease age of onset and disease duration. Increase of colchicine dose, daily or during the perimenstrual period or oral contraceptives were beneficial in preventing these familial Mediterranean fever attacks. No correlation was found with specific mutations causing familial Mediterranean fever.

CONCLUSIONS: Menstruation-associated familial Mediterranean fever attacks are relatively uncommon. They are not related to the age of the women, the chronicity of their disease or to the mutations they bear. Various therapeutic approaches have to be tried in order to abolish these attacks. A decrease in oestrogen level during menstruation may have a role in this unique manifestation of familial Mediterranean fever.

PMID: 11305548 [Indexed for MEDLINE]

4774. Ned Tijdschr Geneeskd. 2001 Mar 31;145(13):658.

[From gene to disease; tumor necrosis factor receptor and familial periodic fever syndrome].

[Article in Dutch]

Zweers EJ.

PMID: 11305219 [Indexed for MEDLINE]

4775. Klin Padiatr. 2001 Mar-Apr;213(2):86-8.

[Familial Mediterranean fever].

[Article in German]

Steiss JO(1), Wiemann J, Rutz A, Wössmann W, Gortner L.

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BACKGROUND: Familial Mediterranean fever (FMF) is characterized by febrile attacks, acute abdominal pain, pleuritis or arthritis and predominantly observed in ethnic groups of the Mediterranean area (Sephardic Jews, Turks, Armenians).



Its most ominous manifestation is amyloidosis potentially leading to chronic renal failure. FMF is an inherited disorder caused by mutations of the FMF-gene, which first was described in 1997.

CASE REPORT: We report a 10-year old turkish boy and his family presenting with an increased blood sedimentation rate (WBC) and recurrent attacks of acute abdominal pain. A molecular analysis was carried out, confirming a typical mutation of the FMF-gene. The patient remained free of symptoms after starting therapy with colchicine.

CONCLUSION: Investigation of the FMF gene enables an early diagnosis in case of clinical suspect findings, subsequent colchicine administration may prevent amyloidosis.

DOI: 10.1055/s-2001-12882

PMID: 11305198 [Indexed for MEDLINE]

4776. Saudi Med J. 2001 Feb;22(2):104-9.

Familial Mediterranean Fever.

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Familial Mediterranean Fever is a genetic disorder frequently diagnosed among the Arabs. It is also prevalent among Jews, Armenians and Turks. The clinical picture consists of febrile and painful attacks that differ in quality across patients and even within the same patient. There may be accompanying joint pain, chest pain, skin manifestations and other findings, and amyloidosis may occur in some patients as a complication. The primary treatment is Colchicine, which decreases the frequency of the attacks and prevents the occurrence of amyloidosis. The gene responsible for Familial Mediterranean Fever, MEFV, has been mapped and cloned and mutations were identified within its coding sequence. It encodes a protein that is expected to be a down regulator of inflammation. The spectrum of mutations in the Arabic population is partially studied. There are still several issues to be solved before we fully understand the disorder, and to enable us to confront it and decrease the morbidity and mortality inflicted by it.

PMID: 11299400 [Indexed for MEDLINE]

4777. Amyloid. 2001 Mar;8(1):58-64.

Abdominal CT findings in nephropathic amyloidosis of familial Mediterranean fever.

Apter S(1), Zemer D, Terhakopian A, Gayer G, Langevitz P, Amitai M, Schwartz T, Atar E, Hertz M, Pras M, Livneh A.

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To evaluate the abdominal CT features of reactive amyloidosis, abdominal CT scans of 20 patients with amyloidosis of familial Mediterranean fever (FMF) were reviewed and compared with abdominal CT scans of 2 control groups: 22 patients with chronic renal failure (CRF) due to non-amyloidotic kidney diseases and 40 patients with normal kidney function. The kidney size of patients with amyloidosis of FMF were found to vary during the course of the disease from normal or slightly larger than normal at the proteinuric phase, to smaller than normal and comparable to kidney size in CRF, at the uremic stage. Compared to kidney disease of other causes, more patients with FMF-amyloidosis had dense kidneys with coarse parenchymal calcification and calcification in other abdominal organs. Patients with FMF-amyloidosis had fewer aortic calcifications than patients with non-amyloidotic kidney disease. These findings suggest that kidney disease of reactive amyloidosis may have abdominal CT findings distinguishing it from other types of kidney diseases.

PMID: 11293826 [Indexed for MEDLINE]

4778. Amyloid. 2001 Mar;8(1):22-9.

Micro-method to isolate and purify amyloid proteins for chemical

characterization.

Kaplan B(1), Murphy CL, Ratner V, Pras M, Weiss DT, Solomon A.

Author information:

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The amyloidoses represent a heterogeneous group of disorders characterized by the pathologic deposition as fibrils of at least 20 different precursor molecules. To establish definitively the specific type of amyloid protein contained in fibrillar deposits, such material must be extracted, purified, and subjected to amino acid sequence analysis. Heretofore, the chemical identification of amyloid components has required gram quantities of tissue. Given the often-limited amounts of sample available, e.g., that derived from diagnostic needle biopsies, we have developed a micro-method to isolate and purify amyloid from minute tissue specimens. The procedure involves micro-extraction of the amyloid with subsequent purification by SDS-PAGE, electroblotting onto PVDF membranes, excision and elution of amyloid protein-related bands, and reversed phase HPLC. Chemical and immunologic studies of isolated amyloid components have demonstrated the purity achieved with this technique and have provided information on the molecular mass, heterogeneity, and immunoreactivity of the amyloid. Further, using this methodology, it has been possible to obtain sufficient material for amino acid sequencing and thus to establish unequivocally the chemical and molecular composition of the fibrillar deposits. Our microtechnique has clinical import and also is applicable to analyses of the amyloid found in experimental small animal models of these disorders.

PMID: 11293822 [Indexed for MEDLINE]

4779. J Urol. 2001 Apr;165(4):1262-3.

Familial Mediterranean fever as an unusual cause of acute scrotum.

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PMID: 11257698 [Indexed for MEDLINE]

4780. Nat Genet. 2001 Mar;27(3):318-21.

Episodic evolution of pyrin in primates: human mutations recapitulate ancestral amino acid states.

Schaner P(1), Richards N, Wadhwa A, Aksentijevich I, Kastner D, Tucker P, Gumucio D.

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Familial Mediterranean fever (FMF; MIM 249100) is an autosomal recessive disease characterized by recurrent attacks of fever with synovial, pleural or peritoneal inflammation. The disease is caused by mutations in the gene encoding the pyrin protein. Human population studies have revealed extremely high allele frequencies for several different pyrin mutations, leading to the conclusion that the mutant alleles confer a selective advantage. Here we examine the ret finger protein (rfp) domain (which contains most of the disease-causing mutations) of pyrin during primate evolution. Amino acids that cause human disease are often present as wild type in other species. This is true at positions 653 (a novel mutation), 680, 681, 726, 744 and 761. For several of these human mutations, the mutant represents the reappearance of an ancestral amino acid state. Examination of lineage-specific dN/dS ratios revealed a pattern consistent with the signature of episodic positive selection. Our data, together with previous human population studies, indicate that selective pressures may have caused functional evolution of pyrin in humans and other primates.

DOI: 10.1038/85893

PMID: 11242116 [Indexed for MEDLINE]

4781. Am J Med. 2001 Mar;110(4):313-6.

Familial periodic fever and amyloidosis due to a new mutation in the TNFRSF1A gene.

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PMID: 11239851 [Indexed for MEDLINE]

4782. Int Urol Nephrol. 2000;32(2):291-2.

Spontaneous regression of bilateral surrenal haematoma and subclinical hypoaldosteronism in a patient with renal amyloidosis secondary to Familial Mediterranean Fever.

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This report describes a patient with Familial Mediterranean Fever (FMF) associated with renal amyloidosis, bilarectal surrenal haematomas and hypoaldosteronism which was clinically asymptomatic. The deposition of AA amyloide was found on the renal and bone marrow biopsies. Bilateral surrenal haematoma regressed after six month from the first events. Colchicine therapy controlled the attacks of the disease.

PMID: 11229653 [Indexed for MEDLINE]

4783. Ned Tijdschr Geneesk. 2001 Jan 13;145(2):77-8.

[From gene to disease; tumor necrosis factor receptor and a syndrome of familial periodic fever].

[Article in Dutch]

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Familial Hibernian fever (FHF) is a rare hereditary syndrome that causes periodic attacks of fever and inflammation. It is an autosomal dominantly inherited disorder. The gene involved in FHF encodes for a receptor for tumour necrosis factor (TNFR1). These mutations are thought to result in impaired shedding of the receptor from the cell membrane, leading to deficient curtailing of the inflammatory reaction. The acronym TRAPS (TNF-receptor associated periodic syndrome) has been proposed as a more accurate name.

PMID: 11225261 [Indexed for MEDLINE]

4784. Ter Arkh. 2000;72(10):43-6.

[Immunological indices in development of periodic disease].

[Article in Russian]

Karagezian KG, Nazaretian EE, Zavrodniaia AM, Ovnanian KO.

AIM: To specify immune changes in periodical disease (PD) in different periods of PD development as well as peculiarities of their changes in colchicin therapy.

MATERIAL AND METHODS: Clinicoimmunological investigations including blast transformation of lymphocytes with lymphocytic mitogen and renal antigen, leukocyte migration inhibition with renal antigen, spontaneous and complementary rosette formation were made in 828 PD patients and 43 donors.

RESULTS: Decreased functional activity and quantity of T-lymphocytes, their suppressory subpopulation was found in PD. The indices did not correlate with the

disease variants and gender but with age and PD complication. In amyloidosis immunological indices deteriorate with positive trend after colchicin treatment.  
CONCLUSION: PD is characterized by strain in immunological process.

PMID: 11220875 [Indexed for MEDLINE]

4785. Ryoikibetsu Shokogun Shirizu. 2000;(32):243-5.

[C5a inhibitor deficiency].

[Article in Japanese]

Nomura A(1), Hara T.

Author information:

(1)Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University.

PMID: 11212707 [Indexed for MEDLINE]

4786. Arthritis Rheum. 2001 Jan;44(1):163-9.

The MICA region determines the first modifier locus in familial Mediterranean fever.

Touitou I(1), Picot MC, Domingo C, Notarnicola C, Cattan D, Demaille J, Koné-Paut I.

Author information:

(1)Laboratory of Genetics, Arnaud de Villeneuve Hospital, Montpellier, France.

OBJECTIVE: Familial Mediterranean fever (FMF) is a genetically recessive inflammatory disease caused by mutations in the MEFV gene. Most patients of non-Ashkenazi Jewish ancestry or those who are homozygous for M694V manifest a severe disease course, but some express a mild form of the disease. We therefore

searched for other genes which could possibly be implicated in the disease phenotype. We tested MICA (major histocompatibility complex class I chain-related gene A) because it has been associated with a number of other inflammatory disorders.

**METHODS:** One hundred fifty FMF probands and their family members were evaluated. The MEFV gene was screened by a combination of denaturing gradient-gel electrophoresis, restriction fragment length polymorphism, and amplification refractory mutation system. The MICA transmembrane polymorphism in exon 5 was analyzed after biotin-labeled polymerase chain reaction products were loaded onto sequencing gels and subjected to autoradiography.

**RESULTS:** The contribution of MICA to the FMF phenotype was confirmed after adjustment for the patient's ancestry and for the MEFV genotype. MEFV was individually the most important prognostic factor for the disease. However, the impact of M694V homozygosity on the age at disease onset (OR 2.3) was aggravated if patients also inherited MICA-A9 (OR 6.3). In contrast, the frequency of attacks was found to be dramatically reduced (OR 0.16) in patients with MICA-A4.

**CONCLUSION:** We have identified the first FMF modifier locus, MICA. FMF is the first model of a Mendelian disease associated with MICA. These results clarify, at least partly, the inconsistent phenotype-MEFV correlation in FMF.

DOI: 10.1002/1529-0131(200101)44:1<163::AID-ANR20>3.0.CO;2-Z

PMID: 11212154 [Indexed for MEDLINE]

4787. Clin Ter. 2000 Nov-Dec;151(6):439-41.

[Familial Mediterranean fever: report of a case].

[Article in Italian]

Parodi MP(1), Coialbu T, Pittaluga M, Cosso R, Bevevino R, Minervini F, Baffico M.

Author information:

(1)Divisione Medicina, Ospedale A. Gallino, Genova, Ponte X, Italia.

Familial Mediterranean fever is an autosomal recessive hereditary disease characterised by recurrent fever, poliserositis, chest and/or abdominal pain. Up to date diagnosis is based on clinical symptoms, familial anamnesis and response



to colchicine. It is an inflammatory reaction affecting serosal tissues but until recently different hypotheses have been suggested to explain the greatly increased chemotactic activity of the polymorfonuclear leucocytes. Identification of the function of the MEFV gene on chromosome 16 and its protein allows us to understand the pathogenesis of familial Mediterranean fever as well as provides a new diagnostic test and therapeutic measures. We describe a case of a young patient and review the literature.

PMID: 11211479 [Indexed for MEDLINE]

4788. Lancet. 2000 Dec 23-30;356(9248):2154.

Familial Mediterranean Fever in a cold climate: read The Lancet.

Stewart L(1), Tolmie J, Galea P, Touitou I.

Author information:

(1)Department of Child Health, Royal Hospital for Sick Children, Yorkhill, Glasgow, UK. Istewart@abel.co.uk

DOI: 10.1016/S0140-6736(00)03498-X

PMID: 11191544 [Indexed for MEDLINE]

4789. Semin Arthritis Rheum. 2001 Feb;30(4):281-7.

Polyarteritis nodosa in patients with Familial Mediterranean Fever (FMF): a concomitant disease or a feature of FMF?

Ozen S(1), Ben-Chetrit E, Bakkaloglu A, Gur H, Tinaztepe K, Calguneri M, Turgan C, Turkmen A, Akpolat I, Danaci M, Besbas N, Akpolat T.

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BACKGROUND: Familial Mediterranean Fever (FMF) is caused by mutations in the gene

encoding pyrin and is characterized by self-limited, recurrent attacks of fever and serositis. Vasculitis has been increasingly reported in FMF. A study evaluating the prognosis in FMF and polyarteritis nodosa (PAN) patients has not been reported previously.

**OBJECTIVES:** To determine the special characteristics and the prognosis of PAN in FMF patients.

**METHODS:** A questionnaire was used for the present survey. The setting was 7 referral centers from Turkey and Israel. Seventeen patients who were diagnosed with FMF and who developed PAN were included. PAN was diagnosed in those who met the Chapel Hill consensus criteria for microscopic polyarteritis or classic PAN. The clinical features of these 17 patients and the outcomes of their vasculitis were analyzed.

**RESULTS:** The age at diagnosis of PAN in these FMF patients ranged from 3.5 to 37 years. All patients had constitutional symptoms, elevated acute phase reactants, and myalgia at the time PAN was diagnosed. The diagnosis of PAN was confirmed by renal angiography in 8 patients, by renal biopsy in 6 patients, and by muscle and/or nodule biopsies in 6 patients. A number of patients had definite features of both classic PAN and microscopic polyarteritis.

**CONCLUSIONS:** When compared with other PAN patients, those with FMF tended to have a younger age at PAN onset, more frequent perirenal hematomas, and an overall better prognosis. The cases with overlapping features of microscopic and classic PAN pose a problem for the current classification of vasculitis. We suggest that the clinical representation of PAN in FMF patients has certain characteristics and may be a feature of FMF per se.

DOI: 10.1053/sarh.2001.19958

PMID: 11182028 [Indexed for MEDLINE]

4790. Eur J Hum Genet. 2001 Jan;9(1):51-5.

Familial Mediterranean fever in Lebanon: mutation spectrum, evidence for cases in Maronites, Greek orthodoxes, Greek catholics, Syriacs and Chiites and for an association between amyloidosis and M694V and M694I mutations.

Mansour I(1), Delague V, Cazeneuve C, Dodé C, Chouery E, Pêcheux C, Medlej-Hashim M, Salem N, El Zein L, Levan-Petit I, Lefranc G, Goossens M, Delpech M, Amselem S, Loiselet J, Grateau G, Mégarbane A, Naman R.

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Seventy-nine unrelated Lebanese patients were tested for 15 mutations in the MEFV gene: A761H, A744S, V726A, K695R, M694V, M694I, M694del, M680I (G --> C), M680I (G --> A) in exon 10, F479L in exon 5, P369S in exon 3, T267I, E167D and E148Q in exon 2, using PCR digestion, ARMS, DGGE and/or sequencing. Mutations were detected in patients belonging to all communities, most interestingly the Maronite, Greek orthodox, Greek catholic, Syriac and Chiite communities. The most frequent mutations are M694V and V726A (27% and 20% of the total alleles respectively). M694I, E148Q and M680I mutations account respectively for 9%, 8% and 5%. Each of the K695R, E167D and F479L mutations was observed once and all the remaining mutations were not encountered. Of the alleles 33% do not carry any of the studied mutations. The mutation spectra, clinical features and severity of the disease differed among the Lebanese communities. The genotype-phenotype analysis showed a significant association ( $P < 0.001$ ) between amyloidosis and the presence of mutations at codon 694 in exon 10 (both M694V and M694I). None of the patients carrying other mutations developed amyloidosis.

DOI: 10.1038/sj.ejhg.5200574

PMID: 11175300 [Indexed for MEDLINE]

4791. Int Urol Nephrol. 1999;31(5):619-31.

Report on 59 patients with renal amyloidosis.

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Author information:

(1)Cukurova University Faculty of Medicine, Department of Internal Medicine, Adana, Turkey.

We studied a group of 59 patients with renal amyloidosis. Mean age (45 male, 14 female) was 33.05+/-13.04 years. All of the cases had secondary amyloidosis. The causes of secondary amyloidosis were as follows: familial Mediterranean fever (FMF) 18 (30.5%), pulmonary tuberculosis 12 (20.33%), chronic osteomyelitis 8 (13.55%), bronchiectasia 9 (15.25%), rheumatic diseases 4 (6.4%), Castleman's

disease 1 (1.6%), unknown aetiology 7 (11.86%). Hypertension was detected in 15.3% of the cases. In patients with less than 20 ml/min creatinine clearance (Ccr) hypertension was found in 20%. Hypotension was detected in 6 patients and all of these cases had severe hypoalbuminaemia (<2.1 g/dl). Nephrotic range proteinuria (>3.5 g/day) was found in 75% of cases. Daily proteinuria was correlated with serum levels of albumin, total lipid and cholesterol, haematocrit and duration of disease. The mean Ccr was 51.03+/-40.60 ml/min. Twenty-nine per cent of patients had Ccr less than 20 ml/min. Renal, subcutaneous fat and rectal biopsies demonstrated amyloid in 100%, 20% and 57.6%, respectively, of patients tested. Patients with secondary amyloidosis were treated with colchicine in addition to the therapy of primary disease (in 6 patients). Nine patients died, and end-stage renal disease developed in 12 patients during four years of follow-up. Proteinuria disappeared or decreased in patients with secondary amyloidosis except secondary to collagen tissue disease, without advanced renal failure. Colchicine did not affect amyloid deposition in 2 patients with normal renal function and negative proteinuria, who were rebiopsied. It can be questioned that "Colchicine may have effect(s) for decrement on proteinuria". At least colchicine can be of use in secondary amyloidosis.

PMID: 10755352 [Indexed for MEDLINE]

4792. Ann Rheum Dis. 2001 Feb;60(2):146-9.

Amyloidosis induced, end stage renal disease in patients with familial Mediterranean fever is highly associated with point mutations in the MEFV gene.

Ben-Chetrit E(1), Backenroth R.

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(1)Rheumatology Unit, Department of Medicine, Hadassah University Hospital, Jerusalem, Israel. eldad@hadassah.org.il

**BACKGROUND:** Familial Mediterranean fever (FMF) is an autosomal recessive disease characterised by recurrent attacks of fever and serositis. Amyloidosis is the most significant complication of FMF, leading to end stage renal disease (ESRD). Recently the gene (MEFV) causing this disease was cloned and more than 18 mutations have been identified. The hypothesis that the development of

amyloidosis is associated with one of these mutations was tested.

**METHODS:** 23 patients with FMF and ESRD were analysed for their MEFV mutations and correlated with their corresponding rectal and renal biopsies. As case controls 23 patients with FMF free of renal disease, but with similar origin, sex, age, and age at onset of FMF, were chosen.

**RESULTS:** All the patients with ESRD induced by amyloidosis were homozygous for the M694V or M694I mutations. This finding was significantly different from that seen in the control group.

**CONCLUSIONS:** Amyloidosis is highly associated with the 694 substitution in the MEFV gene causing FMF. It seems that genetic predisposition plays a part in the development of this complication of FMF.

PMCID: PMC1753463

PMID: 11156548 [Indexed for MEDLINE]

4793. Hum Mutat. 2001;17(1):79.

Y688X, the first nonsense mutation in familial Mediterranean fever (FMF).

Notarnicola C(1), Manna R, Rey JM, Touitou I.

Author information:

(1)Hospital A de Villeneuve, Montpellier, France.

DOI: 10.1002/1098-1004(2001)17:1<79::AID-HUMU23>3.0.CO;2-2

PMID: 11139259 [Indexed for MEDLINE]

4794. Hum Mutat. 2001;17(1):71.

Is the Ala138Gly alteration of MEFV gene important for amyloidosis?

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Comment in

Hum Mutat. 2003 Jan;21(1):96-7.

Progressive systemic amyloidosis is the most important complication of familial Mediterranean fever that inevitably leads to chronic renal failure. Initial studies have suggested that the presence of the Met694Val mutation carry a significant risk for the development of amyloidosis. On the contrary, our data revealed that there was no dominance of any MEFV mutation in relation to amyloidosis. The difference between our mutation data and others led us to study a polymorphism in Turkish population that might be a risk factor for the occurrence of amyloidosis. As some of the previously reported exonic polymorphisms in other disease states found to increase the genetic susceptibility, we aimed to study Ala138Gly of the MEFV gene. Our study group consisted of 124 FMF patients, of which 47 had amyloidosis. Eighty-one individuals without any familial history of FMF were included as control group. There was no statistically significant difference between healthy controls and FMF patients for the Ala138Gly polymorphism ( $p=0.9$ ). However, when FMF/amyloidosis patients ( $n:47$ ) were taken as another group, the difference was significant ( $p= 0.01$ ) indicating that the carriers of 138Gly are more prone to amyloidosis [odds ratio 3.1 (CI 95% 1.57-5.75)].

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DOI: 10.1002/1098-1004(2001)17:1<71::AID-HUMU8>3.0.CO;2-3

PMID: 11139244 [Indexed for MEDLINE]

4795. Clin Exp Rheumatol. 2000 Nov-Dec;18(6):787-8.

Fabry's disease mimicking familial Mediterranean fever.

Dinc A, Simsek I, Pay S, Caglar K, Can C.

PMID: 11138354 [Indexed for MEDLINE]

4796. Scand J Rheumatol. 2000;29(6):394-5.

Severe and prolonged febrile myalgia in familial Mediterranean fever.

Odabas AR(1), Cetinkaya R, Selcuk Y, Kaya H.

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(1)Department of Internal Medicine, Ataturk University, School of Medicine, Erzurum, Turkey. alirizao@yahoo.com

Familial Mediterranean fever (FMF) is characterized by recurrent attacks of fever and serositis. Typical attacks of FMF last 3 to 5 days. Fever and myalgia are not always improved by colchicine therapy and sometimes require steroid therapy. We present two cases of severe prolonged febrile myalgia where steroid therapy was needed.

PMID: 11132210 [Indexed for MEDLINE]

4797. Amyloid. 2000 Dec;7(4):289-93.

Amyloidosis of familial mediterranean fever and the MEFV gene.

Pras M(1).

Author information:

(1)Heller Institute of Medical Research, Sheba Medical Center, Tel Hashomer, Israel.

PMID: 11132099 [Indexed for MEDLINE]

4798. Eur J Pediatr. 2000 Dec;159(12):895-7.

Near fatal acute colchicine intoxication in a child. A case report.

Goldbart A(1), Press J, Sofer S, Kapelushnik J.

Author information:

(1)Paediatric Department B, Soroka University Medical Centre, Ben-Gurion University of the Negev, Beer-Sheva, Israel.

An 8-year-old child with familial Mediterranean fever exhibited signs of colchicine intoxication while receiving prophylactic doses of the drug. She developed gastrointestinal, central nervous system, cardiovascular and haematological disturbances. Over 2 months she had been drinking high doses of natural grapefruit juice which, combined with long-term colchicine therapy and a viral upper respiratory tract infection, increased her susceptibility to the drug. CONCLUSION: To the best of our knowledge, this is the first time colchicine intoxication in this age group has been described in the English literature.

PMID: 11131346 [Indexed for MEDLINE]

4799. Hum Mol Genet. 2000 Dec 12;9(20):3001-9.

Alternative splicing at the MEFV locus involved in familial Mediterranean fever regulates translocation of the marenostin/pyrin protein to the nucleus.

Papin S(1), Duquesnoy P, Cazeneuve C, Pantel J, Coppey-Moisan M, Dargemont C, Amselem S.

Author information:

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Mutations in MEFV, a gene encoding a protein (marenostin/pyrin) of unknown function, are associated with familial Mediterranean fever, a genetic condition characterized by febrile episodes of serosal inflammation. Based on its primary structure, this 781 residue protein is thought to function as a nuclear effector molecule. However, recent transient expression studies indicated a perinuclear cytoplasmic localization. Here, we describe the isolation and expression of a novel human MEFV isoform, MEFV-d2, generated by in-frame alternative splicing of exon 2. This transcript, expressed in leukocytes, predicts a 570 residue protein designated marenostin-d2. To investigate differences in subcellular localization



between the full-length protein (marenostin-fl) and marenostin-d2, while providing against the overexpression of transiently expressed proteins, we have generated CHO cell lines stably expressing these two isoforms fused to the green fluorescent protein. The localization pattern of marenostin-d2 differs dramatically from that of marenostin-fl. Marenostin-fl is homogeneously distributed over the entire cytoplasm, whereas marenostin-d2 concentrates into the nucleus. To map the critical domain(s) specifying these differences, deletion mutants have been generated. Deletion of the putative nuclear localization signals (NLS) does not alter the nuclear localization of marenostin-d2 whereas, despite the lack of discernible NLS in the domain encoded by the exon 1-exon 3 splice junction, deletion of this domain indeed disrupts this localization. These data, which challenge the current domain organization model of marenostin, strongly suggest that MEFV encodes a nuclear protein and raises the possibility that MEFV alternative splicing may control functions of wild-type and mutant marenostin proteins by regulating their translocation to the nucleus.

PMID: 11115844 [Indexed for MEDLINE]

4800. Arch Dermatol. 2000 Dec;136(12):1487-94.

Tumor necrosis factor receptor-associated periodic syndrome: a novel syndrome with cutaneous manifestations.

Toro JR(1), Aksentijevich I, Hull K, Dean J, Kastner DL.

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**BACKGROUND:** Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is an inflammatory disorder characterized by prolonged episodes of periodic fever and localized inflammation and dominantly inherited mutations in TNFRSF1A, the gene encoding the 55-kDa tumor necrosis factor receptor. To our knowledge, the cutaneous pathologic characteristics of TRAPS have not been described previously. **OBJECTIVES:** To characterize the dermatologic manifestations of TRAPS by clinical, microscopic, and molecular methods, and to investigate its immunophenotype.

**DESIGN, SETTING, AND PATIENTS:** At the National Institutes of Health Clinical Center, Bethesda, Md, a tertiary care referral center, 25 patients with a clinical and molecular diagnosis of TRAPS were evaluated clinically and 10 biopsy specimens of lesional skin were examined by light microscopy and immunohistochemistry. Patients were screened for mutations in TNFRSF1A, the gene coding for the p55 tumor necrosis factor receptor.

**MAIN OUTCOME MEASURES:** Clinical, light microscopic, and immunohistochemical features.

**RESULTS:** The skin eruption usually lasted 4 to 21 days (mean, 13 days). Of 25 patients, 21 (84%) presented with migratory erythematous macules and patches and 10 (40%) had edematous dermal plaques. Conjunctivitis, characterized by pain and redness and/or periorbital edema, was present in 11 patients (44%). Most patients had their first skin eruption during the first 2 years of life. All patients had fever associated with the skin eruption. Most patients had associated abdominal pain (22 [88%]) and myalgia (20 [80%]). Other symptoms included arthralgia (13 [52%]), pleuritic chest pain (10 [40%]), and headache (17 [68%]). Microscopic examination of 10 biopsy specimens of lesional skin showed a superficial and deep perivascular and interstitial infiltrate of lymphocytes and monocytes. None of the biopsy specimens showed multinucleated macrophages or granulomatous or leukocytoclastic vasculitis. The results of immunohistochemistry showed a perivascular infiltrate of CD3+, CD4+, CD8+, CD68+, CD79a-, and CD20- cells. All the mutations were missense mutations in exons 2 through 4 of TNFRSF1A, directly affecting the extracellular domain of the protein.

**CONCLUSIONS:** TRAPS is characterized by a spectrum of dermatologic findings, including migratory patches, edematous plaques, periorbital edema, and/or conjunctivitis. TRAPS is characterized by a perivascular dermal infiltrate of lymphocytes and monocytes.

PMID: 11115159 [Indexed for MEDLINE]

4801. Biochim Biophys Acta. 2000 Dec 15;1529(1-3):19-32.

Biochemical and genetic aspects of mevalonate kinase and its deficiency.

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Mevalonate kinase (MK) is an essential enzyme in the mevalonate pathway which produces numerous cellular isoprenoids. The enzyme has been characterized both at the biochemical and the molecular level in a variety of organisms. Despite the fact that mevalonate kinase is not the rate-limiting enzyme in isoprenoid biosynthesis, its activity is subject to feedback regulation by the branch-point intermediates geranyldiphosphate, farnesyldiphosphate and geranylgeranyldiphosphate. Recently, the importance of mevalonate kinase was demonstrated by the identification of its deficiency as the biochemical and molecular cause of the inherited human disorders mevalonic aciduria and hyperimmunoglobulinemia D and periodic fever syndrome. The pathophysiology of these disorders is not yet understood, but eventually will give insight into the in vivo role of mevalonate kinase and isoprenoid biosynthesis with respect to the acute phase response and fever. The subcellular localization of mevalonate kinase is still a matter of debate. The enzyme could be localized predominantly in the cytosol, or in peroxisomes, or it is associated differentially with peroxisomes. Here we review the biochemical and molecular properties of MK, and discuss its biological significance, the regulation of its enzyme activity and finally its subcellular localization.

PMID: 11111075 [Indexed for MEDLINE]

4802. Ugeskr Laeger. 2000 Nov 13;162(46):6264-5.

[Treatment of familial Mediterranean fever. A not so rare diagnosis in Denmark].

[Article in Danish]

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(1)Trop- og rejsemedicinsk Klinik, København.

Familial Mediterranean fever (FMF) is characterised by recurrent episodes of fever and painful serositis. It is inherited as an autosomal recessive disease,

predominantly in people from the Eastern Mediterranean area. The patient described here was followed-up for 6 years. He had FMF diagnosed primarily on clinical grounds, which is now verified by a gene test.

PMID: 11107993 [Indexed for MEDLINE]

4803. Ugeskr Laeger. 2000 Nov 13;162(46):6263-4.

[Familial Mediterranean fever in a 26-year old Lebanese man].

[Article in Danish]

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FMF is a hereditary disorder characterised by periodic fever and acute abdominal, chest, or joint pain. In the long term, amyloidosis may develop and eventually result in kidney failure. A 26-year-old man from Lebanon was diagnosed with FMF by genetic testing and treated with colchicine for two months. Colchicine reduced the frequency, duration, and intensity of his attacks, and thus minimised the risk of amyloidosis developing.

PMID: 11107992 [Indexed for MEDLINE]

4804. Ugeskr Laeger. 2000 Nov 13;162(46):6261-2.

[Familial Mediterranean fever with pseudodominant inheritance].

[Article in Danish]

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(1)Medicinsk-epidemisk afdeling A, Aarhus Universitetshospital, Marselisborg Hospital. [britta.tarp@dadlnet.dk](mailto:britta.tarp@dadlnet.dk)

Familial Mediterranean fever (FMF) is an autosomal, recessively inherited disease, mainly affecting patients from the Mediterranean basin. Owing to the recessive transmission, the disease in most of the affected families only occurs in the members of one generation. However, high consanguinity rates in populations with carrier frequencies as much as 1:5 may account for the occurrence of FMF in two or more successive generations, so-called pseudodominant inheritance. We report a case of pseudodominant inheritance in a Turkish family living in Denmark.

PMID: 11107991 [Indexed for MEDLINE]

4805. Curr Opin Pediatr. 2000 Dec;12(6):563-6.

Periodic fever syndromes.

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The term periodic fever syndrome has been used in a restricted sense to denote two diseases in which episodic fevers occur with a regular periodicity: cyclic neutropenia and the periodic fever, aphthous stomatitis, pharyngitis, and adenopathy (PFAPA) syndrome. Other authors have used the term in a more general sense to encompass a larger group of disorders characterized by recurrent episodes of fever that do not necessarily follow a strictly periodic pattern. These include familial Mediterranean fever, the autosomal dominant familial fevers (also known as Hibernian fever), and the hyperimmunoglobulin D syndrome. This article follows the latter usage, and reviews recent advances in our understanding of the genetics and molecular pathology of this group of diseases, as well as their clinical characterization and treatment.

PMID: 11106276 [Indexed for MEDLINE]

4806. Praxis (Bern 1994). 2000 Oct 26;89(43):1741-4.

[Familial Mediterranean fever--from gene test to clinical aspects].

[Article in German]

Sudeck H(1).

Author information:

(1)Bernhard-Nocht-Institut, Hamburg.

Familial Mediterranean Fever (FMF) is a genetically defined disease affecting mostly families of jewish, turkish or armenian origin whose ancestors originate from the mediterranean basin. The first officially acknowledged description was given by SIEGAL in 1945 but previous cases were reported since 1908. The main clinical signs which are very varying in intensity and appearance are periodic attacks of fever with peritonitis, pleurisy and arthritis. The classical but not always found complication is amyloidosis with renal failure which is preventable by lifelong colchicine therapy. By using a novel genetest it is now possible to definitely diagnose FMF instead of relying on a diagnosis made merely by exclusion. This will emphasize the use of colchicine and should bring us nearer to the pathophysiology of this interesting disease.

PMID: 11103618 [Indexed for MEDLINE]

4807. Nephron. 2000 Nov;86(3):383-4.

Renal amyloidosis in a patient with homozygous sickle cell anemia and M694V/M694V mutation.

Akar H, Keven K, Nergizoglu G, Erturk S, Ates K, Erbay B, Akar N, Duman N, Karatan O.

DOI: 10.1159/000045813

PMID: 11096315 [Indexed for MEDLINE]

4808. Rheumatology (Oxford). 2000 Nov;39(11):1275-9.

Phenotype-genotype correlation in 91 patients with familial Mediterranean fever reveals a high frequency of cutaneomucous features.

Koné Paut I(1), Dubuc M, Sportouch J, Minodier P, Garnier JM, Touitou I.

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**OBJECTIVES:** To describe the clinical manifestations of familial Mediterranean fever (FMF) in 91 patients from 47 families and provide data from the genetic study. **P:atients and methods.** We conducted a retrospective chart review of 91 patients (including 83 children aged <15 yr) from 47 families through a questionnaire and a specific database. The genetic analysis included complete screening of known mutations of the MEFV gene on chromosome 16p13.3. A positive diagnosis required at least two mutations, one on each chromosome.

**RESULTS:** Our panel included 52 females and 39 males, with a mean age of 7.27 yr. Of the 47 families, 31 were non-Ashkenazi Jews, 10 were Armenians and six were from other ethnic groups. Clinical features included fever (100%), peritonitis (86%), pleuritis (56%), arthritis (34%) and myalgias (27%). We observed a high rate of cutaneous manifestations (47%); erythema, oedema and recurrent oral ulcers were the most frequent. Phenotype-genotype correlations showed a significant association of M694V homozygosity with earlier age of onset ( $P = 0.044$ ), fever >39 degrees C ( $P = 0.002$ ), pleural crisis ( $P = 0.0044$ ), splenomegaly ( $P = 0.0005$ ) and arthritis ( $P = 0.001$ ). Associations with mucocutaneous features were as follows: erysipelas-like erythema ( $P = 0.012$ ), oedema ( $P = 0.61$ , not significant) and oral ulcers ( $P = 0.45$ , not significant).

**CONCLUSION:** New phenotype-genotype correlations emerged from our study: homozygosity for the M694V mutation was associated with intensity of fever, splenomegaly and with erysipelas-like erythema. Apart from erysipelas-like erythema, no significant association was found between other cutaneous features and the genotype.

PMID: 11085810 [Indexed for MEDLINE]

4809. Semin Arthritis Rheum. 2000 Oct;30(2):138-43.

The clinical patterns of myalgia in children with familial Mediterranean fever.

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Author information:

(1)Department of Pediatrics, Faculty of Medicine, University of Jordan.

**OBJECTIVES:** To study the frequency and clinical patterns of myalgia in a defined group of children with familial Mediterranean fever (FMF).

**METHODS:** A prospective 4-year (September 1995-September 1999) study of children with FMF seen in the pediatric FMF clinic of Jordan University teaching hospital.

Diagnosis of FMF was made according to published criteria. Once the diagnosis of FMF and myalgia was made, details about myalgia were collected by interview with the child and his/her parents and entered into a special study form.

**RESULTS:** Of 264 children with FMF seen over the study period, 65 (25%) developed myalgia. Three clinical patterns of myalgia were identified: the spontaneous pattern, the exercise-induced pattern, and the protracted febrile myalgia syndrome (PFMS), seen in 8%, 81%, and 11% of patients, respectively. The three patterns differed in the severity of pain, height of fever, and duration of the episode. In 33 children with the exercise-induced myalgia, in which response to colchicine could be reliably assessed, a favorable response was achieved in 97%. Three children with the PFMS had a dramatic response to corticosteroids.

**CONCLUSIONS:** Myalgia in children with FMF is common and can follow three different clinical patterns.

DOI: 10.1053/sarh.2000.16646

PMID: 11071586 [Indexed for MEDLINE]

4810. Immunol Today. 2000 Oct;21(10):470-1.

TNF is here to stay!



Balkwill F(1), Foxwell B, Brennan F.

Author information:

(1)Imperial Cancer Research Fund, Lincoln's Inn Fields, London, UK.

Comment in

Trends Immunol. 2001 Mar;22(3):127-9.

PMID: 11071522 [Indexed for MEDLINE]

4811. Dig Liver Dis. 2000 Aug-Sep;32(6):504-9.

Familial Mediterranean fever. A review of the disease and clinical and laboratory findings in 105 patients.

Ozel AM(1), Demirtürk L, Yazgan Y, Avşar K, Günay A, Gürbüz AK, Gültepe M.

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**BACKGROUND:** The diagnosis of familial Mediterranean fever still remains clinical, since no specific laboratory test exists, other than a molecular genetic test which is not widely available.

**AIM:** To evaluate the clinical findings in 105 Turkish patients; to compare these findings with those in the literature; and to make a brief review of the disease.

**METHODS:** A total of 105 familial Mediterranean fever patients were evaluated either retrospectively (for those diagnosed before 1997), or prospectively (for those after 1997). A diagnostic criteria set was used in addition to the clinical and laboratory findings that can be seen in familial Mediterranean fever, including the newly described manifestations. Previously selected clinical and laboratory parameters were observed for three consecutive days.

**RESULTS:** Of our patients, 88.5% were of Turkish, 3.8% of Armenian and 7.6% of Jewish origin. Family history was positive in 87 (82.8%) patients. Involved site was peritoneum in 97 (92%), joints in 45 (42.8%) and pleura in 19 (18%).

Frequency of myalgia/arthralgia was 24.7%, and skin findings were observed in 16.1% of patients. Splenomegaly, not related to amyloidosis, was present in 21 (20%)

patients. Meningeal, retinal or ovarian/testicular involvement was not observed.  
CONCLUSION: Identification of familial Mediterranean fever gene has led to the application of a molecular genetic test for the diagnosis of Familial Mediterranean Fever. Until genetic methods become widely available, diagnosis will remain clinical. Thus, awareness of various clinical forms and of the correct usage of diagnostic criteria in various patient populations is important.

PMID: 11057926 [Indexed for MEDLINE]

4812. Ann Rheum Dis. 2000 Nov;59(11):910-3.

A survey of phenotype II in familial Mediterranean fever.

Melikoğlu M(1), Ozdoğan H, Korkmaz C, Kasapçopur O, Arisoy N, Akkuş S, Fresko Z, Yazici H.

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(1)Department of Rheumatology, Cerrahpaşa Medical School, University of Istanbul, Istanbul, Turkey.

OBJECTIVE: Phenotype II in familial Mediterranean fever (FMF) is the onset of amyloidosis before the onset of FMF with its typical attacks, or as an isolated finding in a member of an FMF family. Its presence was investigated by looking for proteinuria among the asymptomatic relatives of patients with FMF complicated by amyloidosis and among the asymptomatic relatives of patients with juvenile chronic arthritis (JCA) complicated by amyloidosis, used as controls.

METHODS: The relatives of the index patients (13 with FMF and amyloidosis) and controls (6 with JCA and amyloidosis) were screened for proteinuria. Rectal biopsies were performed when proteinuria was significant ( $\geq 300$  mg/d).

RESULTS: 461 relatives were screened in the FMF group and 269 among the controls. Two of the FMF relatives and one JCA relative had no symptoms of FMF but had significant proteinuria. Rectal biopsy for amyloidosis was negative in all instances of significant proteinuria.

CONCLUSION: Phenotype II is uncommon among the relatives of patients with FMF and amyloidosis.

PMCID: PMC1753025

PMID: 11053071 [Indexed for MEDLINE]

4813. Klin Med (Mosk). 2000;78(9):24-5.

[Immune disorders in periodic disease].

[Article in Russian]

Karagezian KG, Nazaretian EE, Zavgorodniaia AM, Ovnanian KO.

The examination of 404 patients with periodic disease (301 with uncomplicated form and 104 with amyloidosis complication) has detected decreased functional activity of T-lymphocytes and their suppressor subpopulation, their subnormal quantity. There was a rise in T-helper/T-suppressor index, level of B- and O-lymphocytes, sensitivity to the renal antigen. Colchicin therapy stopped the attacks and stimulated T-suppressor activity. Combined treatment with tactivin is proposed.

PMID: 11051734 [Indexed for MEDLINE]

4814. Ren Fail. 2000;22(5):613-21.

High frequency of amyloid lymphadenopathy in uremic patients.

Güz G(1), Ozdemir BH, Sezer S, Yakupoglu U, Demirhan B, Ozdemir FN, Haberal M.

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Amyloid lymphadenopathy has only been reported in case report form, or in small groups of patient groups within large series. We believe that amyloid lymphadenopathy is common in uremic patients, and thus designed this study to determine the frequency of this condition in hemodialysis patients, and to assess its types and patterns. We reevaluated 46 uremic patients' lymph node biopsies

for amyloid deposits. We also immunohistochemically identified the protein origin of these deposits using Amyloid A, kappa, lambda, beta2 microglobulin, and transthyretin antibodies. Histopathologically, we observed for vascular involvement, follicular deposition, and diffuse deposition. We detected amyloid deposits in 10 of the 46 (22%) patients' lymph nodes. The patterns of deposition were vascular involvement alone in six specimens, vascular involvement plus follicular deposition in three, and vascular involvement plus diffuse deposition in one specimen. Amyloid AA type protein was present in seven nodes, beta2 microglobulin-related amyloid in two nodes, and immunoglobulin-derived protein (AL) in one node. We assessed these 10 patients for causes of end-stage renal disease (ESRD) and other conditions that might relate to amyloidosis. The cause of ESRD in the seven patients with AA amyloid were renal amyloidosis secondary to Familial Mediterranean Fever in four, glomerulonephritis in one patient who had bronchiectasis and Castleman's disease, unknown in one patient who had bronchial asthma, and pyelonephritis in one patient who had no characteristics that could be linked with AA type amyloidosis. The causes of ESRD in the two individuals with beta2 microglobulin-related amyloidosis who had been on long-term hemodialysis were pyelonephritis and glomerulonephritis. The cause of ESRD in the patient with AL type protein was glomerulonephritis, and this patient had no systemic disease. We conclude that amyloid lymphadenopathy is, indeed, common in uremic patients. Amyloid type AA is the most prevalent form of amyloid protein in uremic patients, but amyloid type does not always correspond with underlying cause of renal failure, or with the presence of systemic disease.

PMID: 11041293 [Indexed for MEDLINE]

4815. J Lab Clin Med. 2000 Oct;136(4):314-9.

Pregnancy and amyloidosis: II. Suppression of amyloidogenesis during pregnancy.

Shtrasburg S(1), Pras M, Dolitzky M, Pariente C, Gal R, Livneh A.

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(1)Heller Institute of Medical Research, and the Department of Obstetrics and Gynecology, Sheba Medical Center, Tel-Hashomer, Israel.

The observation of a deleterious effect of pregnancy on kidney function in

amyloidosis of familial Mediterranean fever suggests that pregnancy may enhance amyloidogenesis. To determine whether pregnancy may indeed affect amyloidogenesis, pregnant mice were made amyloidotic by administration of amyloid-enhancing factor (AEF) and AgNO<sub>3</sub> at different points in time from conception, and amyloid- deposition was studied with the crush-and-smear technique. A possible effect of exogenous female sex hormones (beta-estradiol and progesterone) on amyloidogenesis was studied by administration of these hormones during amyloid induction in nonpregnant female mice. Amyloidogenesis was found to be significantly suppressed in mice during pregnancy. The reduction was possibly related to the effect of pregnancy on the inflammatory stimulus (AgNO<sub>3</sub>) and not on the administered AEF. Exogenous estrogen and progesterone failed to inhibit amyloidogenesis in nonpregnant mice. These findings suggest that pregnancy may suppress amyloidogenesis in mice. The suppression is caused by an anti-inflammatory effect of pregnancy. Estrogen and progesterone are probably unrelated to this finding.

DOI: 10.1067/mlc.2000.109099

PMID: 11039852 [Indexed for MEDLINE]

4816. QJM. 2000 Oct;93(10):681-4.

Familial Mediterranean fever and systemic amyloidosis in untreated Turkish patients.

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We compared the frequencies of seven MEFV mutations (M694V, M680I, V726A, M694I, K695R, R761H, E148Q) and the clinical findings in 20 Turkish FMF patients who had not developed amyloidosis by the age of 40 years in the absence of colchicine therapy, with those in 27 Turkish amyloidosis patients. No mutation frequency, including that of M694V, was different between the two groups. Family history of amyloidosis and parental consanguinity were noted to be higher in the amyloidosis group. The seven mutations do not appear to be sufficient to explain the development of amyloidosis in Turkish FMF patients. Other genetic factors may be

important for this association.

PMID: 11029479 [Indexed for MEDLINE]

4817. N Engl J Med. 2000 Oct 5;343(14):1044-5.

Treatment of the nephrotic syndrome with etanercept in patients with the tumor necrosis factor receptor-associated periodic syndrome.

Drewe E, McDermott EM, Powell RJ.

DOI: 10.1056/NEJM200010053431412

PMID: 11023397 [Indexed for MEDLINE]

4818. Am J Hum Genet. 2000 Nov;67(5):1136-43. Epub 2000 Oct 3.

Identification of MEFV-independent modifying genetic factors for familial Mediterranean fever.

Cazeneuve C(1), Ajrapetyan H, Papin S, Roudot-Thoraval F, Geneviève D, Mndjoyan E, Papazian M, Sarkisian A, Babloyan A, Boissier B, Duquesnoy P, Kouyoumdjian JC, Girodon-Boulandet E, Grateau G, Sarkisian T, Amselem S.

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Familial Mediterranean fever (FMF) is a recessively inherited disorder predisposing to renal amyloidosis and associated with mutations in MEFV, a gene encoding a protein of unknown function. Differences in clinical expression have been attributed to MEFV-allelic heterogeneity, with the M694V/M694V genotype associated with a high prevalence of renal amyloidosis. However, the variable risk for patients with identical MEFV mutations to develop this severe complication, prevented by lifelong administration of colchicine, strongly suggests a role for other genetic and/or environmental factors. To overcome the

well-known difficulties in the identification of modifying genetic factors, we investigated a relatively homogeneous population sample consisting of 137 Armenian patients with FMF from 127 independent families living in Armenia. We selected the SAA1, SAA2, and APOE genes-encoding serum amyloid proteins and apolipoprotein E, respectively-as well as the patients' sex, as candidate modifiers for renal amyloidosis. A stepwise logistic-regression analysis showed that the SAA1alpha/alpha genotype was associated with a sevenfold increased risk for renal amyloidosis, compared with other SAA1 genotypes (odds ratio [OR] 6.9; 95% confidence interval [CI] 2.5-19.0). This association, which was present whatever the MEFV genotype, was extremely marked in patients homozygous for M694V (11/11). The risk for male patients of developing renal amyloidosis was fourfold higher than that for female patients (OR=4.0; 95% CI=1.5-10.8). This association, particularly marked in patients who were not homozygous for M694V (34.0% vs. 11.6%), was independent of SAA1-allelic variations. Polymorphisms in the SAA2 or APOE gene did not appear to influence susceptibility to renal amyloidosis. Overall, these data, which provide new insights into the pathophysiology of FMF, demonstrate that susceptibility to renal amyloidosis in this Mendelian disorder is influenced by at least two MEFV-independent factors of genetic origin-SAA1 and sex-that act independently of each other.

DOI: 10.1016/S0002-9297(07)62944-9

PMCID: PMC1288556

PMID: 11017802 [Indexed for MEDLINE]

4819. Arthritis Rheum. 2000 Sep;43(9):2034-40.

An autosomal dominant periodic fever associated with AA amyloidosis in a north Indian family maps to distal chromosome 1q.

McDermott MF(1), Aganna E, Hitman GA, Ogunkolade BW, Booth DR, Hawkins PN.

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Erratum in

Arthritis Rheum. 2000 Oct;43(10):2379.

OBJECTIVE: To investigate genetic susceptibility in the first Indian family

identified as having an autosomal dominantly inherited periodic fever syndrome. The inflammatory disease was characterized chiefly by arthralgia, skin rashes, and AA amyloidosis.

**METHODS:** Markers from known periodic fever susceptibility loci were investigated in 7 affected and 11 healthy members of a north Indian family. These included the TNFRSF1A locus (formerly known as TNFRI), which is involved in autosomal dominant tumor necrosis factor receptor-associated periodic syndrome on chromosome 12p13, the familial Mediterranean fever locus (MEFV) on chromosome 16p13, the hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) locus on chromosome 12q24, and the Muckle-Wells syndrome/familial cold urticaria (MWS/FCU) locus on distal chromosome 1q44.

**RESULTS:** Linkage to both TNFRSF1A and MEFV was definitively excluded, and DNA sequencing of these genes revealed no mutations. Furthermore, there was no evidence of linkage to the HIDS locus. In contrast, significant logarithm of odds scores for 5 markers from the MWS/FCU region were obtained in this family, and the disease segregated with the same haplotype in all affected members.

**CONCLUSION:** We have identified an inherited inflammatory disease in a north Indian family with clinical features overlapping some of those of MWS and FCU. The susceptibility gene maps to distal chromosome 1q44, a region already implicated in both MWS and FCU. Different mutations in the same (or a closely related) gene may be responsible for an inflammatory disease with a broad phenotype among diverse ethnic populations.

DOI: 10.1002/1529-0131(200009)43:9<2034::AID-ANR14>3.0.CO;2-J

PMID: 11014353 [Indexed for MEDLINE]

4820. Nephrol Dial Transplant. 2000 Oct;15(10):1713-4.

Regression of nephrotic syndrome in amyloidosis of familial mediterranean fever following colchicine treatment.

Livneh A, Shtrasburg S, Langevitz P.

Comment on

Nephrol Dial Transplant. 2000 Feb;15(2):281-2.

PMID: 11007856 [Indexed for MEDLINE]



4821. Ann Rheum Dis. 2000 Oct;59(10):836-8.

Unusual presentation of familial Mediterranean fever: role of genetic diagnosis.

Nir-Paz R(1), Ben-Chetrit E, Pikarsky E, Hassin D, Hasin Y, Chajek-Shaul T.

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(1)Department of Medicine, Hadassah University Hospital, Jerusalem.

OBJECTIVE: To describe the role of molecular analysis in the diagnosis of an unusual presentation of familial Mediterranean fever (FMF).

CASE REPORT: Two patients presenting with prolonged fever without signs and symptoms of serositis are described. FMF was diagnosed by genetic analysis, which disclosed that both patients were homozygous for the M694V mutation of the Mediterranean fever (MEFV) gene.

CONCLUSION: Molecular analysis of FMF should complement the investigation of patients with fever of unknown origin. This test enables a definite diagnosis of the disease and may promote the diagnosis and treatment of patients with an unusual or incomplete clinical picture of FMF.

PMCID: PMC1753005

PMID: 11005788 [Indexed for MEDLINE]

4822. An Esp Pediatr. 2000 Jan;52(1):59-61.

[Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis: report of three cases].

[Article in Spanish]

Ramos Amador JT(1), Rodríguez Cerrato V, Bodas Pinedo A, Carnicero Pastor MJ, Jiménez Fernández F, Rubio Gribble B.

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PMID: 11003862 [Indexed for MEDLINE]

4823. J Trauma. 2000 Sep;49(3):392-403.

Metabolic correlates of oxygen debt predict posttrauma early acute respiratory distress syndrome and the related cytokine response.

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(1)Department of Surgery and Anatomy, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark 07103, USA.

**BACKGROUND:** The purpose of this study was to quantify the relationship between negative base excess (base deficit) and lactate as correlates of oxygen debt and the probability of the early acute respiratory distress syndrome (ARDS) response and with regard to the mediator and metabolic response characteristic of this disease.

**METHODS:** Eighty patients with multiple trauma were studied (514 samples) during their intensive care unit courses (Injury Severity Score 27.6+/-8.8, 36% deaths). Simultaneous samples of arterial base excess and lactate as correlates of oxygen debt, and enzyme-linked immunosorbent assay-measured mixed venous cytokines were obtained daily. At each sample period, the patient was categorized as having ARDS or non-ARDS.

**RESULTS:** Twenty-nine patients (36%; 19 deaths) developed ARDS over the period studied: 17 in postinjury days 1 to 4 (EARLY ARDS) and 12 in postinjury days 5 or later (LATE ARDS). Patients subsequently developing ARDS had evidence of ischemic acidosis on or within the first 24 hours after hospital admission (lower base excess -7.1 mmol/L and higher lactate 5.2 mmol/L in ARDS versus base excess -3.8 mmol/L and lactate 3.6 mmol/L in non-ARDS;  $p < 0.05$ ). Patients with EARLY ARDS showed even lower ( $p < 0.05$ ) initial 24 hour mean base excess and higher lactate (base excess -9.1 mmol/L and lactate 6.4 mmol/L) compared with LATE ARDS (base excess -4.3 mmol/L and lactate 3.3 mmol/L). In EARLY ARDS, this degree of ischemic acidosis was followed by a greater mean IL-6 response in the postinjury days 1 to 4 (323 pg/mL) compared with the LATE ARDS response (141 pg/mL) ( $p <$

0.05) or compared with the non-ARDS IL-6 response (67 pg/mL;  $p < 0.001$ ). In addition, in EARLY ARDS, mean IL-8 levels in postinjury days 1 to 4 (264 pg/mL) were higher than in LATE ARDS (168 pg/mL) ( $p < 0.05$ ) and the mean IL-1 response in postinjury days 1 to 4 of EARLY ARDS (65 pg/mL) was greater than non-ARDS (32 pg/mL) ( $p < 0.05$ ). Derivation of probability curves suggests a critical threshold of base excess  $-6.6$  mmol/L or greater for an increased risk of EARLY ARDS. CONCLUSION: These data suggest that the maximum posttrauma oxygen debt (quantified by the ischemia correlates of negative base excess and lactate) is a critical primary determinant of the later fulminant autoinflammatory EARLY ARDS response mediated by the host's endogenous cytokine mediators.

PMID: 11003314 [Indexed for MEDLINE]

4824. Mol Genet Metab. 2000 Sep-Oct;71(1-2):256-60.

Molecular genetic testing for familial Mediterranean fever.

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DOI: 10.1006/mgme.2000.3047

PMID: 11001819 [Indexed for MEDLINE]

4825. Ned Tijdschr Geneesk. 2000 Sep 2;144(36):1728-30.

[From gene to disease; marenostrene and familial Mediterranean fever].

[Article in Dutch]

Breuning MH(1), Bakker E.

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Familial mediterranean fever (FMF) is an autosomal recessive hereditary disorder associated with mutations in the gene on chromosome 16 encoding the protein pyrine (marenostrine). Marenostrine is thought to stimulate the production of an inactivator of a chemotactic factor (possibly C5a). The mutations result in ongoing inflammation, a hallmark of FMF. DNA diagnosis of FMF is operational in Leiden University, the Netherlands, for one year now.

PMID: 10992897 [Indexed for MEDLINE]

4826. Yonsei Med J. 2000 Aug;41(4):441-4.

Phagocytic activity in familial Mediterranean fever.

Keskin G(1), Inal A, Sengül A, Cindoruk M, Haznedaroğlu S, Duranay M, Songür Y.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease. Although the possibility of multiple immunologic mechanisms have been studied, the actual mechanism is still unresolved. Forty-one patients with FMF (24 males and 17 females with a mean age and disease duration of 17.8 +/- 4.1 and 4.7 +/- 2.3 years, respectively) and 14 healthy controls (10 males and 4 females with a mean age 23.2 +/- 5.1) were involved in the study. A phagotest was studied in both the patients and control groups with a FACScalibur Flow. All patients were in the acute stages of the disease and had not undergone colchicine treatment for 2 months. The percentage blood phagocytic activity of both granulocytes and monocytes were 84.23 +/- 8.76 and 67.28 +/- 10.15 in the patient group and 94.68 +/- 3.24 and 76.23 +/- 5.7 in the control group, respectively. There was no statistically significant difference in the percentage of phagocytic activity of the granulocytes and monocytes between the FMF patients and healthy controls ( $p > 0.05$  and  $p > 0.05$ , respectively).

DOI: 10.3349/ymj.2000.41.4.441

PMID: 10992804 [Indexed for MEDLINE]

4827. Curr Opin Rheumatol. 2000 Sep;12(5):445-7.

Rheumatic disease mimics in childhood.

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Aches and pains in children can arise from multiple problems, varying from a reaction to minor intercurrent infection that rapidly improves to the presence of severe skeletal lesions such as malignancy; they can also be part of a skeletal dysplasia. All cases require a good history (including family history), a full examination, and basic blood tests, which include the erythrocyte sedimentation rate, hemoglobin, white count, platelets, rheumatoid factor, and antinuclear factor. Other tests need be performed only when suspicion has been aroused. Recognition of unusual syndromes is important; no child should be labeled as having juvenile idiopathic arthritis unless there is a clear history with the presence of soft tissue swelling in appropriate sites and other causes for joint pain have been excluded. The conditions that most frequently mimic systemic onset juvenile arthritis are infections, which may have been partially treated, inflammatory bowel disease, malignancy, familial Mediterranean Fever, and the rarer connective tissue diseases, in particular systemic lupus erythematosus. Bacterial infection should be suspected in a child who is feverish and toxic, with a single hot swollen joint that has limited movement and is often rigidly guarded. Should such a child have already received antibiotics, general symptoms may well be minimal, so one is left with the history and a swollen and painful joint. Aspiration for investigation of the synovial fluid as well as blood tests should be undertaken immediately to establish the nature of any underlying infection.

PMID: 10990184 [Indexed for MEDLINE]

4828. Curr Opin Rheumatol. 2000 Sep;12(5):439-44.

Differential diagnosis of fever of unknown origin in children.

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Fever of unknown origin in children follows two main clinical patterns, namely fever of unknown origin and chronic episodic fever of unknown origin. Fever of unknown origin is characterized by daily fever persisting for more than 3 weeks. The main causes are infectious, rheumatologic disorders, and malignancy. Chronic episodic fever of unknown origin is characterized by fever lasting for a few days to a few weeks, followed by a fever-free interval and a sense of well-being. The main causes are familial Mediterranean fever, the hyper-immunoglobulin D syndrome, familial Hibernian fever, Behcet disease, the syndrome of periodic fever, aphthous stomatitis, pharyngitis and adenitis, and cyclic neutropenia.

PMID: 10990183 [Indexed for MEDLINE]

4829. Rev Med Interne. 2000 Aug;21(8):659.

[Second international conference on familial Mediterranean fever, Antalya (Turkey), 3-7 May 2000].

[Article in French]

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PMID: 10989489 [Indexed for MEDLINE]

4830. Baillieres Best Pract Res Clin Rheumatol. 2000 Sep;14(3):477-98.

Diagnostic and treatment concerns in familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is an autosomal, recessively inherited disease, affecting people of Jewish, Arabic, Turkish and Armenian ancestry. The disease is the prototype of the periodic febrile syndromes. Its hallmark is short attacks of fever and painful manifestations in the abdomen, joints, chest, scrotum and skin. Chronic and protracted manifestations, particularly nephropathic amyloidosis, chronic arthritis, and protracted myalgia, may also occur in the disease. The diagnosis of FMF should be considered in individuals of an appropriate ethnic background who present with febrile disease of episodic nature. The differential diagnosis in this case is broad and includes a large number of infectious, inflammatory and genetic diseases. However, in most cases, the very specific general and site-restricted features of the FMF attacks on the one hand, and the absence of manifestations typical of other conditions on the other hand, determine the diagnosis of FMF. This chapter presents clues and tips that help in the diagnosis and treatment of FMF.

DOI: 10.1053/berh.2000.0089

PMID: 10985982 [Indexed for MEDLINE]

4831. Hum Mutat. 2000 Sep;16(3):271-2.

MEFV mutations in Behçet's disease.

Touitou I(1), Magne X, Molinari N, Navarro A, Quéllec AL, Picco P, Seri M, Ozen S, Bakkaloglu A, Karaduman A, Garnier JM, Demaille J, Koné-Paut I.

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Familial Mediterranean fever (FMF) and Behçet's disease (BD), both inflammatory

diseases, are highly prevalent in the Middle Eastern and Mediterranean populations. FMF is a Mendelian autosomic recessive disease linked to MEFV, a gene of unknown function. BD in contrast is a polyfactorial disease associated with the major histocompatibility complex. Because FMF and BD have epidemiological similarities, we asked whether the FMF gene was implicated in BD. We screened for the common MEFV mutations a cohort of 114 chromosomes from definite BD patients [meeting the criteria of the International study group] and probable cases [meeting at least two of these criteria]. We screened in parallel an ethnically matched cohort of FMF and control chromosomes. The M694V, V726A and E148Q mutations tended to be more frequent in definite BD (2.6%, 2.6%, and 5.2%, respectively) than in controls (0%, 0%, and 2.2%). The P706 polymorphism was found in 10.5% of the probable BD chromosomes, but in only 1.6% of the controls ( $p=0.01$ ). Because some MEFV mutations were more frequent in BD than in controls, we suggest that they may act as additional susceptibility factors in BD.

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DOI: 10.1002/1098-1004(200009)16:3<271::AID-HUMU16>3.0.CO;2-A

PMID: 10980540 [Indexed for MEDLINE]

4832. Neurol Neurochir Pol. 2000 May-Jun;34(3):467-74.

[PLED pattern and its clinical significance in stroke patients].

[Article in Polish]

Niedzielska K(1), Kuran W, Barańska-Gieruszczak M, Romaniak A, Rzeski M, Poniatowska R, Karliński A, Zamysłowski S, Lecka J.

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The pathophysiological connection between periodic lateralized epileptiform discharges (PLED) and epileptic seizures is still not clear. In the study clinical data and EEG findings were analysed in 22 patients aged 43-90 years with a history of stroke in whom EEG disclosed PLED. Eleven patients were studied in the acute phase of stroke and 11 were studied years after stroke when the



diagnosis was established of poststroke epilepsy. In 2 patients in acute stroke group single epileptic seizures occurred and 5 had partial status epilepticus. In the group with poststroke epilepsy 4 had single seizures and 4 had epileptic status with partial epilepsy seizures. Thus, in 15 out of 22 patients PLEDs were noted after epileptic seizures. In all cases PLED appearance was connected with consciousness disturbances, lasting 1 to 17 days. In 6 cases PLED pattern was interrupted by seizure activity over one hemisphere, in 3 of them partial epileptic seizures were associated with it. In acute phase of stroke neuroimaging demonstrated the presence of fresh ischaemic foci, but in cases of poststroke epilepsy no such fresh foci were observed. These results suggest that PLED frequently can be associated with epilepsy, and in some patients it can be a bioelectrical manifestation of partial status epileptic.

PMID: 10979541 [Indexed for MEDLINE]

4833. Arch Otolaryngol Head Neck Surg. 2000 Sep;126(9):1146-9.

Periodic fever and pharyngitis in young children: a new disease for the otolaryngologist?

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**OBJECTIVE:** A clinical entity consisting of periodic fever associated with aphthous stomatitis, pharyngitis and cervical adenitis termed "PFAPA syndrome" in young children (<5 years old) may be unfamiliar to otolaryngologists. We present our 5-year experience of PFAPA syndrome.

**DESIGN:** Case series.

**SETTING:** Tertiary academic.

**PATIENTS:** A 5-year retrospective chart review for children (<5 years old) who have undergone tonsillectomies with and without adenoidectomies was conducted. Medical records from subjects who underwent the procedures for recurrent pharyngitis were reviewed with reference to a history of periodic fever and stomatitis associated with pharyngitis.

INTERVENTIONS: Tonsillectomy with and without adenoidectomy.

MAIN OUTCOME MEASURE: The objective measure was a comparison of the number of visits to the primary care physician for pharyngitis associated with fever in a 3-month period before and after the surgical intervention. The subjective measure was a telephone interview evaluating preoperative and postoperative symptoms.

RESULTS: Of the 117 patients identified, 22 (19%) underwent surgery for recurrent pharyngitis. Five subjects (average age, 2.5 years) were identified as having PFAPA syndrome. The average number of preoperative PFAPA-related complaints was 11.6 compared with 0.2 for the number of postoperative PFAPA-related complaints ( $P=.03$ ).

CONCLUSIONS: Our experience suggests that PFAPA syndrome is an uncommon disease. Most of these children have undergone workup(s) for sepsis performed by their pediatricians because of the associated high fever. The clinical history of this cohort was quite distinctive. This small sample suggests a significant decrease if not cessation of pharyngitis following surgical intervention.

PMID: 10979131 [Indexed for MEDLINE]

4834. Am J Kidney Dis. 2000 Sep;36(3):E18.

Severe hyperkalemia in two renal transplant recipients treated with standard dose of trimethoprim-sulfamethoxazole.

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Hyperkalemia is a serious electrolyte disorder and is a frequent finding in renal transplant recipients. Trimethoprim-induced hyperkalemia has been increasingly reported in recent years. We describe two renal transplant recipients who developed end-stage renal disease secondary to familial Mediterranean fever and presented with severe hyperkalemia secondary to the use of standard dose of trimethoprim. One of the patients had potential underlying adrenal insufficiency, which might be a contributing factor for the development of hyperkalemia. We concluded that renal transplant patients receiving even the standard dose of trimethoprim should be monitored closely for the development of hyperkalemia.

They should be recognized as a group with increased risk in regard to their concurrent renal insufficiency, concomitant use of cyclosporine, and associated tubulointerstitial disease. Patients with secondary amyloidosis are at even greater risk, and subclinical adrenal insufficiency may be an underlying risk factor for the development of severe, life-threatening hyperkalemia among this group of patients.

DOI: 10.1053/ajkd.2000.16220

PMID: 10977811 [Indexed for MEDLINE]

4835. J Pediatr. 2000 Sep;137(3):438-9.

Hyper-IgD syndrome and familial Hibernian fever are true periodic fever syndromes.

Drenth JP, Powell RJ.

Comment on

J Pediatr. 1999 Jul;135(1):15-21.

J Pediatr. 1999 Jul;135(1):98-101.

PMID: 10969277 [Indexed for MEDLINE]

4836. Clin Exp Rheumatol. 2000 Jul-Aug;18(4):525-32.

Mevalonate kinase deficiency and Dutch type periodic fever.

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Dutch type periodic fever (DPF) is an autosomal recessive hereditary fever syndrome. Cases have been reported worldwide, the majority from France and The

Netherlands. From infancy the patients suffer fever attacks that recur every 2-8 weeks, often precipitated by immunizations, infections or emotional stress. Fever lasts 2-7 days and can be accompanied by malaise, headache, diarrhea, abdominal pain, vomiting, skin rashes, arthralgia, arthritis, tender lymphadenopathy, hepatosplenomegaly, and oral and genital ulcers. Laboratory evaluation during fever shows granulocytosis and elevated acute phase reactants. DPF is caused by a deficiency of the enzyme mevalonate kinase (MK). Besides DPF, the spectrum of MK deficiency includes a severe phenotype, mevalonic aciduria (MA). MA patients have less residual MK activity, leading to substantially higher urinary mevalonic acid excretion than in DPF. Mevalonic aciduria is characterized by mental retardation and dysmorphic features in addition to the clinical features of DPF. At the genomic level, several mutations of varying severity have been identified. The DPF phenotype is caused by one particular mild missense mutation. Most patients are compound heterozygotes for this mutation and a more severe mutation. The mechanism by which MK deficiency leads to fever is not understood. The vast majority of DPF patients have persistently elevated serum IgD and can be classified as having hyperimmunoglobulinemia D and periodic fever syndrome (HIDS). Conversely, most HIDS patients have MK deficiency and hence DPF, but the two disorders do not overlap entirely.

PMID: 10949735 [Indexed for MEDLINE]

4837. Arch Pediatr. 2000 Jun;7 Suppl 3:578s-582s.

[Marshall syndrome: results of a retrospective national survey].

[Article in French]

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Marshall's syndrome or periodic fever syndrome was first described in 1987 in the USA based on observations of 12 children under the age of five with periodic fever (> 38 degrees C) and accompanying aphtous stomatitis, pharyngitis, and cervical adenopathy (PFAPA). In 1998, a national retrospective study was carried

out in France by the pediatric infectious pathology group, and a semeiological analysis was made of 22 cases. The main characteristics of Marshall's syndrome found in this patient population were in agreement with those reported in the literature. The onset of symptoms occurred between the age of 3 months and 12 years, with a mean age of 5 years; no geographical or ethnic predisposing factors were noted. The diagnosis of symptoms was subsequently established at an age ranging from 5 months to 16 years, with a mean age of 6.5 years. It was determined that following an initial phase of generalized clinical manifestations (asthenia, cranial neuritis, dysphagia, anorexia), the symptoms become stereotyped, with the sudden appearance of high fever (> 40 degrees C), shivering, aphtous stomatitis, pharyngitis, and cervical adenopathy. Other symptoms such as cranial neuritis, arthralgia, and abdominal pain may also be present (50% of cases in the present study), but due to their variability of appearance they are of lesser diagnostic value. The main characteristic of Marshall's syndrome is its periodic aspect; with fever occurring every 6 to 9 weeks, with a mean interval of 66 days before recurrence of fever compared to the shorter interval of 21 to 28 days reported in the literature. After excluding the presence of an infection, the differential diagnosis includes the following: familial Mediterranean fever, hyper IgD syndrome, and feverish neutropenia. During the periods of fever, an inflammatory syndrome with hyperleucocytosis and a marked increase in C-reactive protein (CRP) levels and sedimentation rate is observed. The most effective treatment seems to be the early administration of corticoids during the initial phase, prior to the appearance of more specific symptoms. The prognosis is excellent, with a progressive decrease in the incidence of periodic fever and an absence of complications. However, the etiology of Marshall's syndrome has not yet been determined.

PMID: 10941483 [Indexed for MEDLINE]

4838. Am J Orthop (Belle Mead NJ). 2000 Jul;29(7):553-5.

Familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is an inherited multisystem disease manifested by painful, febrile attacks affecting the chest, abdomen, joints, and skin. No simple studies confirm the presence of FMF, contributing to the difficulty in diagnosis. A 10-year-old boy initially presented with a diffuse rash and complaints of bilateral joint pain of the hips, knees, and ankles and pain of the right shoulder. The child responded to daily naproxen. One year later, he continued to complain of hip, knee, ankle, and bilateral wrist pain. He also reported mild to moderate recurrent abdominal discomfort. Omeprazole provided intermittent relief. The patient continued to experience episodes of joint and abdominal pain. Two and a half years after he first presented, FMF was considered. In the second case, a 51-year-old man presented to the emergency department with complaints of fever, cough, and abdominal and joint pain. Fever, joint pain, and swelling decreased during the next few days. The patient was maintained on colchicine, with complete resolution of joint pain complaints during the next few days. Colchicine, 1 to 2 mg per day taken continuously during flare and quiescent periods, is the treatment of choice for FMF. Colchicine reduced the severity and frequency of attacks and may also delay or prevent secondary amyloidosis.

PMID: 10926406 [Indexed for MEDLINE]

4839. J Rheumatol. 2000 Jul;27(7):1703-7.

Genotype-phenotype assessment of common genotypes among patients with familial Mediterranean fever.

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OBJECTIVE: To study genotype-phenotype correlation for the 4 most common genotypes found among patients with familial Mediterranean fever (FMF).

METHODS: Thirty patients with the M694V/M694V genotype, 32 with M694V/V726A

genotype, 25 with M694V/E 148Q genotype, and 21 with V726A/V726A genotype were assessed for various clinical manifestations of FMF, and overall disease severity.

**RESULTS:** Patients with the M694V/M694V genotype were found to have an earlier age of onset, higher frequency of joint involvement, higher frequency of erysipelas-like erythema, and required higher doses of colchicine to control the disease compared to the other 3 genotypes.

**CONCLUSION:** The M694V/M694V genotype is associated with more severe disease compared to other common genotypes in patients with FMF.

PMID: 10914855 [Indexed for MEDLINE]

4840. Clin Genet. 2000 Jun;57(6):430-4.

MEFV mutations in multiplex families with familial Mediterranean fever: is a particular genotype necessary for amyloidosis?

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Familial Mediterranean fever (FMF) is an autosomal recessive disease. It is characterized by recurrent febrile episodes in association with peritonitis, pleuritis, and arthritis. Progressive systemic amyloidosis is the most important complication of FMF that inevitably leads to chronic renal failure. Recently, the gene for FMF, MEFV, has been cloned and four missense mutations have been described: M694V, M680I, V726A, and M694I. Initial studies have suggested that the presence of the M694V mutation carries a significant risk for the development of amyloidosis. In this study, we present seven families, in which at least two individuals have been diagnosed with FMF and at least one with amyloidosis. Among 18 individuals, in whom molecular testing was performed for the four aforementioned mutations, ten had amyloidosis. None of these ten individuals was found to be homozygous for the M694V mutation. In three families, there were two sibs with amyloidosis. None of the sib-pairs with amyloidosis was found to have the same genotype. There were two or more sibs with the same genotype in four

families. Only one sib from each family developed amyloidosis in these families. These results provide evidence that FMF patients without the M694V mutation are also at risk for the development of amyloidosis. Particular mutations themselves do not appear to be sufficient to explain the occurrence of amyloidosis in all cases with FMF.

PMID: 10905662 [Indexed for MEDLINE]

4841. Curr Opin Immunol. 2000 Aug;12(4):479-86.

TNFRSF1A mutations and autoinflammatory syndromes.

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The autoinflammatory syndromes are systemic disorders characterized by apparently unprovoked inflammation in the absence of high-titer autoantibodies or antigen-specific T lymphocytes. One such illness, TNF-receptor-associated periodic syndrome (TRAPS), presents with prolonged attacks of fever and severe localized inflammation. TRAPS is caused by dominantly inherited mutations in TNFRSF1A (formerly termed TNFR1), the gene encoding the 55 kDa TNF receptor. All known mutations affect the first two cysteine-rich extracellular subdomains of the receptor, and several mutations are substitutions directly disrupting conserved disulfide bonds. One likely mechanism of inflammation in TRAPS is the impaired cleavage of TNFRSF1A ectodomain upon cellular activation, with diminished shedding of the potentially antagonistic soluble receptor. Preliminary experience with recombinant p75 TNFR-Fc fusion protein in the treatment of TRAPS has been favorable.

PMID: 10899034 [Indexed for MEDLINE]

4842. Scand J Rheumatol. 2000;29(3):174-6.



Protracted febrile myalgia of familial Mediterranean fever. Mutation analysis and clinical correlations.

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Protracted febrile myalgia (PFM) is a rare form of vasculitic disease that affects patients with familial Mediterranean fever (FMF). Mutation analysis performed in 15 patients who suffered from this disorder showed that 9 of the 15 patients were homozygous for M694V. FMF in these 9 patients was associated with more severe symptoms compared to a group of 30 M694V homozygous FMF patients without PFM.

PMID: 10898070 [Indexed for MEDLINE]

4843. J Inherit Metab Dis. 2000 Jun;23(4):367-70.

Molecular basis of classical mevalonic aciduria and the hyperimmunoglobulinaemia D and periodic fever syndrome: high frequency of 3 mutations in the mevalonate kinase gene.

Houten SM(1), Frenkel J, Kuis W, Wanders RJ, Poll-The BT, Waterham HR.

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(1)Department of Clinical Chemistry, Emma Children's Hospital, Academic Medical Center, University of Amsterdam, The Netherlands.

PMID: 10896296 [Indexed for MEDLINE]

4844. J Inherit Metab Dis. 2000 Jun;23(4):363-6.

Mevalonic aciduria in 12 unrelated patients with hyperimmunoglobulinaemia D and

periodic fever syndrome.

Poll-The BT(1), Frenkel J, Houten SM, Kuis W, Duran M, de Koning TJ, Dorland L, de Barse MM, Romeijn GJ, Wanders RJ, Waterham HR.

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PMID: 10896295 [Indexed for MEDLINE]

4845. Clin Exp Rheumatol. 2000 May-Jun;18(3):375-8.

Palindromic rheumatism: effect of dietary manipulation.

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**OBJECTIVE:** Evaluation of the contribution of dietary components in triggering the attacks of palindromic rheumatism (PR), and the effect of dietary manipulation on the frequency and severity of PR attacks.

**METHODS:** Sixteen patients (10 males, 6 females) were diagnosed as having PR during 1994-8 in one center. Their mean age was 45 +/- 6, duration of symptoms prior to diagnosis was 4 +/- 1.4 years, and frequency of PR attacks were 3.1 +/- 1.8/month. All patients were instructed to make a list of the food that was consumed daily and to specify the dates of PR episodes. Data were evaluated after a period of 2-4 months in each patient.

**RESULTS:** In 5 patients (31%) there was an association between episodes of PR and certain foods that were consumed within 36 hours prior to PR episodes. These were fish (2 patients), eggs, canned vegetables and processed cheese (each in one case). Elimination of the relevant food from each patient's diet resulted in complete cessation of the PR attacks in two of the cases, while the other three had milder, infrequent attacks. Four patients were rechallenged with the offending food. In all cases it resulted in recurrence of the PR attacks. No

association between PR episodes and prior consumption of certain foods could be documented in the other 11 patients.

CONCLUSIONS: In some PR patients ingestion of certain foods, specific for each case, can trigger the typical attack. It is suggested that this association should be looked for in any PR patient, as elimination of the offending food from the diet may help in preventing the PR attacks.

PMID: 10895376 [Indexed for MEDLINE]

4846. An Med Interna. 2000 Apr;17(4):213-6.

[Hypergammaglobulinemia D syndrome].

[Article in Spanish]

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Comment in

An Med Interna. 2001 May;18(5):285-6.

An Med Interna. 2001 May;18(5):287.

The hyperimmunoglobulinemia D syndrome is characterized by early onset of attacks of periodic fever and an elevated serum polyclonal Ig D (> 100 U/ml). Symptoms during attacks include joint involvements (arthralgia/arthritis), skin lesions, swollen lymph nodes, headache and abdominal complaints (vomiting, diarrhea and pain). The ethiopathogenia is unknown. It is transmitted by autosomal recessive inheritance. The hyperimmunoglobulinemia D syndrome should be distinguished from other periodic febrile syndroms such as systemic-onset juvenile rheumatoid arthritis, CINCA syndrome, FADA syndrome, familial mediterranean fever and adult-onset Still disease. There is no therapy for the syndrome but the prognosis is good because the frequency and severity of the attacks tends to decrease with age.

PMID: 10893775 [Indexed for MEDLINE]

4847. Blood. 2000 Jul 15;96(2):727-31.

Expression of the familial Mediterranean fever gene and activity of the C5a inhibitor in human primary fibroblast cultures.

Matzner Y(1), Abedat S, Shapiro E, Eisenberg S, Bar-Gil-Shitrit A, Stepensky P, Calco S, Azar Y, Urieli-Shoval S.

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Familial Mediterranean fever (FMF) is an inherited disease whose manifestations are acute but reversible attacks of sterile inflammation affecting synovial and serosal spaces. The FMF gene (MEFV) was recently cloned, and it codes for a protein (pyrin/marennosin) homologous to known nuclear factors. We previously reported the deficient activity of a C5a/interleukin (IL)-8 inhibitor, a physiologic regulator of inflammatory processes, in FMF serosal and synovial fluids. We now describe the concomitant expression of MEFV and C5a/IL-8-inhibitor activity in primary cultures of human fibroblasts. Fibroblasts grown from synovial and peritoneal tissues displayed C5a/IL-8-inhibitor activity that could be further induced with phorbol myristate acetate (PMA) and IL-1 beta. Very low levels of chemotactic inhibitor were evident in skin fibroblast cultures or in peritoneal and skin fibroblasts obtained from FMF patients. MEFV was expressed in peritoneal and skin fibroblasts at a lower level than in neutrophils and could be further induced by PMA and IL-1 beta. In the FMF cultures, the MEFV transcript carried the M694V mutation, consistent with the genetic defect found in patients with this disease. MEFV was also expressed in other cell lines that do not produce C5a/IL-8 inhibitor. These findings suggest that human primary fibroblast cultures express MEFV and produce C5a/IL-8-inhibitor activity. The interrelationship between pyrin, the MEFV product, and the C5a/IL-8 inhibitor requires further investigation. (Blood. 2000;96:727-731)

PMID: 10887141 [Indexed for MEDLINE]

4848. Scand J Infect Dis. 2000;32(3):334-5.

Familial Mediterranean fever diagnosed by PCR.

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The diagnosis of familial Mediterranean fever (FMF) was, until recently, based on exclusion of diseases with related clinical signs. Now an exact diagnosis of FMF is possible by polymerase chain reaction (PCR). We report here a case with 2 different mutations in the gene responsible for FMF, thereby being a compound heterozygote (M694V/V726A).

PMID: 10879615 [Indexed for MEDLINE]

4849. Eur J Pediatr Surg. 2000 Apr;10(2):145-7.

Polyarteritis nodosa involving the hepatobiliary system in an eight-year-old girl with a previous diagnosis of familial Mediterranean fever.

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Polyarteritis nodosa (PAN) is a vasculitis of small- and medium-sized muscular arteries with deposition of immune complex in the vessel wall. Although gastrointestinal involvement is common, the symptomatic involvement of the hepatobiliary system is rare. An eight-year old female patient with a previous diagnosis of familial Mediterranean fever (FMF) was hospitalized for right upper quadrant pain and fever. The thickened gall bladder wall by ultrasonography, called for exploration. Histopathological evaluations of the liver biopsy and gall bladder revealed PAN. Corticosteroid therapy was initiated and the patient

recovered fully. This case represents one of the rarest forms of PAN in childhood.

PMID: 10877088 [Indexed for MEDLINE]

4850. Nephrol Dial Transplant. 2000 Jul;15(7):1098.

Colchicine in the treatment of renal amyloidosis secondary to familial Mediterranean fever.

Sarkissian A, Papazian M, Sanamyan A, Leumann E.

Comment on

Nephrol Dial Transplant. 2000 Feb;15(2):281-2.

PMID: 10862663 [Indexed for MEDLINE]

4851. Eur J Hum Genet. 2000 Apr;8(4):307-10.

Higher than expected carrier rates for familial Mediterranean fever in various Jewish ethnic groups.

Stoffman N(1), Magal N, Shohat T, Lotan R, Koman S, Oron A, Danon Y, Halpern GJ, Lifshitz Y, Shohat M.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease characterised by recurrent attacks of inflammation of serosal membranes. Amyloidosis leading to renal failure is the most severe complication in untreated patients. In Israel FMF is most frequent among Jews of North African origin. Recently the causative gene (MEFV) has been found and the common mutations characterised. The aim of this study was to investigate the carrier rates of the

common MEFV mutations among 400 healthy members of four different ethnic groups (100 in each group) in Israel, and to compare the distribution of the different mutations between FMF carriers and patients. We found a high frequency of carriers among Jews from the various ethnic groups. In North African Jews it was 22%, in Iraqi Jews 39%, in Ashkenazi Jews 21%, and in Iranian Jews 6%. The distribution of the four most common MEFV mutations among healthy individuals (M694V 29%, V726A 16%, M680I 2% and E148Q 53%) was significantly different ( $P < 0.003$ ) from that found in patients (M694V 84.4%, V726A 9.0%, M680I 0% and E148Q 6.6%). Six healthy asymptomatic individuals were found to carry mutations in both alleles: two homozygotes for E148Q and four compound heterozygotes E148Q/other. These results demonstrate a very high carrier rate among all Jewish ethnic groups. They confirm that mutation E148Q is associated with a milder phenotype, which explains the lower prevalence of FMF among the Ashkenazi and Iraqi Jews. This study raises the question of the need for molecular screening for M694V homozygotes in the Israeli North African Jewish community.

DOI: 10.1038/sj.ejhg.5200446

PMID: 10854115 [Indexed for MEDLINE]

4852. Eur J Hum Genet. 2000 Apr;8(4):242-6.

Familial Mediterranean fever in the 'Chuetas' of Mallorca: a question of Jewish origin or genetic heterogeneity.

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Familial Mediterranean fever (FMF) is a hereditary disease commonly found among Jews, Armenians, Turks and Arabs. Recently, FMF was found in the 'Chuetas', a unique community on the island of Mallorca (Spain). To address the question of their possible Jewish origin, we analysed markers known to be linked to the gene responsible for FMF in Jews (MEFV) in this population. We found that 1/3 of the 16p13.3 chromosomes of the 'Chuetas' FMF patients bore the major ancestral haplotypes (S,S2) and their corresponding M694V and E148Q mutations, displayed by Jews from North Africa. Furthermore, we also detected a novel mutation (L110P) in

this community. Yet 2/3 of these patients bore S negative haplotypes and lack the mutations commonly known to cause FMF. These results confirm that at least some of the 'Chuetas' share a common origin with Jews. However, they also provide evidence for the possibility of genetic heterogeneity in this disorder.

DOI: 10.1038/sj.ejhg.5200462

PMID: 10854105 [Indexed for MEDLINE]

4853. Eur Respir J. 2000 May;15(5):958-60.

Marcel Proust (1871-1922): reassessment of his asthma and other maladies.

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Marcel Proust endured severe allergies and bronchial asthma from early childhood. Those who suffer from the frightening and recurrent pangs of asthma often become dependent on their parents particularly mother; Proust was no exception. In his time asthma was poorly understood by physicians who considered the illness to be a type of hysteria. Decades later, we now understand that the severe, poorly controlled, suffocating episodes of asthma were responsible for the complex persona that Marcel Proust had assumed.

PMID: 10853866 [Indexed for MEDLINE]

4854. J Rheumatol. 2000 Jun;27(6):1492-5.

Familial Mediterranean fever: high gene frequency and heterogeneous disease among an Israeli-Arab population.

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**OBJECTIVE:** Familial Mediterranean fever (FMF) is an autosomal recessive disease that primarily affects non-Ashkenazi Jews, Armenians, Arabs, and Turks. The FMF (MEFV) gene responsible for the disease has been recently identified. Four missense mutations in exon 10 of the FMF gene seem to account for 86% of the DNA variations identified in patients with FMF. We conducted a phenotype/genotype correlation study in a homogenous population of Israeli-Moslem Arab patients with FMF and performed a mutational screening analysis on DNA samples from healthy individuals of this ethnic group.

**METHODS:** Sixty-five patients clinically diagnosed as having FMF underwent molecular genetic studies using polymerase chain reaction and restriction endonuclease digestion methods to detect the presence of the 4 mutations (M694V, V726A, M680I, M694I). We then correlated the presence of each mutation with age of onset, clinical manifestations, and disease severity; patients whose allelic combination included M694V were then excluded from further statistical analysis, since the association of severe disease with the M694V allele has already been shown. In addition, we screened for FMF mutations the DNA samples from 318 healthy Moslem Arab individuals for the presence of these mutations.

**RESULTS:** Among the 65 patients who were clinically diagnosed as having FMF, 78.5% had one or 2 mutation-bearing chromosomes. The most prevalent mutation was V726A, followed by M680I, M694V, and M694I. No significant difference in phenotypic characteristics was found between the patients with the diverse mutations. The total carrier frequency for the 4 mutations was 10.4% (95% confidence interval 0.07 to 0.137).

**CONCLUSION:** A high FMF gene frequency was found among an Israeli-Moslem Arab population. Among the FMF patients from this ethnic group, several mutations were detected, none of which was found to correlate with a severe course of the disease.

PMID: 10852276 [Indexed for MEDLINE]

4855. Med Clin (Barc). 2000 Apr 1;114(12):456-9.

[Hyperimmunoglobulinemia D and periodic fever syndrome. A phenotypical analysis of a Spanish family].

[Article in Spanish]

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**BACKGROUND:** Hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) is a disorder diagnosed with low frequency, that produces a very prolonged and recurrent fever with other symptoms and analytical markers of inflammation. Its origin seems to be hereditary with a recessive autosomic pattern, but its pathogenic mechanisms are unclear. The aim of this study is to analyse the clinical characteristics and serum levels of immunoglobulins a Spanish family with HIDS.

**METHODS:** We describe a young woman diagnosed with HIDS and investigate the other memberships of her family (parents and 5 brothers) by clinical interview, physical examination, hematological and biochemical analyses and measurements of IgG, IgA, IgM, IgE, IgD and the kappa/lambda ratio of light chains. Moreover, we also determine the IgD in a control group of 35 healthy blood donors.

**RESULTS:** One male brother of the index case also showed a clinical picture of HIDS. The serum IgD levels were increased (above 100 U/ml) in both and in other two sisters without symptoms and were normal in the rest of the family. With only one exception, all individuals of the control group showed a normal IgD level and this was not associated with sex or age. The other immunoglobulins were normal in the family. In spite of the different treatments tested in the index case, only glucocorticoids aborted her fever attacks.

**CONCLUSIONS:** In HIDS the clinical picture and the high IgD levels are both transmitted with a recessive autosomic pattern, but these are not necessarily associated in the same memberships of the family. Its diagnosis is difficult and there is not effective and long-term safe treatment.

PMID: 10846700 [Indexed for MEDLINE]

4856. Am J Med Genet. 2000 Jun 5;92(4):247-9.

Familial Mediterranean fever in two Bedouin families: mutation analysis and disease severity.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease prevalent among non-Ashkenazi Jews, Armenians, Arabs, and Turks. The Bedouin are nomad Arab tribes residing in desert margins of the Middle East and Arabia. FMF is quite rare in Bedouins, and here we report on two Bedouin families from southern Israel suffering from this disorder. The MEFV mutations found in the Bedouin patients M694I, V726A, and E148Q are consistent with their Arab origin. The disease severity score showed a mild to moderate severity disease in six patients. The Bedouins, leading a unique nomadic life, may prove instrumental in unraveling the role of environmental factors in the course and severity of FMF.

PMID: 10842289 [Indexed for MEDLINE]

4857. Am J Med Genet. 2000 Jun 5;92(4):241-6.

Mutations in the MEFV gene in a large series of patients with a clinical diagnosis of familial Mediterranean fever.

Dodé C(1), Pêcheux C, Cazeneuve C, Cattan D, Dervichian M, Goossens M, Delpech M, Amselem S, Grateau G.

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Familial Mediterranean fever (FMF) is an autosomal recessively inherited disease affecting patients of the Mediterranean basin. FMF is characterized by recurrent episodes of fever accompanied with topical signs of inflammation. Some patients can develop a renal amyloidosis associated (AA) amyloidosis. The administration of colchicine is an effective preventive treatment of both the attacks and amyloidosis. The FMF gene (MEFV) was cloned and missense mutations were found to

be responsible for the disease. We investigated a large series of 303 unselected and unrelated patients of various ethnic backgrounds with a clinical suspicion of FMF to confirm or invalidate the diagnosis of FMF and to determine the spectrum of MEFV mutations. Molecular analysis focused on all the most frequent mutations identified so far, and an exhaustive analysis of exon 10, containing the mutational hotspot, was performed through DNA sequencing. Sixty-two percent of Sephardic, North African Arabs, Armenian and Turkish patients were either homozygous or compound heterozygous for MEFV mutations. In other populations surrounding the Mediterranean Sea such as Greek, Italian, Portuguese, Kurdish and Lebanese populations, mutations were also found. In general, patients without Mediterranean origin had no mutations in the MEFV gene. Two new mis-sense mutations were identified in exon 10 of the MEFV gene: the S675N in an Italian patient and the M680L in a French patient without any known at-risk ethnic ancestry.

PMID: 10842288 [Indexed for MEDLINE]

4858. J Infect Dis. 2000 Jun;181 Suppl 3:S498-504.

Review of microbial infections and the immune response to cardiac antigens.

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Heart disease is the most prevalent cause of morbidity and mortality in rich countries. Multiple pathogens are epidemiologically linked to human heart disease, and autoinflammatory responses to heart-specific epitopes revealed to the host's immune system (e.g., due to the cytopathic effects of cardiotropic viruses) or attacked by autoaggressive lymphocytes activated by mimicking peptides present in bacteria may be causative in the pathogenesis of chronic inflammatory cardiomyopathy. The experimental system of murine chronic autoimmune myocarditis has been used to analyze aspects of the host immune response. This review presents insights gained by use of this murine model system into molecular

mechanisms governing activation of autoaggressive lymphocytes, target organ susceptibility, and cardiopathogenic epitope mapping and discusses mimicking endogenous epitopes found in pathogens.

DOI: 10.1086/315613

PMID: 10839747 [Indexed for MEDLINE]

4859. Ann Rheum Dis. 2000 May;59(5):400.

Non-period leg pain in patients with familial Mediterranean fever.

Dinç A.

PMCID: PMC1753129

PMID: 10836960 [Indexed for MEDLINE]

4860. Abdom Imaging. 2000 May-Jun;25(3):297-300.

Familial Mediterranean fever: abdominal imaging findings in 139 patients and review of the literature.

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**BACKGROUND:** The purpose of this study was to investigate the imaging findings in patients with familial Mediterranean fever (FMF) during and between acute attacks.

**METHODS:** Computerized search of medical records from 1989 to 1998 identified 139 patients with a discharge diagnosis of FMF. Medical records, imaging studies, and pathologic findings were reviewed.

**RESULTS:** Sixty-eight patients had a documented acute attack of FMF, and 71 patients known to have FMF were asymptomatic. Imaging was performed in 68 patients. Radiologic findings included ascites, splenomegaly, hepatomegaly, lymphadenopathy, focal peritonitis, peritoneal cysts, renal changes, and other

incidental findings.

**CONCLUSIONS:** Radiologic findings in symptomatic and asymptomatic FMF patients are not uncommon. Imaging in selected cases may facilitate diagnosis and show complications.

PMID: 10823455 [Indexed for MEDLINE]

4861. Mamm Genome. 2000 Jun;11(6):428-35.

Isolation, genomic organization, and expression analysis of the mouse and rat homologs of MEFV, the gene for familial mediterranean fever.

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Familial Mediterranean fever (FMF) is a recessive disorder characterized by episodes of fever with serositis or synovitis. Recently the FMF gene (MEFV) was cloned; the protein product, pyrin/marenostrin, is thought to regulate inflammation in myeloid cells. In this manuscript we report the mouse and rat homologs of MEFV. The murine gene contains ten exons with a coding sequence of 2304 bp, while the rat homolog has nine exons with a coding sequence of 2253 bp. A considerable amino acid sequence homology was observed between the mouse and human (47.6% identity and 65.5% similarity) and between the mouse and rat genes (73.5% identity and 82.1% similarity). The predicted rodent proteins have several important domains and signals found in human pyrin, including a B-box zinc finger domain, Robbins-Dingwall nuclear localization signal, and coiled-coil domain. However, perhaps because of an ancient frame-shift mutation, neither the mouse nor the rat protein has an intact C-terminal B30.2 domain, in which most FMF-associated mutations have been found in human MEFV. Nevertheless, like the human gene, mouse *Mefv* is expressed in peripheral blood granulocytes but not lymphocytes. Consistent with its expression in granulocytes, *Mefv* was detected at high levels in the primary follicles and marginal zones of the splenic white

pulp. Mefv is localized on mouse Chromosome (Chr) 16, region A3-B1, extending a region of synteny with human Chr 16p13.3. Development of knockout and knockin mouse models may provide further insights into the functional evolution of this gene.

PMID: 10818206 [Indexed for MEDLINE]

4862. Blood. 2000 May 15;95(10):3223-31.

The gene for familial Mediterranean fever, MEFV, is expressed in early leukocyte development and is regulated in response to inflammatory mediators.

Centola M(1), Wood G, Frucht DM, Galon J, Aringer M, Farrell C, Kingma DW, Horwitz ME, Mansfield E, Holland SM, O'Shea JJ, Rosenberg HF, Malech HL, Kastner DL.

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Familial Mediterranean fever (FMF) is a recessive disorder characterized by episodes of fever and neutrophil-mediated serosal inflammation. We recently identified the gene causing FMF, designated MEFV, and found it to be expressed in mature neutrophils, suggesting that it functions as an inflammatory regulator. To facilitate our understanding of the normal function of MEFV, we extended our previous studies. MEFV messenger RNA was detected by reverse transcriptase-polymerase chain reaction in bone marrow leukocytes, with differential expression observed among cells by in situ hybridization. CD34 hematopoietic stem-cell cultures induced toward the granulocytic lineage expressed MEFV at the myelocyte stage, concurrently with lineage commitment. The prepromyelocytic cell line HL60 expressed MEFV only at granulocytic and monocytic differentiation. MEFV was also expressed in the monocytic cell lines U937 and THP-1. Among peripheral blood leukocytes, MEFV expression was detected in neutrophils, eosinophils, and to varying degrees, monocytes. Consistent with the tissue specificity of expression, complete sequencing and analysis of upstream regulatory regions of MEFV revealed homology to myeloid-specific promoters and to

more broadly expressed inflammatory promoter elements. In vitro stimulation of monocytes with the proinflammatory agents interferon (IFN) gamma, tumor necrosis factor, and lipopolysaccharide induced MEFV expression, whereas the antiinflammatory cytokines interleukin (IL) 4, IL-10, and transforming growth factor beta inhibited such expression. Induction by IFN-gamma occurred rapidly and was resistant to cycloheximide. IFN-alpha also induced MEFV expression. In granulocytes, MEFV was up-regulated by IFN-gamma and the combination of IFN-alpha and colchicine. These results refine understanding of MEFV by placing the gene in the myelomonocytic-specific proinflammatory pathway and identifying it as an IFN-gamma immediate early gene.

PMID: 10807793 [Indexed for MEDLINE]

4863. Semin Arthritis Rheum. 2000 Apr;29(5):286-95.

Behçet's disease in Familial Mediterranean fever: characterization of the association between the two diseases.

Schwartz T(1), Langevitz P, Zemer D, Gazit E, Pras M, Livneh A.

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**OBJECTIVES:** Familial Mediterranean fever (FMF) is a genetic disease, characterized by attacks of fever and painful manifestations. Several vasculitides are more common in FMF than in the general population. The aim of the study was to define and characterize the association between FMF and Behcet's disease (BD), a form of vasculitis not previously related to FMF.

**METHODS:** We conducted a retrospective study in which FMF patients, also suffering from BD (FMF-BD), were recruited from about 4,000 patients registered in our clinic, using a computer survey. Patients identified by the screening process were examined, and those meeting the published criteria for the diagnoses of FMF and BD were classified as FMF-BD cases and compared with unselected FMF and BD controls.

**RESULTS:** The prevalence of BD was higher in FMF than in populations known to be rich in BD (eg, 16 per 4,000 in FMF compared with 1 per 104 in Japan,  $P < .001$ ).



FMF-BD cases and FMF or BD controls were comparable in most demographic, clinical, and laboratory aspects studied. However, more cases than FMF-controls were of Iraqi/Turkish origin and responded less favorably to colchicine. A higher proportion of cases than BD controls had skin, central nervous system, and gastrointestinal manifestations, originated from North Africa, and had family history of BD. In most cases, as in most respective controls, the severity of FMF was of intermediate grade and the extensiveness of BD was limited. The HLA B5 antigen was present in 53% of BD cases and 40% of BD controls.

CONCLUSIONS: BD should be included among the vasculitides complicating FMF. BD and FMF in patients with FMF-BD, and in patients suffering from each of these entities alone, are clinically and demographically comparable.

PMID: 10805353 [Indexed for MEDLINE]

4864. Gastroenterol Hepatol. 2000 Mar;23(3):144-8.

[Hereditary familial amyloidosis].

[Article in Spanish]

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PMID: 10804694 [Indexed for MEDLINE]

4865. Ned Tijdschr Geneeskd. 2000 Apr 22;144(17):809-11.

[Periodic fever due to hyper-IgD syndrome].

[Article in Dutch]

Wauters IM(1), Linskens RK, Stehouwer CD.

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Comment in

Ned Tijdschr Geneeskd. 2000 Apr 22;144(17):782-5.

In a 45-year-old man who from early childhood had been suffering of periodic fever, which did not respond to any therapy attempted, the ultimate diagnosis was hyperimmunoglobulinaemia D syndrome (HIDS). HIDS attacks typically occur every 4-6 weeks and last 3-7 days. The most frequent symptoms are fever, diarrhoea, arthralgias, cold shivers, abdominal pain, vomiting and headache. Physical examination often reveals lymphadenopathy, skin lesions, arthritides, splenomegaly and serositis. Laboratory investigation includes an acute-phase response with granulocytosis and enhanced erythrocyte sedimentation rate. The serum concentration of IgD is increased as is the concentration of IgA. There is no causal therapy. A causative gene mutation was recently identified.

PMID: 10800552 [Indexed for MEDLINE]

4866. Ned Tijdschr Geneeskd. 2000 Apr 22;144(17):782-5.

[Identification of the gene for hyper-IgD syndrome: a model of modern genetics].

[Article in Dutch]

Drenth JP(1), Waterham HR, Kuis W, Houten SM, Frenkel J, Wanders RJ, Poll-The BT, van der Meer JW.

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Comment on

Ned Tijdschr Geneeskd. 2000 Apr 22;144(17):809-11.

Hyperimmunoglobulinaemia D and periodic fever syndrome (HIDS) is a rare autosomal recessive disorder. Patients suffer from recurrent attacks (3-6 days) with fever,

abdominal distress, lymphadenopathy, skin lesions and arthralgias. Patients display a constantly elevated serum IgD which serves as a biological marker of the disease. Recently, the gene for HIDS was discovered by two independent groups using positional and functional cloning methods. One group used linkage analysis (positional cloning) and was able to locate the gene for HIDS on the long arm of chromosome 12 (12q24). Mevalonate kinase was an interesting candidate gene because patients with a near complete absence of this enzyme (mevalonic aciduria) do exhibit attacks of fever. Indeed subsequent data showed that there was a decreased enzyme activity due to missense mutations in the mevalonate kinase gene. The other group detected slightly elevated urinary excretion of mevalonic acid during attacks in a HIDS patient (functional cloning). The enzyme activity of mevalonate kinase was lower in cultured cells and sequence analysis identified several missense mutations in cDNA encoding for mevalonate kinase. Mevalonate kinase is a key enzyme in the cholesterol synthesis pathway and it is rather surprising that a defect in the cholesterol metabolism can cause a periodic inflammatory disease such as HIDS.

PMID: 10800545 [Indexed for MEDLINE]

4867. Pediatrics. 2000 May;105(5):E70.

Familial Mediterranean fever: effects of genotype and ethnicity on inflammatory attacks and amyloidosis.

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**OBJECTIVE:** The gene causing familial Mediterranean fever (FMF)-an autosomal recessive disease characterized by recurrent short episodes of fever associated most commonly with peritonitis, pleuritis, and arthritis-has recently been found and several mutations identified. The most severe complication of the disease is amyloidosis, which can lead to renal failure. The aim of this study was to investigate the role of genetic versus nongenetic factors on the phenotype as

well as on the development of amyloidosis in FMF in a large and heterogeneous group of patients.

**METHODOLOGY:** We studied 382 patients from 4 ethnic origins living in different environments: North African Jews, other Jews, Turks, Armenians living in the United States, and Armenians from Yerevan, Armenia. Information regarding amyloidosis was available for 371 patients. We examined the association between the mutation M694V and the development of amyloidosis, and we also compared the clinical characteristics of the inflammatory attacks in patients from different ethnic origins, while controlling for the type of mutation.

**RESULTS:** A significant association was found between amyloidosis and the most common mutation in exon 10 of the FMF gene (MEFV), M694V (for M694V homozygotes, relative risk = 1.77; 95% CI = 1.16-2.71). Amyloidosis was present in 44 of 171 homozygous FMF patients (25.7%), in 22 of 143 compound heterozygous FMF patients (15.4%), and in 7 of 57 patients carrying other mutations (12.3%). In homozygotes for M694V who had not been treated with colchicine before 20 years of age, the risk of amyloidosis developing before this age was 61.0%. In our series, there were no cases of amyloidosis in 16 patients carrying the common mutation E148Q. We found that the type and severity of the FMF inflammatory symptoms were associated with both the genotype and the country of residence of the patient.

**CONCLUSIONS:** In the light of the high frequency of amyloidosis in homozygotes for the mutation M694V, colchicine treatment should be given to this group irrespective of the severity of the inflammatory attacks to prevent the development of amyloidosis. Our findings also suggest that factors other than genotype, such as environment or genes other than MEFV, play a role in the determination of the severity of the inflammatory attacks in FMF. amyloidosis, specific mutation, phenotype-genotype correlation, ethnicity.

PMID: 10799634 [Indexed for MEDLINE]

4868. QJM. 2000 Apr;93(4):223-9.

Clinical versus genetic diagnosis of familial Mediterranean fever.

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The diagnosis of familial Mediterranean fever (FMF) has until recently been based on clinical signs alone. Discovery of the MEFV gene has enabled a molecular approach to diagnosis, which is already well established for diagnosing typical clinical forms of FMF. We evaluated the utility of this molecular approach in a large series of patients with various clinical presentations and ethnic origins. We looked for mutations in the MEFV gene in 303 unselected consecutive patients with a variable (from high to low) clinical suspicion of FMF. Two mutations were found in 133 patients (44%). In 22 patients (7%), the clinical diagnosis of FMF was unlikely according to the Tel Hashomer clinical criteria. Our results suggest that the spectrum of FMF-associated signs is broader than previously believed. Wider indications for genotyping should lead to more frequent diagnosis of FMF.

PMID: 10787450 [Indexed for MEDLINE]

4869. QJM. 2000 Apr;93(4):217-21.

The genetic basis of autosomal dominant familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is classically an autosomal recessive periodic inflammatory disease occurring in Mediterranean and Middle Eastern populations. It is caused by mutations affecting both alleles of MEFV, a gene that encodes pyrin (marennostin), an uncharacterized neutrophil protein. Occasional reports of autosomal dominant FMF have often been discounted, on the basis that asymptomatic FMF carriers are common in certain populations, and give rise to pseudo-dominant inheritance. We performed comprehensive MEFV genotyping in five families in whom FMF appeared to be inherited dominantly. Transmission proved to be

pseudo-dominant in two cases, but true dominant inheritance of FMF with variable penetrance was supported by the genotyping results in the other three families. The disease in these cases was associated with heterozygosity for either pyrin DeltaM694 alone or the compound pyrin variant E148Q/M694I, the latter occurring in two unrelated families. Complete MEFV sequencing failed to identify any coding region abnormality in the other allele in any of these cases, and, in the largest kindred, single-allele disease transmission was further supported by analysis of silent single nucleotide polymorphisms, which proved that affected individuals had at least three different complementary alleles. Studies of two further unrelated British patients with FMF associated with simple heterozygosity for pyrin DeltaM694 were also consistent with autosomal dominant inheritance. The clinical features of dominantly inherited FMF were absolutely typical, including AA amyloidosis in a patient with pyrin DeltaM694. These findings extend the spectrum of FMF, and suggest that the methionine residue at position 694 makes a crucial contribution to pyrin's function, and that a 50% complement of normal pyrin activity does not prevent susceptibility to FMF.

PMID: 10787449 [Indexed for MEDLINE]

4870. Proc Soc Exp Biol Med. 2000 May;224(1):32-40.

The familial mediterranean fever protein interacts and colocalizes with a putative Golgi transporter.

Chen X(1), Bykhovskaya Y, Tidow N, Hamon M, Bercovitz Z, Spirina O, Fischel-Ghodsian N.

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The biological function of pyrin, the protein mutated in Familial Mediterranean Fever (FMF), has not been elucidated. Based on sequence homology, a transcription factor activity was proposed for this neutrophil-specific protein. In a yeast two-hybrid assay, neither transcription activation activity nor any self interaction was detected for pyrin. Screening of an expression cDNA library of

peripheral blood leukocytes using as bait the carboxyl portion of pyrin (amino acids 557-781), which contains most of the FMF mutations, led to the identification of P/M-IP1 (pyrin/marenostrin interacting protein 1). A splice variant of P/M-IP1, GTC-90, had previously been described as a component of the 13S hetero-oligomeric protein complex that stimulates in vitro Golgi transport. We have now shown that P/M-IP1 colocalizes with pyrin in the perinuclear cytoplasm of Cos-7 cells and that the interaction between these two proteins is impaired by FMF causing mutations in pyrin. These data suggest that, at some stage of its functional pathway, pyrin resides in the cytoplasm and might be involved in, or impacted by, cellular protein sorting by the Golgi apparatus. The data also imply that P/M-IP1 may be involved in the abnormal inflammatory response that occurs in patients with FMF.

PMID: 10782044 [Indexed for MEDLINE]

4871. Scand J Rheumatol. 2000;29(2):129-30.

Renal amyloidosis as a first manifestation of Familial Mediterranean Fever.

Konstantopoulos K(1), Michael S, Kanta A, Pecheux C, Grateau J, Helioti H, Stathakis C.

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Amyloid nephropathy was the presenting symptom in a case of Familial Mediterranean Fever (FMF). As recent progress in molecular pathology permits the detection of asymptomatic FMF individuals, it is suggested that relevant cases of renal amyloidosis should be tested for FMF mutations.

PMID: 10777128 [Indexed for MEDLINE]

4872. J Am Acad Dermatol. 2000 May;42(5 Pt 1):791-5.

# Erysipelas-like erythema of familial Mediterranean fever: clinicopathologic correlation.

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**BACKGROUND:** Familial Mediterranean fever (FMF) is an autosomal recessive disease that tends to affect certain ethnic groups. It is characterized by recurrent, self-limited attacks of peritonitis, pleuritis, and synovitis. Erysipelas-like erythema (ELE) is the pathognomonic skin manifestation. Lesions are characterized by tender erythematous plaques, usually located on the lower legs. They may be triggered by physical effort and subside spontaneously within 48 to 72 hours of bed rest. Fever and leukocytosis may accompany this condition.

**OBJECTIVE:** The purpose of this study was to describe the histology and the immunofluorescence findings in ELE and to discuss these observations in relation to the clinical findings in FMF.

**METHODS:** We studied 7 patients with FMF in whom ELE developed. In all patients a biopsy was performed within 18 hours from onset of the lesion. In addition to routine hematoxylin and eosin stains, immunohistochemistry to evaluate the infiltrate and direct immunofluorescence were performed. Patients were followed up for their ELE lesions.

**RESULTS:** Histologic examination revealed edema of the superficial dermis and sparse perivascular infiltrate composed of a few lymphocytes, neutrophils, and nuclear dust. Vasculitis was not observed. Direct immunofluorescence showed, in all cases, deposits of C3 in the wall of the small vessels of the superficial vascular plexus. In some cases fibrinogen and IgM were also observed.

**CONCLUSION:** These findings are in accordance both with those found previously in the erysipelas-like phenomenon and those in the peritoneum of patients with FMF. The sparse infiltrate and the deposition of C3 also are compatible with the clinical picture of self-resolving lesions of short duration. It also suggests that erysipelas-like erythema belongs to the spectrum of neutrophilic dermatoses and supports a pathogenesis that involves abnormal inhibition of the inflammatory cascade.



4873. BMJ. 2000 Apr 22;320(7242):1091-2.

Periodic fevers enter the era of molecular diagnosis.

Drenth JP, van Der Meer JW.

PMCID: PMC1127242

PMID: 10775206 [Indexed for MEDLINE]

4874. Turk J Pediatr. 1999 Jul-Sep;41(3):387-90.

Sacroiliitis in familial Mediterranean fever: an unusual presentation in childhood.

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Familial Mediterranean fever (FMF) is an autosomal recessively transmitted disease characterized by attacks of fever and serositis. The course of arthritis, which is a common manifestation of FMF, is generally benign. Sacroiliitis due to FMF has been reported by several authors, but all the patients described so far had roentgenographic abnormalities, and most of them were adult cases. Here we report the youngest FMF patient with sacroiliitis without any abnormality on sacroiliac x-ray. She is also the first FMF patient in whom sacroiliac involvement was diagnosed by computed tomography (CT) in childhood. It is concluded that CT is a useful technique for the early diagnosis of destructive arthritis in FMF patients even in early childhood.

PMID: 10770103 [Indexed for MEDLINE]

4875. Rev Med Interne. 2000 Mar;21(3):247-55.

[Treatments for amyloidosis beyond symptomatic care].

[Article in French]

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**INTRODUCTION:** Amyloid syndromes are pathogenetically different, each of the various amyloid diseases requiring specific treatment. Unfortunately, those treatments are often preventive and symptomatic, some efficient therapies being limited to particular types of amyloidosis.

**CURRENT KNOWLEDGE AND KEY POINTS:** Colchicine is effective in the prevention of amyloidosis due to familial Mediterranean fever but is less or not effective in other situations. Cytotoxic agents are useful in the treatment of AL amyloidosis with or without hemopoietic stem cell transplantation. Liver transplantation is indicated for familial polyneuropathy and kidney transplantation for dialysis-related beta 2 microglobulin amyloidosis.

**FUTURE PROSPECTS AND PROJECTS:** In vivo binding of serum amyloid P (SAP) (component shared by all amyloid deposits) to amyloid fibril, is a new avenue in the therapeutic approach. Development of radiolabeled SAP scintigraphy allows assessment of the disease outcome and evaluation of treatment-related effects. The various treatments that were assessed until now with the objective of curing the disease are reviewed.

PMID: 10763186 [Indexed for MEDLINE]

4876. Hum Mutat. 2000 Apr;15(4):385-6.

The E148Q mutation in the MEFV gene: is it a disease-causing mutation or a sequence variant?

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Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent attacks of serositis. To date more than 18 mutations responsible for the disease were identified in the MEFV gene, one such a mutation is E148Q in exon 2 of the gene. While screening FMF patients for mutations in the MEFV gene, we have identified 2 individuals parents of 2 unrelated FMF patients, who were homozygous for E148Q mutation. Upon clinical examination they were absolutely disease free and therefore raised the possibility that this mutation is a benign polymorphism rather than a mutation causing disease. To further investigate the role of the E148Q in FMF we analyzed 25 parents of FMF patients and a control group of 70 individuals, Jews of Moroccan extraction to match for ethnicity of the patients. The rate of E148Q in the control group was 6.4%, being 7.8% among the patient group. Among the parents group (obligatory carriers), in addition to the 2 parents that were homozygous E148Q, in 2 families one of the parents was heterozygote for E148Q but transmitted the other allele (apparently with unknown FMF mutation) to the affected child. Two healthy sibs of one of the E148Q homozygous were also homozygous E148Q. These observations are not in accordance to the notion that E148Q is a mutation causing disease.

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DOI: 10.1002/(SICI)1098-1004(200004)15:4<385::AID-HUMU22>3.0.CO;2-A

PMID: 10737995 [Indexed for MEDLINE]

4877. Hum Mutat. 2000 Apr;15(4):384.

Genetic screening of fourteen mutations in Jordanian familial Mediterranean fever patients.

Medlej-Hashim M(1), Rawashdeh M, Chouery E, Mansour I, Delague V, Lefranc G, Naman R, Loiselet J, Mégarbané A.

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Familial Mediterranean fever is an autosomal recessive disorder characterised by

episodic fever, abdominal and pleuritic pain, serositis and arthritis. The FMF gene (MEFV) has been mapped to chromosome 16p13.3 and generates a protein found exclusively in granulocytes. Seventeen mutations have been reported up to the present in FMF patients. This study involves the screening of 14 mutations in 42 Jordanian patients by two methods: RFLP and ARMS. The most frequent mutations were M694V and V726A (20% and 14% of the alleles respectively), followed by M680I and E148Q (9.5% and 7% of the alleles respectively). The A744S mutation accounts for 2.5% and the M694I, T267I and F479L mutations account each for 1% of the alleles. E167D, R761H, P369S, I692del and M694del mutations were not found in this population. Forty-four percent of the alleles did not have any of the 14 mutations. The results show the diversity and the frequency of the mutations in the Jordanian patients, and open the way for further investigations on patients diagnosed to have FMF and in whom no mutations were found. Hum Mutat 15:384, 2000.

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DOI: 10.1002/(SICI)1098-1004(200004)15:4<384::AID-HUMU19>3.0.CO;2-U  
PMID: 10737992 [Indexed for MEDLINE]

4878. Turk J Pediatr. 2000 Jan-Mar;42(1):61-4.

Cyclic neutropenia complicated by renal AA amyloidosis.

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Comment in

Turk J Pediatr. 2001 Apr-Jun;43(2):180.

Cyclic neutropenia is a rare disease characterized by regular cyclic fluctuations in the numbers of neutrophils. Patients with the disease suffer from recurrent infections at regular intervals of nearly three weeks. Recently, recombinant human granulocyte colony-stimulating factor (rhG-CSF) was reported to be an effective treatment for this disease. here we describe 17-year-old cyclic

neutropenic female patient with a very rare association of renal amyloidosis of AA type who was under intermittent rhG-CSF treatment for the previous one and a half years. We conclude that although the disorder is usually benign, reactive amyloidosis may rarely develop in cases who remain untreated for a long period of time. However familial Mediterranean fever (FMF) type II should also be born in mind, particularly in predisposed populations.

PMID: 10731873 [Indexed for MEDLINE]

4879. Isr Med Assoc J. 1999 Oct;1(2):121-2.

Bronchoalveolar carcinoma in a patient with recurrent familial Mediterranean attacks, fibrothorax, and treatment with colchicine.

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PMID: 10731312 [Indexed for MEDLINE]

4880. Clin Exp Rheumatol. 2000 Jan-Feb;18(1):103-6.

Living with a child with familial Mediterranean fever: does it affect the quality of life of the parents?

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OBJECTIVE: The aim of the present study was to assess the quality of life (QOL) and the psychological status of parents of children with familial Mediterranean

fever (FMF).

**METHODS:** The QOL, anxiety and depression of the parents of 35 children with FMF were evaluated and compared to the parents of 23 healthy children.

**RESULTS:** Mothers of FMF children had lower QOL scores than mothers of healthy children: 5.5 +/- 1.1 versus 6.0 +/- 0.6 ( $p = 0.048$ ). They also expressed higher levels of anxiety and depression. Within each group, mothers were more anxious and depressed than fathers. Parents with several FMF children were not significantly different from parents with only one FMF child.

**CONCLUSION:** The QOL and psychological well being of parents with FMF children were found to be slightly impaired, especially that of the mothers.

PMID: 10728454 [Indexed for MEDLINE]

4881. Acta Paediatr. 2000 Feb;89(2):177-82.

Clinical, laboratory and molecular characteristics of children with Familial Mediterranean Fever-associated vasculitis.

Tekin M(1), Yalçinkaya F, Tümer N, Akar N, Misirlioğlu M, Cakar N.

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Familial Mediterranean Fever (FMF) is an autosomal recessive disease characterized by recurrent self-limited attacks of fever accompanied by peritonitis, pleuritis and arthritis. Approximately 5% of individuals with FMF have been reported to have Henoch-Schönlein purpura (HSP) and about 1% have polyarteritis nodosa (PAN). Protracted febrile myalgia is another vasculitis-associated clinical entity among patients with FMF. Recently, the gene responsible for FMF, MEFV, has been cloned and four missense mutations (M680I, M694V, V726A and M694I) have been described. In this report, we present clinical and laboratory findings and mutation results of 23 children with FMF-associated vasculitis. HSP, PAN and protracted febrile attacks have been diagnosed in 11, 2 and 10 children, respectively. Mutation analysis shows that 3 children are homozygotes for the M694V mutation and 11 are compound heterozygotes for 2 of the studied mutations. M694V/V726A mutations were identified in 8, M694V/M694I in 2

and M680I/M694V in 1 of these children. In six children only one mutation was found and in three none of the studied mutations were identified. This study confirms that most children with FMF-associated vasculitis have identifiable mutations in the MEFV gene. Environmental and/or other genetic factors are possibly involved in the pathogenesis of vasculitis in FMF; elucidation of these mechanisms will help to understand pathogenesis of childhood vasculitides.

PMID: 10709887 [Indexed for MEDLINE]

4882. Rev Med Interne. 2000 Feb;21(2):161-6.

[Clinical or biological symptoms leading to the search for amyloidosis].

[Article in French]

Rousset H(1), Sauron C, Barouky R.

Author information:

(1)Service de Médecine Interne, Centre Hospitalier Lyon-Sud, Pierre-Bénite, France.

**INTRODUCTION:** The extracellular, multifocal, disseminated or diffuse localization of amyloidosis accounts for the diversity of clinical presentations and late diagnosis.

**CURRENT KNOWLEDGE AND KEY POINTS:** However, early diagnosis is important, as new drugs have been recently introduced. Both clinical picture and biology help guide diagnosis, including either kidney, heart, skin or neurologic involvement associated with monoclonal gammopathy (primary idiopathic amyloidosis AL); underlying inflammatory or infectious disease, familial Mediterranean fever with proteinuria (secondary amyloidosis AA); cardiac, neurologic or ocular involvement (heredofamilial amyloidosis); carpal tunnel syndrome, joint pain (amyloidosis of hemodialysis). Furthermore, amyloid fibrils are identified on salivary gland biopsy.

**FUTURE PROSPECTS AND PROJECTS:** Due to the introduction of new specific drugs aimed at curing various amyloidoses, early diagnosis is important. Chemotherapy and hematopoietic stem cell transplantation are promising regarding AL amyloidosis, while liver transplantation has proven remarkably successful in

heredofamilial amyloidosis. Progress in molecular biology should allow identification of various forms of familial amyloidosis.

PMID: 10703072 [Indexed for MEDLINE]

4883. Ann Med Interne (Paris). 1999 Dec;150(8):594-7.

[Neuromuscular complications of long-term treatment of inflammatory diseases. 3 cases].

[Article in French]

Tattevin P(1), Arondelle C, Margent P, Broucker De T.

Author information:

(1)Service de Neurologie, Hôpital Delafontaine, Saint-Denis.

Chloroquine and colchicine, widely used in internal medicine practice for a variety of inflammatory diseases including systemic lupus erythematosus, rheumatoid arthritis, familial Mediterranean fever, and Behçet's disease, may induce neuromuscular complications. Physicians must be familiar with this diagnosis as this iatrogenic neuromuscular pathology may simulate polymyositis, leading thus to inappropriate treatment with prednisone whereas the only effective treatment is to discontinue the drug involved whenever possible. We report three cases of toxic myopathy and/or neuropathy related to chronic chloroquine or colchicine therapy for systemic diseases, and outline the main points to be considered in this situation.

PMID: 10686640 [Indexed for MEDLINE]

4884. Ann Genet. 1999;42(4):241-5.

[French Society for Human Genetics. "Genetics in Practice" Commission. Core scientific data of use in genetic counseling. Familial Mediterranean fever].



[Article in French]

Cazeneuve C(1), Dode C, Delpech M, Touitou I, Grateau G, Amselem S.

Author information:

(1)Service de Biochimie Génétique, Hôpital Henri Mondor, Creteil.

PMID: 10674166 [Indexed for MEDLINE]

4885. Neth J Med. 2000 Jan;56(1):21-4.

A homozygous M694V mutation of the MEFV gene in a patient with periodic fever and thoracic pain.

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A Turkish patient with episodic fever and thoracic pain is described in whom a homozygous M694V mutation of the MEFV gene confirmed the clinical diagnosis of familial Mediterranean fever. The role of DNA analysis is discussed with respect to understanding the pathogenesis of the fever and assessing the risk of amyloidosis in specific mutations of the MEFV gene.

PMID: 10667038 [Indexed for MEDLINE]

4886. Blood. 2000 Feb 15;95(4):1451-5.

Hematopoietic-specific expression of MEFV, the gene mutated in familial Mediterranean fever, and subcellular localization of its corresponding protein, pyrin.

Tidow N(1), Chen X, Müller C, Kawano S, Gombart AF, Fischel-Ghodsian N, Koeffler

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Author information:

(1)Department of Medicine and Department of Pediatrics and Medical Genetics, Cedars-Sinai Medical Center, UCLA School of Medicine, Los Angeles, CA 90048, USA.

Familial Mediterranean fever (FMF) is a recessively inherited disorder characterized by recurrent, self-limited attacks of fever and serositis and by infiltration of affected tissues by large numbers of neutrophils. A candidate gene for FMF was identified by positional cloning and named "MEFV." The corresponding protein was named "pyrin." To elucidate the currently unknown function of pyrin, we characterized its tissue distribution, regulation of expression during hematopoietic differentiation, and subcellular localization. Reverse transcription-polymerase chain reaction analysis, followed by hybridization with an internal oligonucleotide, demonstrated expression of MEFV in different populations of peripheral blood cells. Among hematopoietic cell lines, MEFV was almost exclusively expressed in cells of the myeloid lineage. Furthermore, MEFV messenger RNA was strongly expressed within 24 hours of dimethyl sulfoxide-induced granulocytic differentiation of HL-60 cells. Analysis of complementary DNA from human solid tumor-derived cell lines revealed expression of MEFV in several cell lines derived from colon and prostate cancers. Expression of MEFV fused to enhanced green fluorescent protein showed that pyrin localized in distinct patches in the cytoplasm, forming a perinuclear cap. Taken together, MEFV is predominantly expressed in myeloid cells and upregulated during myeloid differentiation, and the corresponding protein, pyrin, is expressed in the cytoplasm. (Blood. 2000;95:1451-1455)

PMID: 10666224 [Indexed for MEDLINE]

4887. Lancet. 2000 Jan 29;355(9201):378-9.

Inflammatory bowel disease in non-Ashkenazi Jews with familial Mediterranean fever.

Cattan D, Notarnicola C, Molinari N, Touitou I.

Erratum in

Lancet 2000 Mar 18;355(9208):1020.

Familial Mediterranean fever and inflammatory bowel disease are two inflammatory conditions. We showed that inflammatory bowel disease was particularly frequent and severe in non-Ashkenazi Jewish patients with familial Mediterranean fever.

DOI: 10.1016/S0140-6736(99)02134-0

PMID: 10665562 [Indexed for MEDLINE]

4888. *Pediatr Surg Int.* 2000;16(1-2):72-4.

The acute scrotum in Arab children with familial Mediterranean fever.

Majeed HA(1), Ghandour K, Shahin HM.

Author information:

(1)Department of Pediatrics, Faculty of Medicine, University of Jordan, Amman, Jordan.

Over a period of 7 years, among 175 boys under the age of 16 years with familial Mediterranean fever (FMF), 16 (9%) developed 28 episodes of scrotal swelling that was unilateral in 26 (93%) and bilateral in 2 (7%). Fever and pain were present in 15 (94%) children; fever was characterized by a gradual onset and pain was moderate in intensity. The episodes were self-limiting and lasted from 8 h to 5 days. Scrotal swelling was the presenting feature of FMF in 4 (25%) patients. Six (38%) children underwent surgery; the operative findings, available in 3, showed a normal testis and epididymis and inflammation of the tunica vaginalis. The self-limiting nature of the episodes lasting for a few days was similar to the clinical course of serositis seen in FMF. This strongly suggests that inflammation of the tunica vaginalis, resulting in scrotal swelling, is another feature of FMF serositis. The gradual onset of fever, pain, swelling, and recurrence in a boy of Mediterranean origin, especially in the presence of a relevant family history, strongly points toward the diagnosis of FMF and conservative management. Early diagnosis and prophylactic colchicine therapy are expected to avert recurrences, which may result in ischemic testicular necrosis and FMF nephropathy.

PMID: 10663841 [Indexed for MEDLINE]

4889. Rheumatology (Oxford). 2000 Jan;39(1):67-72.

Genotype-phenotype correlation in a large group of Turkish patients with familial mediterranean fever: evidence for mutation-independent amyloidosis.

Yalçinkaya F(1), Cakar N, Misirlioğlu M, Tümer N, Akar N, Tekin M, Taştan H, Koçak H, Ozkaya N, Elhan AH.

Author information:

(1)Ankara University Faculty of Medicine and Ankara Social Security Children's Hospital, Ankara, Turkey.

Erratum in

Rheumatology (Oxford) 2000 Oct;39(10):1170.

**OBJECTIVES:** Differences in clinical manifestations of familial Mediterranean fever (FMF) between different ethnic groups have been documented. The FMF gene was recently cloned and four missense mutations (Met694Val, Met680Ile, Val726Ala, and Met694Ile) that account for a large percentage of the patients were identified. The results of initial mutation studies have led to the hypothesis that phenotypic variation of the disease may be attributable to the existence of some of these mutations. The purpose of this study was to evaluate whether this phenotypic variation is associated with the existence of particular mutations in Turkish FMF patients living in Turkey.

**METHODS:** Four missense mutations and genotype-phenotype correlation were investigated in 167 Turkish FMF patients. The patients were grouped according to the presence of the Met694Val and the Met680Ile mutations, and 12 clinical parameters were compared between the groups.

**RESULTS:** The presence of the Met694Val mutation was not found to be associated with a severe form of the disease or the development of amyloidosis. Arthritis frequency was found to be lower in the patients with homozygous Met680Ile mutation.

**CONCLUSIONS:** None of the four missense mutations is associated with a severe disease or the development of amyloidosis in Turkish FMF patients living in Turkey. The influence of unknown environmental factors and/or the presence of other genetic changes are necessary to explain the phenotypic variation of the

disease and the development of amyloidosis.

PMID: 10662876 [Indexed for MEDLINE]

4890. Circulation. 2000 Feb 8;101(5):E71-2.

Recurrent pericarditis as a manifestation of familial Mediterranean fever.

Ercan Tutar H, Imamoglu A, Atalay S.

Comment on

Circulation. 1998 Jun 2;97(21):2183-5.

PMID: 10662763 [Indexed for MEDLINE]

4891. Rheumatol Int. 1999;19(1-2):71-3.

Protracted familial Mediterranean fever arthritis.

Bodur H(1), Uçan H, Seçkin S, Seçkin U, Gündüz OH.

Author information:

(1)hbodur@anh.gov.tr

Familial Mediterranean fever (FMF) is an inherited disorder characterized by recurrent attacks of fever and abdominal, chest, and articular pain. The articular attack of FMF is typically an acute, self-limited, large joint monoarthritis most often affecting the knee or hip. Rarely, a more protracted arthritis may occur. We describe two unusual cases of long-standing FMF arthritis with excellent response to synovectomy.

PMID: 10651088 [Indexed for MEDLINE]

4892. Rheumatol Int. 1999;19(1-2):69-70.

Reflex sympathetic dystrophy arising in a patient with familial Mediterranean fever.

Bodur H(1), Gündüz OH, Yücel M.

Author information:

(1)hbodur@anh.gov.tr

A 14-year-old girl with familial Mediterranean fever (FMF) had had acute attacks of fever, abdominal pain, and arthritis for 4 years. Her last arthritis attack was protracted, leading to reflex sympathetic dystrophy (RSD) in her right lower extremity. Physical therapy along with sympathetic ganglion block and corticosteroid therapy was used for the treatment. To our knowledge, this is the first reported case of RSD arising in a patient with FMF. Early recognition of RSD in FMF patients is important, and physical therapy should be applied along with medical treatment.

PMID: 10651087 [Indexed for MEDLINE]

4893. Nephrol Dial Transplant. 2000 Feb;15(2):281-2.

Regression of nephrotic syndrome due to amyloidosis secondary to familial mediterranean fever following colchicine treatment.

Simşek B, İşlek I, Simşek T, Küçüködük S, Cengiz K.

Comment in

Nephrol Dial Transplant. 2000 Oct;15(10):1713-4.

Nephrol Dial Transplant. 2000 Jul;15(7):1098.

PMID: 10648685 [Indexed for MEDLINE]

4894. Curr Opin Rheumatol. 2000 Jan;12(1):61-4.

The relation between familial Mediterranean fever and amyloidosis.

Grateau G(1).

Author information:

(1)Service de médecine interne, L'Hôtel-Dieu, Paris, France.

Familial Mediterranean fever (FMF) is the most prevalent type of hereditary recurrent fever. Although the inflammatory attacks that characterize the disease may sometimes be debilitating, reactive amyloidosis remains the most serious manifestation of FMF. Daily treatment with colchicine can prevent both the attacks and amyloid deposition, but FMF-associated amyloidosis has not been eradicated and is still a cause of chronic renal failure in children and adults. The discovery of the gene responsible for FMF, Mediterranean fever gene (MEFV), and of associated mutations represents a major advance that now allows researchers to establish a strong, although nonexclusive association between one specific mutation, M694V, and the amyloid phenotype.

PMID: 10647956 [Indexed for MEDLINE]

4895. Med Klin (Munich). 1999 Dec 15;94(12):685-9.

[Familial Mediterranean fever. New aspects with respect to molecular genetics and pathogenesis revealed in three case reports].

[Article in German]

Rengelshausen J(1), Rünzi M, Canbay A, Gerken G, Philipp T.

Author information:

(1)Abteilung für Nieren- und Hochdruckkrankheiten, Universitätsklinikum Essen.

**HISTORY AND CLINICAL PRESENTATION:** Three young Turkish males were admitted because of acute abdominal pain and fever. All 3 patients had recurrent attacks of these symptoms every few weeks since years with each attack lasting 2 to 3 days. One patient developed a renal amyloidosis with an end-stage renal failure.

**DIAGNOSTICS AND CLINICAL COURSE:** All patients presented with local abdominal tenderness and an elevation of inflammatory parameters (WBC, ESR, CRP and fibrinogen). X-ray studies, ultrasound and upper endoscopy were normal. In 1 patient histology yielded amyloid fibrils in the antrum of the stomach. In a molecular genetic analysis 2 patients were compound heterozygous for 2 common mutations of the gene responsible for the familial Mediterranean fever (FMF). In all patients the symptoms vanished spontaneously according to an acute attack of FMF. After symptomatic treatment a prophylaxis with colchicine was started.

**CONCLUSION:** Cloning of the FMF gene and its mutations and identification of the gene product "pyrin" reveals new aspects on genetics and pathophysiology. The improved diagnostic procedure enables an early start of colchicine treatment, especially to prevent renal amyloidosis.

PMID: 10641511 [Indexed for MEDLINE]

4896. Clin Rheumatol. 1999;18(6):446-9.

Familial Mediterranean fever and acute rheumatic fever: a pathogenetic relationship?

Tekin M(1), Yalçinkaya F, Tümer N, Cakar N, Koçak H.

Author information:

(1)Ankara University School of Medicine, Turkey. mtekin@hsc.vcu.edu

The frequency of acute rheumatic fever (ARF) in patients with familial Mediterranean fever (FMF) was documented and the effects of preceding streptococcal infections on the exacerbation of FMF were determined. In the first part of the study, 162 individuals with FMF were investigated for a history of ARF in a retrospective study. In the second part of the study, antistreptolysin-O (ASO) titres were measured in 130 individuals with FMF. Thirty-six patients had an arthritic attack (group A1), 55 patients had a typical FMF attack without arthritis (group A2) and 39 patients were in the attack-free interval (group B) during the investigation. Nine patients with FMF (5.5%) were considered to have ARF and three of them (1.85%) also had rheumatic heart disease. This prevalence of rheumatic heart disease in FMF is higher than that of the normal population (0.65%) reported in Turkey. Elevated ASO titres were found in 75%, 42% and 38% of



the patients in groups A1, A2 and B, respectively. These percentages were found to be significantly higher in group A1 than in both groups A2 ( $p<0.01$ ) and B ( $p<0.01$ ). We concluded that patients with FMF might be more prone to the late complications of streptococcal infections.

PMID: 10638768 [Indexed for MEDLINE]

4897. J Clin Gastroenterol. 2000 Jan;30(1):98-9.

The coexistence of familial Mediterranean fever and Addison disease.

Kadayifci A, Uygun A, Dagalp K, Kepekci Y.

PMID: 10636223 [Indexed for MEDLINE]

4898. Klin Med (Mosk). 1999;77(11):57-9.

[Possible explanations of molecular mechanisms underlying etiology and pathogenesis of periodic disease].

[Article in Russian]

Arutiunian VM, Grigorian EG, Karagezian KG, Vasilian AA, Arutiunian MS, Ovsian GA.

PMID: 10635639 [Indexed for MEDLINE]

4899. N Engl J Med. 2000 Jan 6;342(1):60.

Molecular diagnosis of familial Mediterranean fever.

Nir-Paz R, Ben-Chetrit E.

Comment on

N Engl J Med. 1999 Aug 19;341(8):593-9.

DOI: 10.1056/NEJM200001063420115

PMID: 10627216 [Indexed for MEDLINE]

4900. QJM. 1999 Jun;92(6):309-18.

Familial Mediterranean fever in children: the expanded clinical profile.

Majeed HA(1), Rawashdeh M, el-Shanti H, Qubain H, Khuri-Bulos N, Shahin HM.

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(1)Department of Pediatrics, Faculty of Medicine, University of Jordan, Amman, Jordan. pal@go.com.jo

Erratum in

QJM 1999 Sep;92(9):545.

The clinical picture of familial Mediterranean fever (FMF) has been appreciably expanded in the last 10 years. Over 8 years, we studied the expanded clinical profile of FMF in 476 children. Of these, 81% had abdominal pain, 41% chest pain, 42% arthritis, 12% severe myalgia, 12% skin manifestations, 4% scrotal swelling, 3% recurrent episodic fever, and one child (0.2%) developed recurrent hyperbilirubinaemia. Two (0.4%) children developed renal complications which were reversed by colchicine; however of 19 probands, 36 family members suffered from chronic renal failure. Our study indicates a familial predisposition to nephropathy in certain families with FMF. This study is the first to report the expanded clinical profile of FMF in a large group of Arab children, giving an opportunity to compare the findings with those in children with FMF in other ethnic groups, and to help in the study of genotype-phenotype correlation.

PMID: 10616706 [Indexed for MEDLINE]

4901. Transplant Proc. 1999 Dec;31(8):3221-3.

Impact of amyloidosis on long-term survival in kidney transplantation.

Karakayali H(1), Demirag A, Moray G, Ersoy E, Turan M, Bilgin N, Haberal M.

Author information:

(1)Department of General Surgery, Baskent University Faculty of Medicine, Ankara, Turkey.

PMID: 10616451 [Indexed for MEDLINE]

4902. Hum Mutat. 2000 Jan;15(1):118-9.

MEFV mutations in Turkish patients suffering from Familial Mediterranean Fever.

Akar N(1), Misiroglu M, Yalcinkaya F, Akar E, Cakar N, Tümer N, Akcokus M, Tastan H, Matzner Y.

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(1)Pediatric Molecular Pathology and Nephrology Departments, Ankara University, Ankara, Turkey.

Familial Mediterranean fever (FMF) is a recessive inherited disorder affecting Sephardic Jews, Arabs, Armenians and Turks. The gene responsible for FMF was recently cloned and several disease-associated mutations have been described. We have evaluated seven MEFV mutations in 460 chromosomes of 230 unrelated patients with FMF living in Turkey, using PCR methods. The M694V allele accounted for 43.5% of the alleles studied and 19.1% of the patients were homozygous. The M680I, V726A and M694I mutations were responsible for 12.0%, 11.1% and 2.8% of the patients respectively. R761H, K695R and E148Q were rarely encountered. Two thirds of the disease alleles were attributed to three common mutations: M694V, M680V and V726A, but only 54% of the patients carried one or two of the three mutations. Adding the four rarer mutations increased these figures to 72% and 60%, respectively. Altogether, 79.6% of the patients bore at least one of the main mutations, and 84.3% carried at least one of the seven mutations studied. The 28 patients suffering also from amyloidosis carried at least one of five mutations, M694V being the most common. These results suggest that the origin of FMF in Turkey is heterogenous, all common mutations are associated with

amyloidosis. Further, rapid and accurate molecular diagnosis of FMF is feasible in most cases.

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DOI: 10.1002/(SICI)1098-1004(200001)15:1<118::AID-HUMU29>3.0.CO;2-5

PMID: 10612841 [Indexed for MEDLINE]

4903. Amyloid. 1999 Dec;6(4):301-2.

MEFV mutation analysis in Turkish familial Mediterranean fever patients with amyloidosis.

Akar N, Yalçinkaya F, Akar E, Cakar N.

Comment on

Amyloid. 1999 Mar;6(1):1-6.

PMID: 10611954 [Indexed for MEDLINE]

4904. Clin Exp Rheumatol. 1999 Nov-Dec;17(6):745-9.

New interest in an old disease: familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is characterized by recurrent attacks of fever and serositis. Identifying the mutated gene has shed light on the pathogenesis of the disease. Typical attacks of FMF last 3 to 5 days. Arthritis is present in almost half of all patients and is localized to the ankle, knee or hip. Recently vasculitic features have been increasingly reported in FMF patients, and it may be speculated that vasculitis constitutes a feature of this disease. Genetic

analysis is very important to confirm the diagnosis in patients with a European ancestry. However, at present the yield of genetic testing is not satisfactory; new sequencing techniques permitting more rapid screening and definition of all mutations are necessary. Colchicine is the drug of choice. A trial of colchicine may also help in the differential diagnosis with other periodic fever syndromes.

PMID: 10609078 [Indexed for MEDLINE]

4905. J Clin Endocrinol Metab. 1999 Dec;84(12):4405-9.

Mendelian diseases among Roman Jews: implications for the origins of disease alleles.

Oddoux C(1), Guillen-Navarro E, Ditivoli C, Dicave E, Cilio MR, Clayton CM, Nelson H, Sarafoglou K, McCain N, Peretz H, Seligsohn U, Luzzatto L, Nafa K, Nardi M, Karparkin M, Aksentijevich I, Kastner D, Axelrod F, Ostrer H.

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The Roman Jewish community has been historically continuous in Rome since pre-Christian times and may have been progenitor to the Ashkenazi Jewish community. Despite a history of endogamy over the past 2000 yr, the historical record suggests that there was admixture with Ashkenazi and Sephardic Jews during the Middle Ages. To determine whether Roman and Ashkenazi Jews shared common signature mutations, we tested a group of 107 Roman Jews, representing 176 haploid sets of chromosomes. No mutations were found for Bloom syndrome, BRCA1, BRCA2, Canavan disease, Fanconi anemia complementation group C, or Tay-Sachs disease. Two unrelated individuals were positive for the 3849 + 10C->T cystic fibrosis mutation; one carried the N370S Gaucher disease mutation, and one carried the connexin 26 167delT mutation. Each of these was shown to be associated with the same haplotype of tightly linked microsatellite markers as that found among Ashkenazi Jews. In addition, 14 individuals had mutations in the familial Mediterranean fever gene and three unrelated individuals carried the factor XI type III mutation previously observed exclusively among Ashkenazi Jews. These findings suggest that the Gaucher, connexin 26, and familial Mediterranean fever mutations are over 2000 yr old, that the cystic fibrosis 3849 + 10kb C->T

and factor XI type III mutations had a common origin in Ashkenazi and Roman Jews, and that other mutations prevalent among Ashkenazi Jews are of more recent origin.

DOI: 10.1210/jcem.84.12.6268

PMID: 10599695 [Indexed for MEDLINE]

4906. Rev Rhum Engl Ed. 1999 Oct;66(10):484-91.

Autosomal dominant recurrent fevers. Clinical and genetic aspects.

McDermott MF(1).

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(1)Department of Diabetes and Metabolic Medicine, St. Bartholomew's and the Royal London School of Medicine and Dentistry, Queen Mary, UK.

M.F.McDermott@mds.qmw.ac.uk

PMID: 10567977 [Indexed for MEDLINE]

4907. J Assist Reprod Genet. 1999 Oct;16(9):504-7.

The effect of colchicine treatment on spermatozoa: a cytogenetic approach.

Kastrop P(1), Kimmel I, Bancsi L, Weima S, Giltay J.

Author information:

(1)University Hospital Utrecht, The Netherlands.

PMCID: PMC3455632

PMID: 10530407 [Indexed for MEDLINE]

4908. Am J Med Genet. 1999 Nov 5;87(1):30-5.

Late-onset familial Mediterranean fever (FMF): a subset with distinct clinical, demographic, and molecular genetic characteristics.

Tamir N(1), Langevitz P, Zemer D, Pras E, Shinar Y, Padeh S, Zaks N, Pras M, Livneh A.

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To determine the prevalence and characterize demographic, clinical, and genetic features of familial Mediterranean fever (FMF) of late onset, all patients experiencing their first FMF attack at age 40 years or more were identified using the computerized registry of our FMF clinic, and then thoroughly interviewed and examined. The control group consisted of 40 consecutive FMF patients, who arrived at the FMF clinic for their regular follow-up visit and were 40 years of age or older at the time of the examination. The severity of the disease in patients and controls was determined using a modified score, developed previously. Mutational analysis in the FMF gene was performed using a commercial kit. Only 20 of 4000 (0.5%) patients had late-onset FMF. These patients were mostly men, of non-North African origin,  $P < 0.05$  compared to controls. All had abdominal attacks and in most these were the only manifestation of their disease,  $P < 0.001$ . None had chronic or prolonged manifestations of FMF, for example, amyloidosis, chronic arthritis, or protracted myalgia,  $P < 0.001$ . The response to treatment was good despite using low colchicine dose,  $P < 0.05$ . The overall severity score indicated a mild disease,  $P < 0.001$ . Mutational analysis revealed absence of M694V homozygosity,  $P < 0.01$ , compared to our regular FMF population. We conclude that the onset of FMF in a late age defines a milder form of disease with typical clinical, demographic, and molecular genetic characteristics.

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PMID: 10528243 [Indexed for MEDLINE]

4909. Acta Paediatr. 1999 Sep;88(9):1045-6.

Recurrent pericarditis in familial Mediterranean fever.

Tutar HE, Imamoglu A, Atalay S.

Comment on

Acta Paediatr. 1998 May;87(5):603-4.

PMID: 10519355 [Indexed for MEDLINE]

4910. Arch Pediatr. 1999 Sep;6(9):931-4.

[Familial Mediterranean fever: discovery of the responsible gene and the implications].

[Article in French]

Delpech M, Grateau G.

PMID: 10519025 [Indexed for MEDLINE]

4911. Curr Opin Rheumatol. 1999 Sep;11(5):393-8.

Vasculopathy, Behçet's syndrome, and familial Mediterranean fever.

Ozen S(1).

Author information:

(1)Department of Pediatric Rheumatology and Nephrology, Hacettepe University Faculty of Medicine, Ankara, Turkey. sozen@gen.hun.edu.tr

Within the past year information has accumulated on the role of infections in the pathogenesis of vasculitis. Superantigens play an important role in the stimulation of the immune system. Behçet's syndrome is a vasculitis that affects children as well as adults. Recently published childhood studies highlight the importance of family history and geographic differences in this disease. Familial Mediterranean fever is a genetic disease manifesting frequently in children.



Studies on the function of the mutated protein pyrin in this disease are in progress. Some researchers have proposed that pyrin is an anti-inflammatory protein. Understanding its mode of action will help us understand more of the general inflammatory pathway.

PMID: 10503660 [Indexed for MEDLINE]

4912. Rheumatology (Oxford). 1999 Aug;38(8):794-6.

A case of familial Mediterranean fever and polyarteritis nodosa complicated by spontaneous bilateral perirenal and subcapsular splenic haemorrhage.

Basaranoglu M, Mert A, Tabak F, Apaydin S, Aktuglu Y, Ozdogan H.

PMID: 10501441 [Indexed for MEDLINE]

4913. Clin Nephrol. 1999 Sep;52(3):197.

Colchicine toxicity.

Güven M, Dogukan A, Cetin M.

PMID: 10499320 [Indexed for MEDLINE]

4914. J Rheumatol. 1999 Sep;26(9):1983-6.

Serum soluble intercellular adhesion molecule 1 and interleukin 8 levels in familial Mediterranean fever.

Direskeneli H(1), Ozdogan H, Korkmaz C, Akoglu T, Yazici H.

Author information:

(1)Division of Rheumatology, Faculty of Medicine, Marmara University, Turkey.

**OBJECTIVE:** Familial Mediterranean fever (FMF) is a disease of unknown etiology characterized by recurrent attacks of polyserositis (peritonitis, pleuritis, and arthritis) and fever. We measured levels of soluble intercellular adhesion molecule 1 (sICAM-1) and interleukin 8 (IL-8), which are important mediators in leukocyte-endothelial adhesion and leukocyte accumulation in tissues.

**METHODS:** sICAM-1 and IL-8 levels were studied in 30 patients with FMF during attacks and remission, along with 23 healthy and 26 disease controls. sICAM-1 and IL-8 levels were measured with commercial ELISA systems.

**RESULTS:** Median levels of sICAM-1 were significantly elevated in patients with FMF during attacks (FMF-a) and remission periods (FMF-r) compared to healthy controls (HC) (FMF-a: 600 ng/ml, FMF-r: 520 ng/ml, HC: 353 ng/ml; FMF-a vs. HC:  $p < 0.0001$ , FMF-r vs. HC:  $p = 0.002$ ). IL-8 levels were also significantly elevated in FMF-a compared to HC (37 vs. 25 pg/ml;  $p = 0.009$ ), but not during remission (26 pg/ml;  $p = 0.7$ ). A significant correlation was observed between sICAM-1 and IL-8 levels ( $r = 0.33$ ,  $p = 0.01$ ). sICAM-1 levels also correlated significantly with erythrocyte sedimentation rate, C-reactive protein, and fibrinogen levels of patients with FMF.

**CONCLUSION:** Increased levels of sICAM-1 and IL-8 in FMF suggest that neutrophils are active with increased adhesion in FMF. Since increased levels of sICAM-1 are also observed during remission, subclinical disease activity and inflammation seem to be present in some patients.

PMID: 10493680 [Indexed for MEDLINE]

4915. Curr Opin Pulm Med. 1999 Sep;5(5):326-31.

Pulmonary associations in familial Mediterranean fever.

Livneh A(1), Langevitz P, Pras M.

Author information:

(1)Heller Institute of Medical Research, Sheba Medical Center, Tel-Hashomer, Israel.

Familial Mediterranean fever (FMF) is a hereditary periodic fever syndrome expressed by acute episodes of fever and painful manifestations. In this report,

the pulmonary manifestations of FMF are reviewed, the most prominent of which are chest attacks due to pleuritis. Nephropathic amyloidosis of the AA type, which complicates FMF in most untreated patients, may progress to affect other organs, including the lungs, but this rarely produces noticeable symptoms. The common association between FMF and vasculitis makes pulmonary hemorrhage, infarction, or infiltrates highly possible. These complications, however, have been reported only rarely. Asthma was found to occur less often than expected in patients with FMF, but methodologic faults make this finding doubtful. Finally, the occurrence of mesothelioma in five patients with FMF who were not exposed to asbestos suggests a role for recurrent FMF serositis in the pathogenesis of this malignancy.

PMID: 10461539 [Indexed for MEDLINE]

4916. N Engl J Med. 1999 Aug 19;341(8):593-9.

Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 25-1999. A 16-year-old boy with recurrent abdominal pain.

[No authors listed]

Comment in

N Engl J Med. 2000 Jan 6;342(1):60.

DOI: 10.1056/NEJM199908193410808

PMID: 10451466 [Indexed for MEDLINE]

4917. Postgrad Med J. 1999 Mar;75(881):171-3.

A patient with recurrent acute abdominal pain.

Ahmad M(1), Rasul FM.

Author information:

(1)Department of Medicine, Shands Hospital at Lake Shore, Lake City, Florida, USA.

PMCID: PMC1741166

PMID: 10448500 [Indexed for MEDLINE]

4918. Hum Mutat. 1999;14(1):91.

Direct detection of common mutations in the familial Mediterranean fever gene (MEFV) using naturally occurring and primer mediated restriction fragment analysis. Mutation in brief no. 257. Online.

Gershoni-Baruch R(1), Kepten I, Shinawi M, Brik R.

Author information:

(1)Department of Human Genetics, Rambam Medical Center, and The Bruce Rappoport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa.

The MEFV gene involved in familial Mediterranean fever was recently cloned and four distinct sequence alterations (M680I, M694V, M694I and V726A) were identified at the 3'-most exon. We genotyped 170 unrelated FMF patients from various ethnic groups in Israel and found that mutation M694V predominates in North African Jews, that mutation V726A is common in Jewish patients other than North African Jews and that all four mutations occur in patients of Arabian origin, namely, Moslems, Christians and Druze. Since these four distinct sequence alterations seem to account for the majority of mutations identified in FMF patients from the middle east, we have devised a simple protocol using PCR mediated site directed mutagenesis or naturally occurring recognition sites to scan for these mutations.

DOI: 10.1002/(SICI)1098-1004(1999)14:1<91::AID-HUMU21>3.0.CO;2-B

PMID: 10447272 [Indexed for MEDLINE]

4919. Gastroenterol Clin Biol. 1999 May;23(5):589-90.

[Molecular diagnosis of periodic disease].

[Article in French]

Touitou I(1).

Author information:

(1)Laboratoire de Génétique Moléculaire et Chromosomique, Hôpital Arnaud-de-Villeneuve, Montpellier.

PMID: 10429872 [Indexed for MEDLINE]

4920. Ugeskr Laeger. 1999 Jun 21;161(25):3853-5.

[Familial Mediterranean fever. No longer an elimination diagnosis].

[Article in Danish]

Dragsted UB(1), Eugen-Olsen J, Mathiesen LR.

Author information:

(1)H:S Hvidovre Hospital, infektionsmedicinsk afdeling og forskningsenheden.  
u.dragsted@post.uni2.dk

Familial Mediterranean Fever (FMF) is a recessive trait mainly affecting Jews, Turks and Arabs. FMF is characterized by recurrent episodes of painful serositis and fever leaving no sequelae. Involvement of the peritoneum is the most common clinical form. In 1997 the gene that causes FMF (MEFV-gene) was cloned, thus given clinicians an opportunity to diagnose the disease. We have established the method in our laboratory. We describe the first patient diagnosed with FMF in our department by this method.

PMID: 10412306 [Indexed for MEDLINE]

4921. Clin Exp Rheumatol. 1999 May-Jun;17(3):387-8.

Familial Mediterranean fever with HLA B-27 positive ankylosing spondylitis in a young Armenian man.

Kaushik P, el-Sobkie NI, Shehab D, Malaviya AN.

PMID: 10410279 [Indexed for MEDLINE]

4922. J Rheumatol. 1999 Jul;26(7):1638-9.

Prevalence of juvenile chronic arthritis and familial Mediterranean fever in Turkey: a field study.

Ozdoğan H, Kasapçopur O, Arisoy N.

Comment on

J Rheumatol. 1998 Dec;25(12):2445-9.

PMID: 10405960 [Indexed for MEDLINE]

4923. Tidsskr Nor Laegeforen. 1999 May 30;119(14):2035-6.

[Familial Mediterranean fever].

[Article in Norwegian]

Lorentsen T(1), Gerlyng P.

Author information:

(1)Medisinsk avdeling, Lovisenberg Diakonale Sykehus, Oslo.

Familial Mediterranean fever is a hereditary disease prevalent among populations in the Mediterranean area, characterized by sporadic episodes of acute inflammation primarily of the pleural, peritoneal and joint spaces. There is no diagnostic test for routine use. The disease is still uncommon in Norway, but we expect an increased incidence because of immigration. Due to the lack of pathognomonic features many patients undergo unnecessary explorative laparotomy before the diagnosis is established. In this report we present a patient with a

typical history of familial Mediterranean fever. To our knowledge this is the first case ever published in Norway. It is important to keep the disease in mind as a differential diagnosis in patients with recurrent fever and pain, as colchicine represent an efficient treatment in order to prevent both further attacks and secondary amyloidosis.

PMID: 10394279 [Indexed for MEDLINE]

4924. J Pediatr. 1999 Jul;135(1):15-21.

Periodic fever syndrome in children.

Thomas KT(1), Feder HM Jr, Lawton AR, Edwards KM.

Author information:

(1)School of Medicine, Vanderbilt University, Nashville, Tennessee, USA.

Comment in

J Pediatr. 1999 Jul;135(1):1-5.

J Pediatr. 2000 Sep;137(3):438-9.

**OBJECTIVES:** To describe the presentation, clinical course, therapeutic response, and long-term follow-up of patients with a syndrome of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA).

**STUDY DESIGN:** Patients with PFAPA (n = 94) referred over a 10-year period completed a registry form and provided medical records. Follow-up telephone calls were made in late 1997 to determine the persistence of episodes and sequelae.

**RESULTS:** PFAPA episodes lasted 4.8 days (95% confidence interval 4.5 to 5.1) and recurred every 28 days (confidence interval 26 to 30), with a maximal temperature of 40.5 degrees C (confidence interval 40. 4 degrees to 40.6 degrees ). Of the 83 children available for follow-up, 34 no longer had episodes. In the remainder the episodes did not differ in character but recurred less frequently over time. The affected children had no long-term sequelae. Glucocorticoids were highly effective in controlling symptoms. Tonsillectomy and cimetidine treatment were associated with remission in a small number of patients.

**CONCLUSIONS:** PFAPA is a not uncommon cause of periodic fever in children. In some children the syndrome resolves, whereas symptoms in others persist. Long-term

sequelae do not develop. The syndrome is easily diagnosed when regularly recurring episodes of fever are associated with aphthous stomatitis, pharyngitis, or cervical adenitis.

PMID: 10393598 [Indexed for MEDLINE]

4925. J Pediatr. 1999 Jul;135(1):98-101.

Periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome: clinical characteristics and outcome.

Padeh S(1), Brezniak N, Zemer D, Pras E, Livneh A, Langevitz P, Migdal A, Pras M, Passwell JH.

Author information:

(1)Department of Pediatrics, Heller Institute of Medical Research, Sheba Medical Center, affiliated with the Tel-Aviv University, Sackler School of Medicine, Tel Hashomer, Israel.

Comment in

J Pediatr. 1999 Jul;135(1):1-5.

J Pediatr. 2000 Sep;137(3):438-9.

We report 28 patients (20 male) with a syndrome characterized by abrupt onset of fever, malaise, aphthous stomatitis, tonsillitis, pharyngitis, and cervical adenopathy (PFAPA syndrome). Episodes of fever occurred at intervals of  $5.1 \pm 1.3$  weeks beginning at the age of  $4.2 \pm 2.7$  years. Fever, malaise, tonsillitis with negative throat cultures, and cervical adenopathy were reported in all 28 patients, aphthae in 19, headache in 5, abdominal pain in 5, and arthralgia in 3. Mild hepatosplenomegaly was observed in 6 patients. Mild leukocytosis, elevation of the erythrocyte sedimentation rate, and fibrinogen were found during attacks. These episodes of illness resolved spontaneously in  $4.3 \pm 1.7$  days. Serum IgD was found elevated ( $>100$  U/mL) in 12 of the 18 patients tested ( $140.2 \pm 62.4$  U/mL). Affected children grow normally, have no associated diseases, and have no long-term sequelae. Attacks were aborted by a single dose of oral prednisone (2 mg/kg) at the beginning of the attack in all 15 patients in whom this medication was prescribed. In 9 patients the syndrome has completely resolved (beginning at



the age of 2.9 +/- 1.3 and lasting 8 +/- 2.5 years). In 3 other patients complete resolution of the attacks occurred after tonsillectomy was performed. PFAPA is sporadic, and no ethnic predilection was found. Increased awareness of the clinical syndrome has resulted in more frequent diagnosis and adequate treatment.

PMID: 10393612 [Indexed for MEDLINE]

4926. J Pediatr. 1999 Jul;135(1):1-5.

Syndrome of Periodic Fever, Aphthous stomatitis, Pharyngitis, and Adenitis (PFAPA)--what it isn't. What is it?

Long SS.

Comment on

J Pediatr. 1999 Jul;135(1):98-101.

J Pediatr. 1999 Jul;135(1):15-21.

PMID: 10393593 [Indexed for MEDLINE]

4927. J Rheumatol. 1999 Jun;26(6):1415.

Migrating monopredominant arthritis in children of Assyrian ancestry.

Miller JJ 3rd, Henrickson M.

Comment on

J Rheumatol. 1996 Nov;23(11):2002.

J Rheumatol. 1996 Nov;23(11):2003.

J Rheumatol. 1996 Nov;23(11):2002.

J Rheumatol. 1996 Jan;23(1):178-80.

J Rheumatol. 1996 Nov;23(11):2004.

J Rheumatol. 1996 Nov;23(11):2002-3; author reply 2003-4.

PMID: 10381069 [Indexed for MEDLINE]

4928. Arch Pediatr. 1999;6 Suppl 2:425s-426s.

[Mechanisms for treatment: periodic disease].

[Article in French]

Delpech M(1).

Author information:

(1)Laboratoire de biochimie et génétique moléculaire, Hôpital Cochin, Institut Cochin de génétique moléculaire, Paris, France.

PMID: 10370558 [Indexed for MEDLINE]

4929. Nat Genet. 1999 Jun;22(2):178-81.

Mutations in the gene encoding mevalonate kinase cause hyper-IgD and periodic fever syndrome. International Hyper-IgD Study Group.

Drenth JP(1), Cuisset L, Grateau G, Vasseur C, van de Velde-Visser SD, de Jong JG, Beckmann JS, van der Meer JW, Delpech M.

Author information:

(1)Laboratoire de Génétique Moléculaire Humaine, Institut Cochin de Génétique Moléculaire and Hôpital Cochin, Assistance Publique-Hopitaux de Paris, France.

Comment in

Nat Genet. 1999 Jun;22(2):121-2.

Hyperimmunoglobulinaemia D and periodic fever syndrome (HIDS; MIM 260920) is a rare, apparently monogenic, autosomal recessive disorder characterized by recurrent episodes of fever accompanied with lymphadenopathy, abdominal distress, joint involvement and skin lesions. All patients have high serum IgD values (>100 U/ml) and HIDS 'attacks' are associated with an intense acute phase reaction

whose exact pathophysiology remains obscure. Two other hereditary febrile disorders have been described. Familial Mediterranean fever (MIM 249100) is an autosomal recessive disorder affecting mostly populations from the Mediterranean basin and is caused by mutations in the gene MEFV (refs 5,6). Familial Hibernian fever (MIM 142680), also known as autosomal dominant familial recurrent fever, is caused by missense mutations in the gene encoding type I tumour necrosis factor receptor. Here we perform a genome-wide search to map the HIDS gene. Haplotype analysis placed the gene at 12q24 between D12S330 and D12S79. We identified the gene MVK, encoding mevalonate kinase (MK, ATP:mevalonate 5-phosphotransferase; EC 2.7.1.36), as a candidate gene. We characterized 3 missense mutations, a 92-bp loss stemming from a deletion or from exon skipping, and the absence of expression of one allele. Functional analysis demonstrated diminished MK activity in fibroblasts from HIDS patients. Our data establish MVK as the gene responsible for HIDS.

DOI: 10.1038/9696

PMID: 10369262 [Indexed for MEDLINE]

4930. Rev Pneumol Clin. 1999 Mar;55(1):39-41.

[Recurrent bilateral pleurisy in an 80-year-old man].

[Article in French]

Herry I(1), Schaison F, Martin A, Christoforov B, Boissonnas A.

Author information:

(1)Service de Médecine Interne, Hôpital Cochin, Paris.

An 80-year-old man was admitted with recurrent asphyxiating pleurisy, first attributed to heart failure. During the recurrent episodes, the patient presented fever, signs of inflammation, no signs of heart failure, and subnormal cardiac function, prompting further investigations which disclosed that the patient was a homozygous carrier of the severe type of periodic disease mutation. The patient's age at symptom onset and the clinical features of this case of periodic disease are exceptional. These points emphasize the usefulness of available genetic tests in difficult diagnostic cases. It also reflects current difficulties in trying to establish correlations between genotype and phenotype in periodic disease.

PMID: 10367315 [Indexed for MEDLINE]

4931. Am J Hum Genet. 1999 Jul;65(1):88-97.

MEFV-Gene analysis in armenian patients with Familial Mediterranean fever: diagnostic value and unfavorable renal prognosis of the M694V homozygous genotype-genetic and therapeutic implications.

Cazeneuve C(1), Sarkisian T, Pêcheux C, Dervichian M, Nédelec B, Reinert P, Ayvazyan A, Kouyoumdjian JC, Ajrapetyan H, Delpech M, Goossens M, Dodé C, Grateau G, Amselem S.

Author information:

(1)1Service de Biochimie et de Génétique Moléculaire and the Institut National de la Santé et de la Recherche Médicale (Unité 468), Hôpital, Mondor, France.

Familial Mediterranean fever (FMF) is a recessively inherited disorder that is common in patients of Armenian ancestry. To date, its diagnosis, which can be made only retrospectively, is one of exclusion, based entirely on nonspecific clinical signs that result from serosal inflammation and that may lead to unnecessary surgery. Renal amyloidosis, prevented by colchicine, is the most severe complication of FMF, a disorder associated with mutations in the MEFV gene. To evaluate the diagnostic and prognostic value of MEFV-gene analysis, we investigated 90 Armenian FMF patients from 77 unrelated families that were not selected through genetic-linkage analysis. Eight mutations, one of which (R408Q) is new, were found to account for 93% of the 163 independent FMF alleles, with both FMF alleles identified in 89% of the patients. In several instances, family studies provided molecular evidence for pseudodominant transmission and incomplete penetrance of the disease phenotype. The M694V homozygous genotype was found to be associated with a higher prevalence of renal amyloidosis and arthritis, compared with other genotypes ( $P=.0002$  and  $P=.006$ , respectively). The demonstration of both the diagnostic and prognostic value of MEFV analysis and particular modes of inheritance should lead to new ways for management of FMF-including genetic counseling and therapeutic decisions in affected families.

DOI: 10.1086/302459

PMCID: PMC1378078

PMID: 10364520 [Indexed for MEDLINE]

4932. Ann Intern Med. 1999 May 4;130(9):780.

Genetics of familial Mediterranean fever.

Roda PI.

Comment on

Ann Intern Med. 1998 Oct 1;129(7):581-2.

PMID: 10357703 [Indexed for MEDLINE]

4933. Ann Intern Med. 1999 May 4;130(9):780.

Genetics of familial Mediterranean fever.

Levin M.

PMID: 10357702 [Indexed for MEDLINE]

4934. Arch Pediatr. 1998 Mar;5(3):280-4.

[Pseudo-periodic disease with hyperimmunoglobulinemia D: a never-ending story with probable prenatal onset].

[Article in French]

Grouteau E(1), Chaix Y, Graber D, Breton A, Claeysens S, Kuhlein E, Carrière JP.

Author information:

(1)Service de médecine infantile A, rhumatologie pédiatrique, hôpital Purpan, Toulouse, France.

Diagnosis of inflammatory non-infectious diseases with a neonatal onset is often retrospective. It may lead to aggressive and iatrogenic procedures. **PATIENT:** A 6-year-old boy was suffering, since birth, from recurrent febrile attacks including rashes, gastrointestinal manifestations and inflammatory joint involvement. This syndrome, partially improved with steroids, could have been of antenatal onset. Since the age of 4 years, the patient is considered as having hyper-IgD syndrome (HIDS).

**DISCUSSION:** HIDS must be distinguished from familial Mediterranean fever. Patients suffer from recurrent fever concomitant to inflammatory joint involvement, abdominal distress, skin lesions, swollen lymph nodes and hepatosplenomegaly (especially seen in children). All patients have high serum IgD (> 100 UI/mL) and IgA levels. Nevertheless, a high IgD level is not specific. Our case could also be part of the CINCA (chronic, infantile, neurological, cutaneous and articular) syndrome, which includes similar early manifestations associated with a constant neurological and frequent ophthalmological involvement and epiphyseal changes; to date, these last three manifestations are not present in our patient.

**CONCLUSION:** HIDS and CINCA syndrome are not known to be modified by any effective therapeutic agent. When presenting at birth, these inflammatory diseases must be considered as entities with a rarely described potential severity.

PMID: 10327995 [Indexed for MEDLINE]

4935. Eur J Hum Genet. 1999 Apr;7(3):287-92.

Phenotype-genotype correlation in familial Mediterranean fever: evidence for an association between Met694Val and amyloidosis.

Shohat M(1), Magal N, Shohat T, Chen X, Dagan T, Mimouni A, Danon Y, Lotan R, Ogur G, Sirin A, Schlezinger M, Halpern GJ, Schwabe A, Kastner D, Rotter JI, Fischel-Ghodsian N.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease characterised by recurrent attacks of inflammation of serosal membranes. Amyloidosis is the most severe complication of the disease. The aim of this study was to investigate the genotype-phenotype correlation and specifically the association between amyloidosis and the four common mutations in exon 10 of the gene causing FMF (MEFV) in a total of 83 FMF families from three ethnic groups: North African Jews, Armenians and Turks. A significant association was found between amyloidosis and the specific mutation at the MEFV gene: Met694Val (RR = 1.41, P = 0.02). Amyloidosis was present in 18 out of 87 homozygous FMF patients (20.7%) and in only two out of the 41 compound heterozygous FMF patients (4.9%). No patients carrying other mutations had amyloidosis. There was no significant association between the various mutations and the type or severity of the FMF symptoms. This finding underscores the importance of performing molecular studies on all suspect FMF patients. In addition to providing accurate diagnosis, these tests allow identification of presymptomatic genetically affected individuals, detection of carriers and assessment of the risk for amyloidosis in later life.

DOI: 10.1038/sj.ejhg.5200303

PMID: 10234504 [Indexed for MEDLINE]

4936. J Rheumatol. 1999 Apr;26(4):890-7.

Activation of the cytokine network in familial Mediterranean fever.

Gang N(1), Drenth JP, Langevitz P, Zemer D, Brezniak N, Pras M, van der Meer JW, Livneh A.

Author information:

(1)Heller Institute of Medical Research and Department of Medicine, Sheba Medical Center, Tel-Hashomer, Israel.

**OBJECTIVE:** To elucidate the role of cytokines in the pathogenesis of familial Mediterranean fever (FMF), an inherited disease characterized by attacks of serosal membrane inflammation.

**METHODS:** Blood samples were obtained from patients with FMF during attacks and remission. The cytokine concentrations in plasma and in supernatants from whole blood stimulated by bacterial lipopolysaccharide (LPS) were determined.

**RESULTS:** There were 27 patients with FMF, of whom 8 were studied during attacks,

9 during remission and 10 during both attack and remission. FMF attacks did not affect levels of plasma tumor necrosis factor-alpha (TNF-alpha) or interleukin 1beta (IL-1beta). In contrast, compared to remission, FMF attacks were associated with significantly higher mean levels of plasma IL-6 [8.4 pg/ml, 95% confidence interval (CI) 7.8-8.9 in remission vs 59 pg/ml, CI 21.4-96.7 during attacks;  $p=0.0005$ ], sTNFr p55 (1.3 ng/ml, CI 1.2-1.4, vs 1.98 ng/ml, CI 1.6-2.3;  $p=0.005$ ), and sTNFr p75 (2.9 ng/ml, CI 2.5-3.3, vs 4.09 ng/ml, CI 3.2-4.9;  $p=0.0249$ ). The TNF-alpha, IL-1beta, and IL-6 content in supernatants derived from LPS stimulated blood cells was not modified by the attacks of FMF. Significant lower TNF-alpha release in LPS stimulated whole blood was detected in patients who were sampled in a later stage of the attacks ( $r=-0.54$ ,  $p=0.047$ ).

**CONCLUSION:** Our results suggest that the cytokine network is activated during attacks of FMF. IL-6 appears to play an important role in the evolution of FMF attacks. Whether TNF-alpha or IL-1beta has a function in initiating the attacks remains to be established.

PMID: 10229412 [Indexed for MEDLINE]

4937. *Pediatr Nephrol.* 1999 Feb;13(2):132-4.

Crescentic glomerulonephritis in hyper IgD syndrome.

Tsimaratos M(1), Koné-Paut I, Daniel L, Gubler MC, Dussol B, Picon G.

Author information:

(1)Unité de Néphrologie Pédiatrique, Service de Pédiatrie Multidisciplinaire, Hôpital d'Enfants de la Timone, Marseille, France. gpicon@aphml.ap-hm.fr

The hyperimmunoglobulinemia D syndrome (HIDS) is a well-defined entity resembling familial Mediterranean fever. HIDS is a systemic inflammatory disease associated with stimulation of T-cell-mediated immunity. These patients are at low risk for amyloidosis and are not known to develop nephropathy. We report a boy of Mediterranean ancestry who exhibited typical HIDS and end-stage renal failure. Kidney biopsy revealed pauci-immune crescentic glomerulonephritis (cGN). We hypothesized that the glomerular involvement was secondary to the cytokine network activation observed in HIDS. Thus, cGN should be considered as part of the syndrome, and kidney biopsy should be performed early in the course of the



renal disease in patients with HIDS.

DOI: 10.1007/s004670050579

PMID: 10229000 [Indexed for MEDLINE]

4938. Lancet. 1999 Apr 24;353(9162):1415.

Acute phase response and evolution of familial Mediterranean fever.

Tunca M, Kirkali G, Soytürk M, Akar S, Pepys MB, Hawkins PN.

DOI: 10.1016/S0140-6736(99)00990-3

PMID: 10227232 [Indexed for MEDLINE]

4939. Pediatrics. 1999 May;103(5):e70.

Familial Mediterranean fever: clinical and genetic characterization in a mixed pediatric population of Jewish and Arab patients.

Brik R(1), Shinawi M, Kepten I, Berant M, Gershoni-Baruch R.

Author information:

(1)Department of Pediatrics, Rambam Medical Center and Technion-Israel Institute of Technology Faculty of Medicine, Haifa, Israel. r\_brik@rambam.health.gov.il

**OBJECTIVE:** Familial Mediterranean fever (FMF) is an autosomal recessive hereditary disease which primarily affects non-Ashkenazi Jews, Armenians, Arabs, and Turks. The gene responsible for the disease (MEFV/FMF) has been recently identified. Four common mutations in exon 10 of the MEFV gene seem to account for 86% of the DNA variations identified in patients with FMF. We conducted a phenotype/genotype correlation study in a mixed population of Jewish and Arab children with FMF.

**STUDY DESIGN:** Seventy patients clinically diagnosed as having FMF underwent molecular genetic studies using polymerase chain reaction and restriction endonuclease digestion methods to detect the presence of the four mutations (M694V, M680I, V726A, M694I). We then correlated the presence of each mutation with ethnic origin, age of onset, clinical manifestations, disease severity, and

occurrence of amyloidosis.

**RESULTS:** The M694V mutation, which is predominant in non-Ashkenazi Jews, was found in 92% of our Jewish patients and in only 30% of the Arab patients. All four mutations were identified among 94% of the Arab patients, but with no particular prevalence for any one of them. The presence of a homozygous M694V mutation was significantly associated with a more severe form of the disease: the clinical onset of the disease manifested at an earlier age; the number of attacks per month was higher; the global assessment by the treating physician and the severity of pain scored higher; and arthritis was more frequent. Only patients with the M694V mutation had a family history of amyloidosis. No association was found between the type of mutation and the predominance of fever, abdominal pain, pleuritis, skin eruption, or response to colchicine in the clinical picture.

**CONCLUSIONS:** Homozygosity for the M694V mutation, predominant among North African Jews, is associated with a severe course and prognosis for FMF. This mutation is less common among Arabs and, when present, occurs almost only in heterozygous form. In Arab patients, the disease tends to run a milder course and seems to bear a better prognosis. The phenotype/genotype patterns that are evident from our study of a mixed series of Jewish and Arab children with FMF might provide a rational basis for counseling about the natural history of the disease and for clinical treatment of FMF patients and their families.

PMID: 10224214 [Indexed for MEDLINE]

4940. Amyloid. 1999 Mar;6(1):1-6.

MEFV mutation analysis in patients suffering from amyloidosis of familial Mediterranean fever.

Livneh A(1), Langevitz P, Shinar Y, Zaks N, Kastner DL, Pras M, Pras E.

Author information:

(1)Heller Institute of Medical Research, Sheba Medical Center, Tel Hashomer, Israel.

Comment in

Amyloid. 1999 Dec;6(4):301-2.

Familial Mediterranean fever (FMF) is a major cause of AA amyloidosis. Recently, the gene (MEFV) causing this disease was cloned and 16 disease associated mutations have been described. We have analyzed 178 FMF patients, 30 of whom also suffered from amyloidosis, for 4 mutations in MEFV. Mutations were identified in 29 of the FMF amyloidosis patients. 27 FMF amyloidosis patients were homozygous for M694V. One patient was found to be homozygous for both V726A and E148Q. In another patient E148Q and V726A were found on one allele, while V726A was found on the second allele. Amyloidosis was far more common among patients homozygous for M694V compared to patients with other mutations ( $P < 0.0001$ ). In 3 patients homozygous for M694V, amyloidosis was the sole manifestation of the disease.

PMID: 10211405 [Indexed for MEDLINE]

4941. Am J Med Sci. 1999 Apr;317(4):238-42.

Polyarteritis nodosa: a report from Israel.

Gur H(1), Tchakmakjian L, Eherenfeld M, Sidi Y.

Author information:

(1)Department of Medicine C, The Chaim Sheba Medical Center, Tel Hashomer, Israel.

**BACKGROUND:** The clinical manifestations and outcome of all adult patients with polyarteritis nodosa (PAN), allocated during a 15-year period in the largest medical center in Israel, were examined.

**METHODS:** A retrospective analysis of patients with PAN who fulfilled the American College of Rheumatology (ACR) 1990 Classification Criteria and were either biopsy- or angiography-proven.

**RESULTS:** Nine patients were included in the report. The clinical and laboratory manifestations were similar to those in previous studies. All patients were treated with combinations of cyclophosphamide and corticosteroids. There were two (22%) deaths, 2 and 5 months after initiation of treatment in patients who probably had microscopic polyangiitis (MPA) rather than classical PAN.

Considering the patients with a complete follow-up, 71% had a complete and long-term remission. Moreover, by exclusion of the two patients with probable MPA who died, all of the five patients with classical PAN were alive and well as of

this writing. Two patients (22%) had a long history, since childhood, of familial Mediterranean fever (FMF).

CONCLUSIONS: The clinical presentation and course of PAN in Israeli patients is comparable with reports elsewhere. However, a distinction should be made between PAN and MPA. The present report emphasizes the good long-term prognosis of patients with typical PAN who are treated adequately. In addition, a possible association of PAN with FMF in Israeli patients is suggested.

PMID: 10210359 [Indexed for MEDLINE]

4942. Eur J Med Res. 1999 Apr 27;4(4):161-4.

Familial Mediterranean fever. No role of Mycobacterium tuberculosis in ten patients.

Akcan Y(1), Tuncer S, Unal S, Sökmensuer C, Haznedaroglu CI, Arslan S.

Author information:

(1)Kültür Mah. Namik Kemal Sok. Pestemalci, Apt. No:8/5, 14310 Düzce / BOLU, Turkey. yakcan@hotmail.com.

BACKGROUND: Tuberculosis (TB) and Familial mediterranean fever (FMF) are two common diseases in our region, Turkey. Both share some properties in common: Both cause AA type amyloidosis and have association with some immunological abnormalities. Upon incidentally observing Mycobacterium tuberculosis in bone marrow biopsies of three patients with FMF in a previous study, we intended to elucidate this association prospectively.

MATERIAL AND METHODS: In this study, we examined prospectively 10 FMF patients, 5 male and 5 female, with a median duration of 31 years disease activity. All were under colchicine therapy. They had no sign of renal involvement. The bone marrow biopsies of these patients were examined for the presence of M. tuberculosis by Polymerase chain reaction (PCR), BACTEC culture and pathological stains.

Pathological examination was performed for the existence of granuloma and amyloid deposition by hematoxylin-eosin, Crystal Violet and Congo red stains.

RESULTS: The examination of all bone marrow specimens by the mentioned methods suggest that Mycobacterium tuberculosis has no role in the ethiopathogenesis of FMF. Although the patients had a positive family history of 60% for tuberculosis

and in 80% of them with positive tuberculin skin test.

CONCLUSIONS: We concluded that although there seemed to be a kind of association between both diseases, this relationship is not via the direct existence of bacteria itself. Considering high family history and skin test positivity, one should look for the presence of autoimmune mechanisms under this suspicious relationship between tuberculosis and FMF. Also, this is the first study examined the state of amyloidosis in the bone marrow at an earlier stage of FMF without overt renal findings.

PMID: 10205292 [Indexed for MEDLINE]

4943. Cell. 1999 Apr 2;97(1):133-44.

Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes.

McDermott MF(1), Aksentijevich I, Galon J, McDermott EM, Ogunkolade BW, Centola M, Mansfield E, Gadina M, Karenko L, Pettersson T, McCarthy J, Frucht DM, Aringer M, Torosyan Y, Teppo AM, Wilson M, Karaarslan HM, Wan Y, Todd I, Wood G, Schlimgen R, Kumarajeewa TR, Cooper SM, Vella JP, Amos CI, Mulley J, Quane KA, Molloy MG, Ranki A, Powell RJ, Hitman GA, O'Shea JJ, Kastner DL.

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Autosomal dominant periodic fever syndromes are characterized by unexplained episodes of fever and severe localized inflammation. In seven affected families, we found six different missense mutations of the 55 kDa tumor necrosis factor receptor (TNFR1), five of which disrupt conserved extracellular disulfide bonds. Soluble plasma TNFR1 levels in patients were approximately half normal.

Leukocytes bearing a C52F mutation showed increased membrane TNFR1 and reduced receptor cleavage following stimulation. We propose that the autoinflammatory phenotype results from impaired downregulation of membrane TNFR1 and diminished shedding of potentially antagonistic soluble receptor. TNFR1-associated periodic syndromes (TRAPS) establish an important class of mutations in TNF receptors. Detailed analysis of one such mutation suggests impaired cytokine receptor

clearance as a novel mechanism of disease.

PMID: 10199409 [Indexed for MEDLINE]

4944. Am J Hum Genet. 1999 Apr;64(4):949-62.

Mutation and haplotype studies of familial Mediterranean fever reveal new ancestral relationships and evidence for a high carrier frequency with reduced penetrance in the Ashkenazi Jewish population.

Aksentijevich I(1), Torosyan Y, Samuels J, Centola M, Pras E, Chae JJ, Oddoux C, Wood G, Azzaro MP, Palumbo G, Giustolisi R, Pras M, Ostrer H, Kastner DL.

Author information:

(1)Genetics Section, Arthritis and Rheumatism Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD 20892-1820, USA  
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Comment in

Am J Hum Genet. 1999 Apr;64(4):939-42.

Familial Mediterranean fever (FMF) is a recessive disorder characterized by episodes of fever with serositis or synovitis. The FMF gene (MEFV) was cloned recently, and four missense mutations were identified. Here we present data from non-Ashkenazi Jewish and Arab patients in whom we had not originally found mutations and from a new, more ethnically diverse panel. Among 90 symptomatic mutation-positive individuals, 11 mutations accounted for 79% of carrier chromosomes. Of the two mutations that are novel, one alters the same residue (680) as a previously known mutation, and the other (P369S) is located in exon 3. Consistent with another recent report, the E148Q mutation was observed in patients of several ethnicities and on multiple microsatellite haplotypes, but haplotype data indicate an ancestral relationships between non-Jewish Italian and Ashkenazi Jewish patients with FMF and other affected populations. Among approximately 200 anonymous Ashkenazi Jewish DNA samples, the MEFV carrier frequency was 21%, with E148Q the most common mutation. Several lines of evidence indicate reduced penetrance among Ashkenazi Jews, especially for E148Q, P369S, and K695R. Nevertheless, E148Q helps account for recessive inheritance in an

Ashkenazi family previously reported as an unusual case of dominantly inherited FMF. The presence of three frequent MEFV mutations in multiple Mediterranean populations strongly suggests a heterozygote advantage in this geographic region.

PMCID: PMC1377819

PMID: 10090880 [Indexed for MEDLINE]

4945. Am J Hum Genet. 1999 Apr;64(4):939-42.

The genetic basis for periodic fever.

Mulley JC.

Comment on

Am J Hum Genet. 1999 Apr;64(4):949-62.

PMCID: PMC1377817

PMID: 10090878 [Indexed for MEDLINE]

4946. J Rheumatol. 1999 Mar;26(3):753-4.

Rheumatology training at the American University of Beirut.

Uthman I, Arayssi T, Masri AF.

Comment on

J Rheumatol. 1998 Jun;25(6):1037-40.

PMID: 10090199 [Indexed for MEDLINE]

4947. Am J Med Genet. 1999 Feb 19;82(5):442.

Clinical differences between North African and Iraqi Jews with familial

Mediterranean fever.

Ehrenfeld M, Levy M.

Comment on

Am J Med Genet. 1998 Jan 13;75(2):216-9.

PMID: 10069719 [Indexed for MEDLINE]

4948. Nephrol Dial Transplant. 1999 Feb;14(2):475-9.

Familial Mediterranean fever--renal involvement by diseases other than amyloid.

Tekin M(1), Yalçinkaya F, Tümer N, Cakar N, Koçak H, Ozkaya N, Gençgönül H.

Author information:

(1)Ankara University Faculty of Medicine, Turkey.

**BACKGROUND:** In patients with familial Mediterranean fever (FMF) renal involvement is usually in the form of AA amyloidosis. There is increasing evidence that renal involvement may be due to diseases other than amyloid as well.

**METHODS:** Amongst 302 children with FMF we observed and followed 28 with typical clinical and laboratory features of vasculitis. The diagnosis of FMF was established according to the Tel Hashomer criteria.

**RESULTS:** Polyarteritis nodosa, protracted febrile attacks and Henoch-Schönlein purpura were diagnosed in 4, 13, and 11 patients, respectively. The presentation was often difficult to distinguish from FMF attacks, but protracted febrile attacks lasting several weeks, hypertension, thrombocytosis, and dramatic responses to corticosteroid therapy that were observed in many cases were different from what is observed in classical FMF.

**CONCLUSIONS:** We suggest that FMF, perhaps as a consequence of impaired control of inflammatory responses, predisposes to vasculitis with renal involvement.

PMID: 10069219 [Indexed for MEDLINE]



4949. Nephrol Dial Transplant. 1999 Jan;14(1):21-3.

Glomerular lesions other than amyloidosis in patients with familial Mediterranean fever.

Yalçinkaya F, Tümer N.

PMID: 10052466 [Indexed for MEDLINE]

4950. QJM. 1998 Sep;91(9):603-6.

Pyrin/marenostrin mutations in familial Mediterranean fever.

Booth DR(1), Gillmore JD, Booth SE, Pepys MB, Hawkins PN.

Author information:

(1)Immunological Medicine Unit, Imperial College School of Medicine, Hammersmith Hospital, London, UK.

Familial Mediterranean fever (FMF) is an inherited inflammatory disease that is frequently complicated by reactive systemic (AA) amyloidosis. It is principally recognized in certain Mediterranean populations, and the diagnosis depends on clinical features. Four mutations strongly linked to FMF have lately been identified in a gene encoding a novel protein that has been named pyrin or marenostrin. We studied 27 consecutive patients of varied ethnic origin, including an English man, who had classical, probable or possible FMF. Pyrin/marenostrin genotypes were determined, and AA amyloidosis was sought using serum amyloid P component scintigraphy. Among the 23 patients with classical or probable FMF, 17 were homozygotes or compound heterozygotes for pyrin/marenostrin mutations, and in five, only single allele mutations were identified. Two new mutations, T6811 and delta M694, were discovered in addition to the four described previously. No mutations were identified in three of the four patients with possible FMF. Nine patients had AA amyloidosis, but this association was not restricted to any particular genotype. Most patients with FMF have mutations in both pyrin/marenostrin alleles, and genotyping at this locus is a valuable diagnostic test. Unidentified second mutations are likely to occur in FMF patients who have apparently solitary mutations, and therefore genotype results

must be interpreted in conjunction with the clinical picture.

PMID: 10024914 [Indexed for MEDLINE]

4951. *Biochim Biophys Acta*. 1999 Feb 16;1444(2):218-30.

Identification and characterization of a zinc finger gene (ZNF213) from 16p13.3.

Chen X(1), Hamon M, Deng Z, Centola M, Sood R, Taylor K, Kastner DL, Fischel-Ghodsian N.

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(1)Ahmanson Department of Pediatrics, Steven Spielberg Pediatric Research Center, Medical Genetics Birth Defects Center, Cedars-Sinai Medical Center and UCLA School of Medicine, 8700 Beverly Blvd., Los Angeles, CA 90048, USA.

During our search for the familial Mediterranean fever (FMF) gene, we identified by cDNA selection a 1.2 kb cDNA fragment representing a novel human gene that is expressed in a wide variety of tissues. This gene spans approx. 8.0 kb genomic DNA and has seven exons. Its 3' untranslated region contains a long tandem repeat that gives rise to a polymorphism with two alleles of approx. 1.1 kb and 1.0 kb, with the 1.1 kb allele in strong linkage disequilibrium with FMF in patients of different ethnic backgrounds. However, both genetic and mutational analyses have excluded this gene as the one responsible for FMF. The predicted 424 amino acid protein, designated ZNF213, contains three C2H2 zinc fingers, a Kruppel associated A box and a leucine rich motif (LeR domain/SCAN box), strongly suggestive of a transcription factor.

PMID: 10023065 [Indexed for MEDLINE]

4952. *Lancet*. 1999 Jan 30;353(9150):382.

Non-Mediterranean periodic fever.

Deckers S, Delgrange E, Hoebeke M, Dahan K, Donckier J.

DOI: 10.1016/S0140-6736(05)74956-4  
PMID: 9950455 [Indexed for MEDLINE]

4953. Curr Opin Rheumatol. 1999 Jan;11(1):B13-23.

Bibliography. Current world literature. Systemic disorders with rheumatic manifestations.

[No authors listed]

PMID: 9894638 [Indexed for MEDLINE]

4954. Curr Opin Rheumatol. 1999 Jan;11(1):75-8.

Hereditary fevers.

Grateau G(1), Drenth JP, Delpech M.

Author information:

(1)Service de Medicine Interne, L'Hotel-Dieu de Paris, France.

Hereditary fevers are a group of rare disorders of the inflammatory response. Clinical features include recurrent attacks of fever and organ-localized inflammation. Minimal clinical variations, a unique biochemical-specific abnormality, and the mode of genetic inheritance distinguish the three main diseases: familial Mediterranean fever, hyperimmunoglobulinemia D and periodic fever syndrome, and autosomal dominant recurrent fever. The complete elucidation of pathogenesis of these intriguing disorders will be provided by the genetic studies currently in progress.

PMID: 9894634 [Indexed for MEDLINE]

4955. Gastroenterol Clin North Am. 1998 Sep;27(3):595-614, vi.

Systemic amyloidosis and the gastrointestinal tract.

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Author information:

(1)Division of Gastroenterology, Mount Sinai Medical Center, New York, New York, USA.

Systemic amyloidosis is caused by a variety of different diseases and frequently involves the gastrointestinal tract. Each type of amyloid affects the gastrointestinal tract differently. This article reviews the unique pathogenesis, pattern of gastrointestinal disposition, diagnosis, and treatment of the five systemic amyloidoses, and discusses the gastrointestinal diseases that cause systemic amyloidosis: inflammatory bowel disease and familial Mediterranean fever.

PMID: 9891699 [Indexed for MEDLINE]

4956. Adv Nephrol Necker Hosp. 1998;28:343-54.

Cloning of the familial Mediterranean fever gene: expectations for learning about the pathogenesis of amyloid A amyloidosis.

Pras M(1).

Author information:

(1)Sackler School of Medicine, Tel Aviv University, Israel.

PMID: 9889998 [Indexed for MEDLINE]

4957. Mol Biol Evol. 1998 Dec;15(12):1696-705.

B30.2-like domain proteins: update and new insights into a rapidly expanding family of proteins.

Henry J(1), Mather IH, McDermott MF, Pontarotti P.

Author information:

(1)Centre National de la Recherche Scientifique URA 1485, Faculté de Médecine, Limoges, France.

The B30.2 domain is a conserved region of around 170 amino acids associated with several different protein domains, including the immunoglobulin folds of butyrophilin and the RING finger domain of ret finger protein. We recently reported several novel members of this family as well as previously undescribed protein families possessing the B30.2 domain. Many proteins have subsequently been found to possess this domain, including pyrin/marenostrin and the midline 1 (MID1) protein. Mutations in the B30.2 domain of pyrin/marenostrin are implicated in familial Mediterranean fever, and partial loss of the B30.2 domain of MID1 is responsible for Opitz G/BBB syndrome, characterized by developmental midline defects. In this study, we scrutinized the available sequence data bases for the identification of novel B30.2 domain proteins using highly sensitive database-searching tools. In addition, we discuss the chromosomal localization of genes in the B30.2 family, since the encoded proteins are likely to be involved in other forms of periodic fever, autoimmune, and genetic diseases.

DOI: 10.1093/oxfordjournals.molbev.a025896

PMID: 9866204 [Indexed for MEDLINE]

4958. J Rheumatol. 1998 Dec;25(12):2481-2.

Soluble tumor necrosis factor receptor levels in familial Mediterranean fever.

Dror Y, Hahn T, Barash Y.

PMID: 9858459 [Indexed for MEDLINE]

4959. J Rheumatol. 1998 Dec;25(12):2445-9.

Prevalence of juvenile chronic arthritis and familial Mediterranean fever in

Turkey: a field study.

Ozen S(1), Karaaslan Y, Ozdemir O, Saatci U, Bakkaloglu A, Koroglu E, Tezcan S.

Author information:

(1)Faculty of Medicine, Hacettepe University, Ankara, Turkey.

Comment in

J Rheumatol. 1999 Jul;26(7):1638-9.

**OBJECTIVE:** To investigate the prevalence of juvenile chronic arthritis (JCA), familial Mediterranean fever (FMF), and Behçet's disease in Turkish children through a field survey.

**METHODS:** The field survey was based on cluster centering with 2 level strata. A total of 46,813 children were screened. For the diagnosis of chronic arthritis and Behçet's previously suggested criteria were used. We have developed criteria for the diagnosis of probable FMF. Children previously diagnosed to have these diseases were also defined and included.

**RESULTS:** JCA was found in 6.4/10,000. 2.8/10,000 children were previously diagnosed as FMF (minimum phenotype frequency). Together with the probable diagnosis of FMF, the prevalence increased to 9.3/10,000. The findings were also compared with those of our center. None of the 46,813 children had Behçet's disease.

**CONCLUSION:** The prevalence of chronic arthritis is similar to the other childhood populations reported. However, FMF has a very high prevalence.

PMID: 9858443 [Indexed for MEDLINE]

4960. Arch Pediatr. 1998;5 Suppl 4:397S-406S.

[Genetic diseases in the Mediterranean region: a historical perspective].

[Article in French]

Battin J(1).

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(1)Clinique de pédiatrie et génétique médicale, CHU Pellegrin, hôpital d'enfants, Bordeaux, France.

PMID: 9853091 [Indexed for MEDLINE]

4961. Mol Genet Metab. 1998 Nov;65(3):197-202.

Amyloidosis in familial mediterranean fever is associated with a specific ancestral haplotype in the MEFV locus.

Shohat M(1), Lotan R, Magal N, Danon Y, Ogur G, Tokguz G, Schlezinger M, Schwabe A, Halpern G, Fischel-Ghodsian N, Kastner D, Shohat T, Rotter JI.

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Familial Mediterranean fever (FMF) is a recessive disease characterized by recurrent attacks of inflammation of serosal membranes, and the gene responsible, MEFV, has been recently identified. Amyloidosis is considered to be the most severe complication. Since colchicine is effective in preventing FMF amyloidosis and since this process can develop even prior to the FMF symptoms, lifelong colchicine treatment is recommended for all FMF patients. Identification of the factor which determines amyloidosis will allow treatment to be directed only to those at risk. In order to investigate the association between amyloidosis and MEFV haplotypes, we studied 56 families from three ethnic groups. We compared the haplotypes of FMF patients with and without amyloidosis in each ethnic group separately and identified 14 different MEFV core haplotypes. A significant association ( $P < 0.004$ ) was found between amyloidosis and a specific core haplotype, 153bp:104bp at markers D16S3370 and D16S2617, respectively. Amyloidosis was present in 20 out of 70 homozygotes for this haplotype and in 6 out of 35 compound heterozygotes for this and other core haplotypes. None of the patients who did not carry this allele had amyloidosis. There was no association between the various haplotypes and severity of the FMF symptoms, age of onset, or age at commencement of colchicine. Further investigation of the MEFV haplotypes in additional patients is recommended as such an association may save many mildly affected or asymptomatic patients with non-amyloidotic genotypes from receiving unnecessary lifelong colchicine treatment.

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DOI: 10.1006/mgme.1998.2757

PMID: 9851884 [Indexed for MEDLINE]

4962. Ryoikibetsu Shokogun Shirizu. 1998;(22 Pt 3):496-8.

[Familial Mediterranean fever].

[Article in Japanese]

Hamai K(1), Miura AB.

Author information:

(1)Third Department of Internal Medicine, Akita University School of Medicine.

PMID: 9851199 [Indexed for MEDLINE]

4963. Med Hypotheses. 1998 Nov;51(5):377-80.

Does the lack of the P-glycoprotein efflux pump in neutrophils explain the efficacy of colchicine in familial Mediterranean fever and other inflammatory diseases?

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Author information:

(1)Department of Medicine, HadassAh University Hospital, Jerusalem, Israel.

Colchicine is an alkaloid drug commonly used in familial Mediterranean fever (FMF), gout, Behcet's syndrome, psoriasis and Sweet's syndrome. The exact mechanism of its action in these diseases is not entirely known. However, it has been shown that colchicine may inhibit neutrophil chemotaxis, thereby decreasing the inflammatory process. Recently, it was shown that colchicine accumulates in neutrophils in higher concentrations than in lymphomonocytes. Studies dealing



with the multiple drug resistance (MDR) issue disclosed that neutrophils lack the P-glycoprotein (P-gly) membranal pump (encoded by the MDR1 gene). We propose that the preferential accumulation of colchicine in neutrophils compared with lymphomonocytes is due to the absence of the P-gly efflux pump in the former. This may explain the effectiveness of colchicine in diseases where increased chemotaxis is evident. The hypothesis may also provide an explanation for FMF patients who do not respond to the drug.

PMID: 9848464 [Indexed for MEDLINE]

4964. Rev Esp Anesthesiol Reanim. 1998 Oct;45(8):353.

[Anesthetic complications of familial Mediterranean fever].

[Article in Spanish]

Martínez Herrero E, Marcote Oliva C, Prieto Cabrera A, Rubí Cassinello G, Santiago J, Muñoz Blanco F.

PMID: 9847647 [Indexed for MEDLINE]

4965. Genome Res. 1998 Nov;8(11):1172-91.

Construction of an approximately 700-kb transcript map around the familial Mediterranean fever locus on human chromosome 16p13.3.

Centola M(1), Chen X, Sood R, Deng Z, Aksentijevich I, Blake T, Ricke DO, Chen X, Wood G, Zaks N, Richards N, Krizman D, Mansfield E, Apostolou S, Liu J, Shafran N, Vedula A, Hamon M, Cercek A, Kahan T, Gumucio D, Callen DF, Richards RI, Moyzis RK, Doggett NA, Collins FS, Liu PP, Fischel-Ghodsian N, Kastner DL.

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(1)Arthritis and Rheumatism Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health (NIH), Bethesda, Maryland 20892-1820, USA.

We used a combination of cDNA selection, exon amplification, and computational prediction from genomic sequence to isolate transcribed sequences from genomic DNA surrounding the familial Mediterranean fever (FMF) locus. Eighty-seven kb of genomic DNA around D16S3370, a marker showing a high degree of linkage disequilibrium with FMF, was sequenced to completion, and the sequence annotated. A transcript map reflecting the minimal number of genes encoded within the approximately 700 kb of genomic DNA surrounding the FMF locus was assembled. This map consists of 27 genes with discreet messages detectable on Northern blots, in addition to three olfactory-receptor genes, a cluster of 18 tRNA genes, and two putative transcriptional units that have typical intron-exon splice junctions yet do not detect messages on Northern blots. Four of the transcripts are identical to genes described previously, seven have been independently identified by the French FMF Consortium, and the others are novel. Six related zinc-finger genes, a cluster of tRNAs, and three olfactory receptors account for the majority of transcribed sequences isolated from a 315-kb FMF central region (between D16S468/D16S3070 and cosmid 377A12). Interspersed among them are several genes that may be important in inflammation. This transcript map not only has permitted the identification of the FMF gene (MEFV), but also has provided us an opportunity to probe the structural and functional features of this region of chromosome 16.

PMCID: PMC310791

PMID: 9847080 [Indexed for MEDLINE]

4966. Clin Exp Rheumatol. 1998 Nov-Dec;16(6):721-4.

Effects of colchicine on inflammatory cytokines and selectins in familial Mediterranean fever.

Kiraz S(1), Ertenli I, Arici M, Calgüneri M, Haznedaroglu I, Celik I, Pay S, Kirazli S.

Author information:

(1)Hacettepe University, School of Medicine, Department of Internal Medicine, Ankara, Turkey.

**OBJECTIVE:** To evaluate whether basal levels of circulating cytokines and selectins exhibit a distinct profile in attack-free, non-colchicine taking familial Mediterranean fever (FMF) patients compared to normal healthy controls, and to determine the effect of colchicine treatment on these parameters.

**METHODS:** Serum levels of interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)-alpha, and soluble P-, E-, and L-selectin in attack-free, asymptomatic, non-colchicine using FMF patients (n = 11) and in normal controls (n = 10) were studied. Following 2 months of colchicine treatment the same parameters were evaluated again in the FMF patients.

**RESULTS:** Before colchicine treatment the serum levels of all parameters except soluble P-selectin were significantly higher in FMF patients than in controls. After two months of treatment statistically significant decreases were observed in these parameters ( $p < 0.05$ ).

**CONCLUSION:** A distinct profile of IL-6, IL-8, TNF-alpha, and soluble E- and L-selectin levels was observed in FMF patients, which could reflect the presence of sustained inflammation in attack-free FMF patients. The effect of colchicine on these parameters suggests its therapeutic potential.

PMID: 9844766 [Indexed for MEDLINE]

4967. Drug Saf. 1998 Nov;19(5):389-410.

Treatment of inflammatory rheumatic disorders in pregnancy: what are the safest treatment options?

Ostensen M(1), Ramsey-Goldman R.

Author information:

(1)Department of Rheumatology, University Hospital of Trondheim, Norway.

The interaction of pregnancy and the rheumatic diseases varies, ranging from life-threatening conditions such as thromboembolic events and progressive renal disease in some autoimmune disorders, to minor flares of peripheral arthritis in inflammatory rheumatic disease. As a consequence, treatment strategy will vary according to the maternal or fetal compromise expected. All nonsteroidal anti-inflammatory drugs (NSAIDs), including high dose aspirin (acetylsalicylic acid), can cause adverse effects during pregnancy related to the inhibition of

prostaglandin synthesis. Prolongation of gestation and labour, constriction of the ductus arteriosus, persistent fetal circulation, impairment of renal function and bleeding are risks of third trimester exposure of pregnant women to all inhibitors of cyclo-oxygenase. Most of these adverse effects can be prevented by discontinuing NSAIDs 8 weeks prior to delivery. Low dose aspirin has not been associated with fetal or neonatal toxicity. Some corticosteroids such as prednisone and prednisolone do not readily cross the placenta and can be safely used during pregnancy as immunosuppressive drugs. Maternal complications related to corticosteroids may occur and close monitoring is therefore mandatory. There is limited information on the safety of disease-modifying antirheumatic drugs including gold, antimalarials, penicillamine (D-penicillamine), sulfasalazine and cyclosporin. Of these agents, sulfasalazine has the best record for tolerability and can be used by pregnant patients. Gold compounds and penicillamine should be discontinued when pregnancy is recognised. Hydroxychloroquine has not been associated with congenital malformations and seems preferable to chloroquine in patients requiring treatment with antimalarials. Use of cyclosporin may be an alternative to other therapy in pregnant patients with severe rheumatic disease. Indications for treatment with colchicine during pregnancy are few, except for familial Mediterranean fever. Azathioprine can be used when the maternal condition requires a cytotoxic drug during the first trimester. Cyclophosphamide, chlorambucil and methotrexate are contraindicated during pregnancy because of their teratogenic potential. Their use may be considered in late pregnancy if the mother has a life-threatening condition.

DOI: 10.2165/00002018-199819050-00006

PMID: 9825952 [Indexed for MEDLINE]

4968. Stomatologiya (Mosk). 1998;77(5):4-7.

[The local immune mechanisms of the involvement of the teeth and periodontium in periodic disease].

[Article in Russian]

Akopian GV.

The aim of our investigations was to elucidate some immune aspects of combination of caries and periodontitis with periodic disease (PD), also known as familial

Mediterranean fever. In this regard in patients with active and non-active stage of PD we have studied dynamic changes of concentration of secretory immunoglobulin A (SIgA) in saliva and phagocytic activity of neutrophils derived from gum blood. It has been shown that in patients with PD these indices of local immunity of oral cavity had tendency to a decrease especially in case of PD and periodontitis combination. Disturbances of local immunity was significant in active stage of PD. Based on the obtained data and analysis of latest literature data we suppose that above mentioned changes in local immunity depended on the exhaustion of adaptive properties of patients' local immunity more pronounced in case of chronic inflammation and infection foci formation in oral cavity.

PMID: 9819974 [Indexed for MEDLINE]

4969. J Rheumatol. 1998 Nov;25(11):2236-9.

First International Conference on familial Mediterranean fever, Jerusalem, Israel, September 7-11, 1997.

Direskeneli H, Ozdogan H, Yazici H.

PMID: 9818670 [Indexed for MEDLINE]

4970. Amyloid. 1998 Sep;5(3):200-7.

Clinical benefits of diagnosing incipient AA amyloidosis in pediatric rheumatic diseases as estimated from a retrospective study.

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Author information:

(1)Rheumatic Children's Hospital, Garmisch-Partenkirchen, Germany.  
rheuma-kinderklinik@t-online.de

OBJECTIVE: The diagnosis of AA amyloidosis could not be made in eight patients with pediatric rheumatic diseases as later verified employing the more sensitive

combination of Congo red and additional immunocytochemistry (CRIC). The objective of this paper is to estimate the benefit of CRIC by reevaluating the historical charts with respect to the question as to which of the diagnostic and therapeutic measures would have been altered if the correct diagnosis had been known at the time of the primary biopsy.

**METHODS:** All subsequent biopsies of eight children with historically missed AA amyloidosis in their primary biopsies were retrieved, together with the historical data including the Congo red stains of the biopsies. The biopsies were reexamined blindly for the presence of amyloid and the results were compared with the historical data concerning diagnostic and therapeutic measures.

**RESULTS:** Using CRIC, AA amyloidosis could be identified an average of approximately three years earlier as compared to the historical data. This gain in time would certainly have altered the diagnostic as well as the therapeutic options, i.e. 10 out of 21 biopsies would have been spared and the earlier diagnosis would have initiated more significant antiinflammatory therapy.

**CONCLUSION:** Very early detection of amyloid reduces the diagnostic burden and unveils an option for a consequent antiinflammatory therapy very early in the course of AA amyloidosis.

PMID: 9818057 [Indexed for MEDLINE]

4971. Eur J Pediatr. 1998 Oct;157(10):853-5.

Colchicine-induced myoneuropathy in childhood.

Harel L(1), Mukamel M, Amir J, Straussberg R, Cohen AH, Varsano I.

Author information:

(1)Department of Paediatrics C, Schneider Children's Medical Centre, Petach Tikvah, Israel.

Colchicine is used in the treatment of gouty arthritis, familial Mediterranean fever, amyloidosis, Behcet disease and dermatoses. Myoneuropathy is a rare side-effect reported either with intoxication or in elderly patients with chronic renal insufficiency causing elevated plasma drug levels. We report the first two cases of myoneuropathy in children, both taking appropriate doses of colchicine, and having normal renal function. The myoneuropathic changes were reversible

after stopping treatment. The cause of colchicine myoneuropathy is unclear. CONCLUSION: In children treated with colchicine, neuromuscular phenomena of unknown aetiology may be related to the drug, even with a lack of intoxication or renal insufficiency.

PMID: 9809829 [Indexed for MEDLINE]

4972. Clin Rheumatol. 1998;17(5):397-9.

Coexistence of familial Mediterranean fever with sacroiliitis and Behçet's disease: a rare occurrence.

Birlik M(1), Tunca M, Hizli N, Soytürk M, Yeniçerioğlu Y, Ozcan MA, El O.

Author information:

(1)Department of Internal Medicine, Dokuz Eylül University School of Medicine, Izmir, Turkey.

Familial Mediterranean fever (FMF) and Behçet's disease are relatively rare but may still coexist in the same patient. Sacroiliitis is another feature whose significance is controversial in either of the diseases. We report a case of longstanding FMF with sacroiliitis who later developed typical characteristics of Behçet's disease. Although occurrence by chance cannot be ruled out, this unusual patient may enhance the claims that FMF and Behçet's disease have common aetiopathogenetic mechanisms. It would be appropriate to include this coexistence in the list of differential diagnoses of the two diseases.

PMID: 9805187 [Indexed for MEDLINE]

4973. J Med Liban. 1998 Jan-Feb;46(1):12-5.

Recurrent episodic fever. A presenting feature of familial Mediterranean fever.

Majeed HA(1), Rawashdeh M, Qubain H.

Author information:

(1)Department of Pediatrics, Faculty of Medicine, University of Jordan, Amman, Jordan.

**OBJECTIVES:** To study the natural course and outcome of recurrent episodic fever without serositis as a presenting feature of familial Mediterranean fever (FMF).

**PATIENTS:** Of 309 children with FMF seen over a period of 5 years, 8 presented with recurrent episodes of fever without serositis, imposing a difficult diagnostic problem.

**RESULTS:** The age at onset of fever ranged between 5 months and 8 years with a mean of 2.5 years. Five patients eventually developed serositis. The duration between onset of fever and onset of serositis ranged between 1.5-3 years with a mean of 2 years. Of the 3 patients who did not develop serositis, 2 had a family history of FMF. Therapeutic response to colchicine was dramatic in 7 children (one refused colchicine prophylaxis).

**CONCLUSION:** Episodic fever alone without serositis is a presenting feature of FMF. In patients from Mediterranean ancestors and/or the presence of family history of FMF, a therapeutic diagnostic test with colchicine could be rewarding.

PMID: 9795516 [Indexed for MEDLINE]

4974. Nephrol Dial Transplant. 1998 Oct;13(10):2633-5.

M680I(Arm2)/M694V(Med) mutations in a patient with familial Mediterranean fever and polyarteritis nodosa.

Akpolat T(1), Yilmaz E, Ozen S, Akpolat I, Danaci M, Kandemir B.

Author information:

(1)Department of Nephrology, Ondokuz Mayıs University, School of Medicine, Samsun, Turkey.

PMID: 9794574 [Indexed for MEDLINE]

4975. Clin Transplant. 1998 Oct;12(5):375-8.



## Transplantation in renal amyloidosis.

Türkmen A(1), Yildiz A, Erkoç R, Ecder T, Görçin B, Türk S, Aydın AE, Eldegez U, Ark E, Sever MS.

Author information:

(1)Istanbul School of Medicine, Department of Nephrology, Turkey.

In this report, the results of renal transplantation in patients with renal amyloidosis were retrospectively analysed and compared with the control group. Fifteen (3.04%) of the 493 renal transplant recipients whom were followed up in Istanbul School of Medicine transplant outpatient clinic, between 1983 and 1997, were included in the study. The etiology of amyloidosis was familial Mediterranean fever in all patients. The mean follow-up period was  $38.3 \pm 31.8$  (range 7-65) months. Twelve of the patients were male and 3 female with the mean age  $34.13 \pm 10.87$  (range 21-60) years. Seven patients had living related, 4 living-unrelated and 4 cadaveric donors. Five patients were lost because of different complications: Three patients died from cardiac amyloidosis all with well functioning grafts, 2, 3 and 36 months after the operation. Sepsis and cardiovascular failure was the probable cause of death in 1 patient who also had chronic rejection. Another one patient with chronic rejection died from hepatic failure. Acute rejection developed in 2 patients. Renal functions of these patients improved by anti-rejection therapies. Chronic rejection developed in 3 patients. In the control group, acute rejection and chronic rejection were diagnosed in 5 and 1 patients, retrospectively. While 1 patients returned to hemodialysis in control group, the others are alive with satisfactory graft function. There was no death in control group. The 5-yr graft and patient survival rates in amyloidosis and the control groups were 75, 77, 95 and 100%, respectively. It was concluded that although transplantation is not a contraindication for the treatment of end stage renal failure in patients with renal amyloidosis, it carries high risk of cardiac complications in the postoperative period. Detailed preoperative cardiovascular evaluations are mandatory in these patients and this intervention should improve the prognosis by excluding the patients who have already been complicated with this problem.

PMID: 9787944 [Indexed for MEDLINE]

4976. Genomics. 1998 Oct 1;53(1):97-103.

Identification of two Krüppel-related zinc finger genes (ZNF200 and ZNF210) from human chromosome 16p13.3.

Deng Z(1), Centola M, Chen X, Sood R, Vedula A, Fischel-Ghodsian N, Kastner DL.

Author information:

(1)Arthritis and Rheumatism Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, Maryland, 20892-1820, USA.

During the course of cloning the gene for familial Mediterranean fever (FMF), we identified a number of transcripts from a 275-kb genomic region on 16p13.3. Two of the transcripts were found to contain multiple C2H2-type zinc finger motifs in tandem arrays, indicating that they are members of the Krüppel-type family. One transcript was found to be an alternatively spliced form of a previously reported zinc finger gene, ZNF200. The other transcript, ZNF210, is 2017 bp and encodes an open reading frame of 504 aa. Northern blot analysis indicates that ZNF210 is expressed in all the tissues tested with the highest expression in heart, skeletal muscle, pancreas, prostate, ovary, and colon. On the other hand, the strongest expression of ZNF200 is in testis, with very low levels in all the other tissues tested. Sequence analysis reveals eight C2H2 zinc finger motifs at the C-terminus of ZNF210 and five in ZNF200. In addition, ZNF210 also possesses a Krüppel-associated box at its N-terminus, indicating that it might function as a transcription repressor. The intron-exon structures of both genes were determined and showed that ZNF210 has seven exons while the coding part of ZNF200 is distributed in four exons. The locations of ZNF200 and ZNF210 are 10 and 120 kb telomeric to the FMF gene, respectively.

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DOI: 10.1006/geno.1998.5430

PMID: 9787081 [Indexed for MEDLINE]

4977. Med J Aust. 1998 Sep 21;169(6):342.

Hypokalaemic periodic paralysis mimicking Guillain-Barré syndrome.

Warren JD, Thompson PD.

PMID: 9785539 [Indexed for MEDLINE]

4978. Eur J Hum Genet. 1998 Jan;6(1):95-7.

Phenotype-genotype correlation in Jewish patients suffering from familial Mediterranean fever (FMF).

Dewalle M(1), Domingo C, Rozenbaum M, Ben-Chétrit E, Cattan D, Bernot A, Dross C, Dupont M, Notarnicola C, Levy M, Rosner I, Demaille J, Touitou I.

Author information:

(1)Hôpital A de Villeneuve, Montpellier, France.

Familial Mediterranean Fever is one of the most frequent recessive disease in non-Ashkenazi Jews. The gene responsible for the disease (MEFV) has very recently been identified. The M694V ('MED') mutation was found in about 80% of the FMF Jewish (Iraqi and North African) chromosomes. To see if the presence of this mutation could be correlated with particular traits of the disease, we examined a number of clinical features in a panel of 109 Jewish FMF patients with 0, 1 or 2 MED mutations. We showed that homozygosity for this mutation was significantly associated with a more severe form of the disease. In homozygous patients, the disease started earlier (mean age 6.4 +/- 5 vs 13.6 +/- 8.9) and both arthritis and pleuritis were twice as frequent as in patients with one or no M694V mutation. Moreover, 3/3 patients with amyloidosis displayed two MED mutations. No association was found with fever, peritonitis, response to colchicine and erysipeloid eruption. The present result strongly suggests the potential prognostic value of the presence of this mutation.

DOI: 10.1038/sj.ejhg.5200170

PMID: 9781020 [Indexed for MEDLINE]

4979. Rev Med Interne. 1998 Jul;19(7):522-3.

[Periodic bursitis in the iliac psoas].

[Article in French]

Dubois A, Ferru JM, Dubois A.

PMID: 9775207 [Indexed for MEDLINE]

4980. Rev Med Interne. 1998 Jul;19(7):486-91.

[Genetic diagnosis of periodic disease].

[Article in French]

Touitou I(1).

Author information:

(1)Laboratoire de génétique moléculaire et chromosomique, Hôpital A-de-Villeneuve, Montpellier, France.

**INTRODUCTION:** Periodic disease is a hereditary disorder. Until recently its diagnosis was essentially based on clinical criteria. When the clinical picture was incomplete or atypical, it often required elimination of other diagnoses which sometimes involved extensive and useless investigations. Diagnosis was consequently delayed or irrelevant, with the risk of renal failure when the patient was not treated (or tardily treated).

**CURRENT KNOWLEDGE AND KEY POINTS:** Efforts of molecular geneticists have allowed to track and recently to identify the gene (MEFV) responsible for this disease. Today blood sampling enables identification of the causative mutations, sometimes even before the onset of symptoms.

**FUTURE PROSPECTS AND PROJECTS:** Four mutations clustered on exon 10 already account for 74% of cases in patients originating from the most affected populations and presenting with complete clinical picture. Identification of rare mutations should progressively allow improvement of the test sensitivity, especially in patients with a less typical form of the disease.

PMID: 9775197 [Indexed for MEDLINE]

4981. Rev Med Interne. 1998 Jul;19(7):467-9.

[Familial mediterranean fever is a hereditary disorder of the neutrophil].

[Article in French]

Grateau G.

PMID: 9775194 [Indexed for MEDLINE]

4982. Rev Med Interne. 1998 Jun;19(6):427-30.

[Malignant peritoneal mesothelioma occurring in periodic disease: apropos of a case].

[Article in French]

Belange G(1), Gompel H, Chaouat Y, Chaouat D.

Author information:

(1)Service de médecine interne, Fondation A-de-Rothschild, Paris, France.

**INTRODUCTION:** Peritoneal mesothelioma is a rare malignant neoplasm that might be linked to chronic peritoneal inflammation. As well, the association peritoneal mesothelioma-familial Mediterranean fever is uncommon.

**EXEGESIS:** We report the case of a 60-year-old man who presented for 30 years with standard periodic familial Mediterranean fever accompanied by acute abdominal episodes, sensitive to colchicine. Between 1988 and 1995, acute abdominal episodes were accompanied by more and more profuse recurrent ascites, partially resolving under colchicine treatment. In 1995, the last episode was severe (with loss of weight and inability to tolerate feeding) and conducted to the patient's death due to peritoneal mesothelioma, as confirmed by the biopsy.

**CONCLUSION:** Profuse and recurrent ascites is unusual in standard periodic familial Mediterranean fever. Asbestos exposure at the origin of peritoneal

mesothelioma is not well documented. Furthermore, the disease clinical and paraclinical features are misleading, and the diagnosis is based on histology. The prognosis is severe, and treatment is usually disappointing. Our observation clearly demonstrates the interconnection between an unusual form of profuse and relapsing ascites that occurred in the course of a periodic disease and peritoneal mesothelioma. The potential role of recurrent peritonitis related to familial Mediterranean fever in the pathogenesis of the tumor is discussed.

PMID: 9775184 [Indexed for MEDLINE]

4983. Histopathology. 1998 Aug;33(2):163-7.

Familial mediterranean fever and acute myocardial infarction secondary to coronary vasculitis.

Serrano R(1), Martínez MA, Andrés A, Morales JM, Samartin R.

Author information:

(1)Department of Pathology, Hospital 12 de Octubre, Madrid, Spain.

AIMS: We report a case study to elucidate the pathogenesis of polyarteritis nodosa (PAN) type vasculitis, a rare complication of familial mediterranean fever (FMF).

METHODS AND RESULTS: A woman with amyloidosis complicating FMF underwent a cadaveric renal transplantation and 5 years later suffered an acute myocardial infarction secondary to an isolated coronary vasculitis.

CONCLUSIONS: The histopathological findings of the vasculitis were not in keeping with PAN. We postulated that the pathogenesis of vasculitis in FMF is different from that of the classic PAN and might be similar to the mechanism of the serosal inflammation.

PMID: 9762550 [Indexed for MEDLINE]

4984. Arch Pediatr. 1998;5 Suppl 2:198s-199s.

[Periodic fever in the child. Survey of Marshall syndrome. Pediatric Infectious Disease Pathology Group].

[Article in French]

Reinert P(1), Bry ML.

Author information:

(1)Service de pédiatrie, centre hospitalier intercommunal, Créteil, France.

PMID: 9759259 [Indexed for MEDLINE]

4985. Ann Intern Med. 1998 Oct 1;129(7):581-2.

Genetics of familial Mediterranean fever and its implications.

Ehrlich GE.

Comment in

Ann Intern Med. 1999 May 4;130(9):780.

Comment on

Ann Intern Med. 1998 Oct 1;129(7):539-42.

PMID: 9758581 [Indexed for MEDLINE]

4986. Ann Intern Med. 1998 Oct 1;129(7):539-42.

Diagnosis of familial Mediterranean fever by a molecular genetics method.

Eisenberg S(1), Aksentijevich I, Deng Z, Kastner DL, Matzner Y.

Author information:

(1)Hadassah University Hospital, Mount Scopus, Jerusalem, Israel.

Comment in

Ann Intern Med. 1998 Oct 1;129(7):581-2.

**BACKGROUND:** Familial Mediterranean fever is a recessively inherited disorder characterized by episodes of fever with abdominal pain, pleurisy, or arthritis. The familial Mediterranean fever gene, designated MEFV, was recently cloned, and at least three missense mutations (M680I, M694V, and V726A) that account for a large percentage of patients with this disease were identified.

**OBJECTIVE:** To establish a diagnostic test for familial Mediterranean fever.

**DESIGN:** Cross-sectional study of a convenience sample of patients attending familial Mediterranean fever clinics.

**SETTING:** Tertiary referral hospitals.

**PATIENTS:** 107 patients with familial Mediterranean fever, their family members, and controls.

**MEASUREMENTS:** Mutations in the 107 samples were assessed by amplifying genomic DNA with use of primers that selectively amplify the normal or altered DNA sequence of the 3 MEFV mutations (amplification refractory mutation system [ARMS]). Mutations were independently assessed by automated sequencing of genomic DNA amplified by polymerase chain reaction to evaluate the sensitivity and specificity of the ARMS assay.

**RESULTS:** The ARMS assay correctly identified M680I, M694V, and V726A mutations in 82 persons with mutations documented by DNA sequencing (21 homozygotes, 2 compound heterozygotes, and 59 simple heterozygotes). Of 7 persons known from family studies to be noncarriers and 18 unrelated persons who were negative for these mutations by sequencing, none had MEFV mutations according to ARMS.

**CONCLUSION:** The ARMS assay is a rapid, cost-effective, and accurate method for detecting three common mutations in familial Mediterranean fever.

PMID: 9758573 [Indexed for MEDLINE]

4987. Hum Mol Genet. 1998;7(10):1581-8.

The hereditary periodic fever syndromes: molecular analysis of a new family of inflammatory diseases.

Centola M(1), Aksentijevich I, Kastner DL.



Author information:

(1)Arthritis and Rheumatism Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH Building 10, Room 9N210, 9000 Rockville Pike, Bethesda, MD 20892-1820, USA.

The hereditary periodic fever syndromes are a group of Mendelian disorders characterized by episodic fever and serosal or synovial inflammation. Familial Mediterranean fever (FMF) and the hyperimmunoglobulinemia D and periodic fever syndrome are both recessively inherited, while three dominantly inherited syndromes have been described, the best-characterized of which is familial Hibernian fever (FHF). The last year has seen two major developments in this field: the FMF gene was identified on chromosome 16p by positional cloning, and a second major periodic fever locus was mapped to distal chromosome 12p. The FMF gene (MEFV) encodes a novel 781 amino acid protein; to date, eight different missense mutations and a number of polymorphisms have been described. Seven of the eight mutations occur within a region of 82 amino acids near the C-terminus. Computational analysis of the conceptual protein reveals five different domains/motifs compatible with a nuclear effector function. MEFV is expressed preferentially in granulocytes and myeloid bone marrow precursors, giving rise to speculation that the protein may serve as a transcriptional regulator of inflammation in granulocytes. The second periodic fever locus was mapped by two different groups: one studying FHF, the other studying a similar dominantly inherited syndrome designated familial periodic fever. Both genes map to the same 19 cM region on distal chromosome 12p, strongly suggesting a common locus. The molecular characterization of the periodic fever genes should provide important new insights into the regulation of inflammation in general.

PMID: 9735379 [Indexed for MEDLINE]

4988. Ann Intern Med. 1998 Sep 1;129(5):424.

Treating familial Mediterranean fever with prazosin hydrochloride.

Kataoka H, Kumagai H, Hanai H.

PMID: 9735077 [Indexed for MEDLINE]

4989. J Rheumatol. 1998 Sep;25(9):1865-7.

Increased serum eosinophil cationic protein levels in familial Mediterranean fever.

Konca K, Erken E, Ydrýsoglu S.

PMID: 9733478 [Indexed for MEDLINE]

4990. Semin Arthritis Rheum. 1998 Aug;28(1):48-59.

Colchicine: 1998 update.

Ben-Chetrit E(1), Levy M.

Author information:

(1)Department of Medicine, Hadassah University Hospital, Jerusalem, Israel.

**OBJECTIVE:** To present an update of the use of colchicine in patients with familial Mediterranean fever (FMF) and other rheumatic and nonrheumatic diseases.

**DATA SOURCES:** Published studies on colchicine retrieved from MEDLINE searches from 1987 to 1997 and reports presented at national and international meetings.

**STUDIES SELECTION AND EXTRACTION:** All studies were reviewed by the authors. Reports addressing the topics of colchicine pharmacokinetics, biological effects, indications for use, and side effects were selected.

**DATA SYNTHESIS:** Colchicine is an alkaloid that may interfere with microtubule formation, thereby affecting mitosis and other microtubule-dependent functions. It has a bioavailability of 25% to 50% when administered orally. Colchicine and its metabolites are excreted through the urinary and biliary tracts. It may be used while breast feeding; however, amniocentesis should be performed when used in pregnancy. The drug may be given to children with FMF. The efficacy of colchicine has been proved in FMF, gout, Behcet's disease, and cirrhosis. Its place in the treatment of scleroderma, sarcoidosis, and skin disorders remains to be determined. Gastrointestinal side effects occur early and are most common manifestations of colchicine toxicity. Severe colchicine toxicity results in

multiple organ failure, convulsions, coma, and death. Potentially, effective treatment with Fab anti-colchicine antibodies unfortunately is unavailable; therefore, treatment is supportive.

CONCLUSIONS: Colchicine is a relatively safe and effective medication for several disorders when used in appropriate dosage in patients with normal kidney and liver function.

PMID: 9726336 [Indexed for MEDLINE]

4991. Arch Dermatol. 1998 Aug;134(8):929-31.

Familial Mediterranean fever.

Muhn CY(1), Rosenthal D, Browne C, Jakubovic H, Fisher BJ.

Author information:

(1)Division of Dermatology, McMaster University, Faculty of Health Sciences, Hamilton, Toronto, Ontario.

PMID: 9722722 [Indexed for MEDLINE]

4992. Nephrol Dial Transplant. 1998 Aug;13(8):1919-20.

Familial Mediterranean fever: from inflammation to amyloidosis.

Grateau G.

PMID: 9719137 [Indexed for MEDLINE]

4993. Medicine (Baltimore). 1998 Jul;77(4):268-97.

Familial Mediterranean fever at the millennium. Clinical spectrum, ancient mutations, and a survey of 100 American referrals to the National Institutes of

Health.

Samuels J(1), Aksentijevich I, Torosyan Y, Centola M, Deng Z, Sood R, Kastner DL.

Author information:

(1)Arthritis and Rheumatism Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Maryland 20892-1820, USA.

Regarded as the most common and best understood of the hereditary periodic fever syndromes, familial Mediterranean fever (FMF) is a recessively inherited disease of episodic fever with some combination of severe abdominal pain, pleurisy, arthritis, and a characteristic ankle rash. The flares typically last for up to 3 days at a time, and most patients are completely asymptomatic between attacks; if untreated with prophylactic colchicine, some patients later develop amyloidosis and renal failure. The recent cloning of the FMF gene on the short arm of chromosome 16p, and the subsequent finding that its tissue expression is limited to granulocytes, has helped to explain the dramatic accumulation of neutrophils at the symptomatic serosal sites; the wild-type gene likely acts as an upregulator of an anti-inflammatory molecule or as a downregulator of a pro-inflammatory molecule. For nearly half a century, FMF was thought to cluster primarily in non-Ashkenazi Jews, Arabs, Armenians, and Turks, although the screening of the 8 known mutations in an American cohort has identified substantial numbers of people from the Ashkenazi Jewish and Italian populations in the United States who also have this disease. Nevertheless, the symptoms often go unrecognized and patients remain undiagnosed for years, not receiving the highly efficacious colchicine therapy; their histories often include multiple laparotomies, laparoscopies, and psychiatric evaluations. The combinations of clinical manifestations among FMF patients are quite heterogeneous, but our American cohort did not establish any connections between individual mutations and specific clinical pictures--as is seen in other diseases like cystic fibrosis, in which distinct genotypes target certain organ systems. Specifically, the data from our American series are insufficient to evaluate the hypothesis that the M694V/M694V genotype confers a more severe phenotype, or increases the risk of amyloidosis; but both our data and the recent literature (160) indicate that amyloidosis can occur in FMF patients with only 1 copy, or no copies, of the M694V mutation. It appears that specific MEFV mutations are probably not the sole determinants of phenotype, and that unknown environmental factors or modifying genes act as accomplices in this disease. Although we hope the discovery of the

FMF gene will allow the diagnosis of FMF to become genetically accurate, the reality is that both clinical and genetic tools must still be used together unless mutations are identified on both of a patient's chromosomes. Physicians should be careful not to rule out the diagnosis in patients of high-risk ethnic backgrounds just because of atypical clinical features, as our data indicate that MEFV mutations are sometimes demonstrable in such patients. At the same time, physicians cannot yet rely solely on a genetic diagnosis because we have not yet identified a sufficient spectrum of mutations, and it is not currently feasible to examine every patient's full DNA sequence for the entire gene; screening an ethnically consistent and clinically positive patient for the 8 known mutations frequently identifies a mutation on only 1 chromosome, and genetic analysis of other classic cases will often reveal none of the 8 mutations. Still, our data suggest that ethnic background is an important predictor of finding 1 of the presently known mutations, and the knowledge of ancestries atypical for FMF can suggest the diagnosis of other hereditary periodic fever syndromes. As the list of FMF-associated MEFV mutations is expanded, and/or new sequencing technologies permit more rapid screening, the value and interpretation of genetic testing for FMF will become more straightforward. Moreover, as the pathophysiology of this disorder becomes less of a hypothesis and more of an understood entity, it is likely that treatment options will broaden beyond the use of daily prophylactic colchicine. (ABSTRACT TRUNCATED)

PMID: 9715731 [Indexed for MEDLINE]

4994. Ann Rheum Dis. 1998 Apr;57(4):259-60.

Azoospermia in familial Mediterranean fever patients: the role of colchicine and amyloidosis.

Ben-Chetrit E, Backenroth R, Haimov-Kochman R, Pizov G.

PMCID: PMC1752571

PMID: 9709191 [Indexed for MEDLINE]

4995. Arthritis Rheum. 1998 Aug;41(8):1516-7.

Familial Mediterranean fever diagnostic criteria: comment on the article by Livneh et al.

Tunca M.

Comment on

Arthritis Rheum. 1997 Oct;40(10):1879-85.

DOI: 10.1002/1529-0131(199808)41:8<1516::AID-ART31>3.0.CO;2-O

PMID: 9704657 [Indexed for MEDLINE]

4996. Ter Arkh. 1998;70(6):61-2.

[Hard-to-control blood hypertension in patients with renal amyloidosis in periodic disease].

[Article in Russian]

Nikolaev Alu, Milovanov luS, Trofimova El.

PMID: 9695232 [Indexed for MEDLINE]

4997. Ann Trop Paediatr. 1998 Mar;18(1):13-5.

Recurrent hyperbilirubinaemia, a feature of familial Mediterranean fever: report of a child and review of the literature.

Majeed HA(1), Halabi I, al-Taleb O.

Author information:

(1)Department of Pediatrics, Faculty of Medicine, University of Jordon, Amman.

Recurrent hyperbilirubinaemia was described as a feature of familial Mediterranean fever in the 1950s and early 1960s. However, over the last 33 years only one case has been published. We present a 12-year-old Arab boy who developed

recurrent hyperbilirubinaemia in the course of familial Mediterranean fever. His response to colchicine was excellent. Review of the literature reveals that hyperbilirubinaemia of familial Mediterranean fever has a distinct clinical picture characterized by concurrent peritonitis, minimal jaundice and short duration. Factors contributing to the paucity of reports in recent literature are discussed.

PMID: 9691995 [Indexed for MEDLINE]

4998. Panminerva Med. 1998 Jun;40(2):157-60.

Familial Mediterranean fever in two Italian brothers.

Breda L(1), Magrí M, Morgese G, Chiarelli F.

Author information:

(1)Department of Pediatrics, University of Chieti, Italy.

Familial Mediterranean fever (FMF) is an autosomal recessive disease of unknown etiology, characterized by recurrent self limited episodes of fever and polyserositis. Some patients develop generalized amyloidosis, which can be fatal. Colchicine therapy modifies the natural history of the disease by decreasing the attack frequency and preventing amyloid deposition. The disease is common among Sephardic Jews, Arabs, Armenians and has also been sporadically found in other ethnic groups of Mediterranean origin. We report two cases of FMF in brothers living in Abruzzo, Italy. They were born from consanguineous parents and complained typical symptoms since childhood. The boy suffered from one febrile attack every week; he presented three episodes of acute scrotum at age 8 and 9. The elder sister showed a spontaneous partial relief during adolescence. Juvenile rheumatoid arthritis was suspected and Aspirin was used for many years without any clinical improvement. Treatment with colchicine 1 mg/day was established at age 13 and 17 respectively, and a sudden reduction of frequency of attacks was obtained. A gingival biopsy did not show amyloid. The three elder brothers are, at present, in good health. Our experience point out the diagnostic difficulties of FMF especially in a country where the disease is uncommon.

PMID: 9689839 [Indexed for MEDLINE]

4999. Am J Med Sci. 1998 Jul;316(1):53-5.

Superior vena cava thrombosis and obstructive sleep apnea in a patient with familial Mediterranean fever.

Ustündag Y(1), Bayraktar Y, Emri S.

Author information:

(1)Department of Internal Medicine, Hacettepe University School of Medicine, Ankara, Turkey.

Familial Mediterranean fever (FMF), a paroxysmal, self-limited, inflammatory disease of unknown etiology, may result in thrombotic complications after the development of nephrotic syndrome due to amyloidosis. It has been suggested that there is increased thrombogenic activity in the blood of patients with FMF who did not develop nephrotic syndrome. We describe a patient with FMF who presented with thrombosis in the superior vena cava (SVC) in the absence of nephrotic syndrome, and discuss the contributory role of increased procoagulant activity detected in this disorder. Moreover, the patient was proved to have obstructive sleep apnea (OSA) which we believe was secondary to SVC thrombosis that lead to soft tissue edema in the upper airways. To our knowledge, this is the second reported case in the literature in which OSA occurred secondary to the SVC thrombosis.

PMID: 9671044 [Indexed for MEDLINE]

5000. Hum Mol Genet. 1998 Aug;7(8):1317-25.

Non-founder mutations in the MEFV gene establish this gene as the cause of familial Mediterranean fever (FMF).

Bernot A(1), da Silva C, Petit JL, Cruaud C, Caloustian C, Castet V, Ahmed-Arab M, Dross C, Dupont M, Cattani D, Smaoui N, Dodé C, Pêcheux C, Nédelec B, Medaxian J, Rozenbaum M, Rosner I, Delpech M, Grateau G, Demaille J, Weissenbach J,



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Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurring attacks of fever and serositis. It affects primarily North African Jews, Armenians, Turks and Arabs, in which a founder effect has been demonstrated. The marenostirin-pyrin-encoding gene has been proposed as a candidate gene for the disease (MEFV), on the basis of the identification of putative mutations clustered in exon 10 (M680V, M694I, M694V and V726A), each segregating with one ancestral haplotype. In a search for additional MEFV mutations in 120 apparently non-founder FMF chromosomes, we observed eight novel mutations in exon 2 (E148Q, E167D and T267I), exon 5 (F479L) and exon 10 (I692del K695R, A744S and R761H). Except for E148Q and K695R, all mutations were found in a single chromosome. Mutation E148Q was found in all ethnic groups studied and in association with a novel ancestral haplotype in non-Ashkenazi Jews (S2). Altogether, these new findings definitively establish the marenostirin/pyrin-encoding gene as the MEFV locus.

PMID: 9668175 [Indexed for MEDLINE]

5001. Genomics. 1998 Jun 1;50(2):147-60.

A transcriptional Map of the FMF region.

Bernot A(1), Heilig R, Clepet C, Smaoui N, Da Silva C, Petit JL, Devaud C, Chiannilkulchai N, Fizames C, Samson D, Cruaud C, Caloustian C, Gyapay G, Delpech M, Weissenbach J.

Author information:

(1)Généthon, CNRS-URA 1922, Evry, France. [bernot@genoscope.cns.fr](mailto:bernot@genoscope.cns.fr)

Familial Mediterranean fever (FMF) is a recessively inherited disorder characterized by attacks of fever and serositis, which affects primarily non-Ashkenazi Jews, Armenians, Turks, and Arabs. We present here a transcriptional map covering the FMF locus that we constructed in the course of

the positional cloning of the gene responsible for this disease. This map was established from a contig constructed with YAC, BAC, and cosmid clones and covers about 500 kb of 16p13.3. It contains nine transcriptional units corresponding to known genes or to genes belonging to known gene families, 23 gene fragments characterized by partial sequences, and an endogenous retrovirus sequence. It thus considerably increases the number of genes in this interval and improves our knowledge concerning some of the genes or gene families present in this region. Data accumulated in this region were also used in a comparative study of different methods of exon detection.

PMID: 9653642 [Indexed for MEDLINE]

5002. Lupus. 1998;7(4):259-65.

Childhood vasculitis.

Dillon MJ(1).

Author information:

(1)Great Ormond Street Hospital for Children, London, UK.

Vasculitis can and does occur in childhood. Apart from the relatively common vasculitides (Henoch-Schönlein purpura, Kawasaki disease and in world wide terms Takayasu disease) there are a number of important but comparatively rare disorders affecting children. These include macroscopic and microscopic polyarteritis, cutaneous polyarteritis, Wegener's granulomatosis, Churg-Strauss syndrome, primary angiitis of the central nervous system, hypersensitivity angiitis, hypocomplementaemic urticarial vasculitis, vasculitis associated with various connective tissue disorders and vasculitis associated with conditions such as Behçets syndrome, familial Mediterranean fever and Cogan's syndrome. Distinguishing these conditions from other disorders is often difficult and requires clinical acumen and appropriate investigative procedures. With modern therapeutic agents, it is possible to implement appropriate therapy but in spite of this, there remains a not inconsequential morbidity and mortality.

DOI: 10.1191/096120398678920064

PMID: 9643315 [Indexed for MEDLINE]

5003. Clin Transplant. 1998 Jun;12(3):159-64.

Renal transplantation in secondary systemic amyloidosis.

Heering P(1), Hetzel R, Grabensee B, Opelz G.

Author information:

(1)Department of Nephrology and Rheumatology, Heinrich Heine University, Düsseldorf, Germany.

When renal amyloidosis has progressed to end-stage renal failure, most patients are severely affected by systemic amyloidosis and nephropathy. An alternative to chronic dialysis is renal transplantation. We present a patient with amyloid nephropathy who developed recurrent transplant amyloidosis. Renal transplantation was performed in 1985 with a living related donor. In 1990 the patient developed amyloidosis of the graft with membranous nephropathy and tubular acidosis due to hyporeninemic hypoaldosteronism. Secondary amyloidosis has been reported to involve glandular organs inducing hypothyroidism, hypocortisolism and hypoaldosteronism. Cyclosporine has been reported to induce hyporeninemic hypoaldosteronism and tubular acidosis, but not hypocortisolism and hypothyroidism. Progression of the amyloidosis of the graft was confirmed by a renal biopsy in 1993. Data published in the literature indicate that the survival rate of amyloidotic graft recipients is worse than those of non-amyloidotic graft recipients. This was confirmed in an analysis of the current CTS data which showed an impaired survival rate at 5-yr of  $66 \pm 4\%$  ( $\pm$  SE) for patients with amyloidosis ( $n = 413$ ) as compared with  $86 \pm 1\%$  ( $p < 0.0001$ ) for patients with glomerulonephritis and  $84 \pm 1\%$  ( $p < 0.01$ ) for patients with polycystic kidney disease. Graft survival after 5 years was  $55 \pm 4\%$  in patients with amyloidosis as compared with  $63 \pm 1\%$  ( $p = 0.02$ ) in patients with glomerulonephritis and  $68 \pm 1\%$  in patients with polycystic kidney disease. Graft survival was improved in amyloidotic patients treated with cyclosporine as compared with patients on steroids and azathioprine ( $55 \pm 4\%$  vs.  $38 \pm 8\%$ ,  $p < 0.05$ ). It is concluded that renal transplantation is the renal replacement therapy of choice for patients with AA-type amyloidosis although the overall patient survival is impaired in comparison with patients with other diseases.

PMID: 9642504 [Indexed for MEDLINE]

5004. Am J Hum Genet. 1998 Jun;62(6):1446-51.

Linkage of familial Hibernian fever to chromosome 12p13.

McDermott MF(1), Ogunkolade BW, McDermott EM, Jones LC, Wan Y, Quane KA, McCarthy J, Phelan M, Molloy MG, Powell RJ, Amos CI, Hitman GA.

Author information:

(1)Medical Unit, St. Bartholomew's and the Royal London Hospital School of Medicine and Dentistry, Whitechapel, London, UK. M.F.McDermott@mds.qmw.ac.uk

Autosomal dominant periodic fevers are characterized by intermittent febrile attacks of unknown etiology and by recurrent abdominal pains. The biochemical and molecular bases of all autosomal dominant periodic fevers are unknown, and only familial Hibernian fever (FHF) has been described as a distinct clinical entity. FHF has been reported in three families-the original Irish-Scottish family and two Irish families with similar clinical features. We have undertaken a genomewide search in these families and report significant multipoint LOD scores between the disease and markers on chromosome 12p13. Cumulative multipoint linkage analyses indicate that an FHF gene is likely to be located in an 8-cM interval between D12S77 and D12S356, with a maximum LOD score (Z max) of 3.79. The two-point Z max was 3.11, for D12S77. There was no evidence of genetic heterogeneity in these three families; it is proposed that these markers should be tested in other families, of different background, that have autosomal dominant periodic fever, as a prelude to identification of the FHF-susceptibility gene.

DOI: 10.1086/301886

PMCID: PMC1377165

PMID: 9585614 [Indexed for MEDLINE]

5005. Allerg Immunol (Paris). 1998 Apr;30(4):99-100, 103.

[Urticarial vasculitis].

[Article in French]

Doutre MS(1).

Author information:

(1)Service de Dermatologie, CHU de Bordeaux, Hôpital Haut Lévêque, Pessac.

Urticarial vasculitis is defined by association of an urticaria and/or angio oedema and a vasculitis of the small dermal vessels, leucocytoclastic or mononuclear. Sometimes it is an acute urticaria, of infectious or drug origin. Urticarian vasculitis may also be due to pressure or cold. But usually, it is a chronic urticaria that readily accompanies systemic signs and immunological anomalies, in particular hypocomplementemia. The clinical-biological picture becomes a true entity or is associated with another condition, most often a collagenosis.

PMID: 9631690 [Indexed for MEDLINE]

5006. Circulation. 1998 Jun 2;97(21):2183-5.

Colchicine treatment for recurrent pericarditis. A decade of experience.

Adler Y(1), Finkelstein Y, Guindo J, Rodriguez de la Serna A, Shoenfeld Y, Bayes-Genis A, Sagie A, Bayes de Luna A, Spodick DH.

Author information:

(1)Department of Cardiology, Rabin Medical Center, Petah Tiqva, Israel.

Comment in

Circulation. 2000 Feb 8;101(5):E71-2.

**BACKGROUND:** The most troublesome complication of acute pericarditis is recurrent episodes of pericardial inflammation, occurring in 15% to 32% of cases. The cause of the recurrence is usually unknown, although in some cases it may be traced to viral infection or may be a consequence of coronary artery bypass grafting. The optimal method for prevention has not been fully established; accepted modalities include nonsteroidal anti-inflammatory drugs, corticosteroids, immunosuppressive

agents, and pericardiectomy.

**METHODS AND RESULTS:** Based on the proven efficacy of colchicine therapy for familial Mediterranean fever (recurrent polyserositis), several small studies have used colchicine successfully to prevent recurrence of acute pericarditis after failure of conventional treatment. Recently, we reported the results from the largest multicenter international study on 51 patients who were treated with colchicine to prevent further relapses and who were followed up for  $\leq 10$  years.

**CONCLUSIONS:** In light of new trial data that have accumulated in the past decade, we review the evidence for the efficacy and safety of colchicine for the prevention of recurrent episodes of pericarditis. Clinical and personal experience shows that colchicine may be an extremely promising adjunct to conventional treatment and may ultimately serve as the initial mode of treatment, especially in idiopathic cases.

PMID: 9626180 [Indexed for MEDLINE]

5007. Am J Hum Genet. 1998 Apr;62(4):884-9.

Gene localization for an autosomal dominant familial periodic fever to 12p13.

Mulley J(1), Saar K, Hewitt G, Rüschemdorf F, Phillips H, Colley A, Sillence D, Reis A, Wilson M.

Author information:

(1)Department of Cytogenetics and Molecular Genetics, Center for Medical Genetics, Women's and Children's Hospital, North Adelaide, SA 5006, Australia.  
mulleyj@mail.wch.sa.gov.au

We report gene localization in a family with a benign autosomal dominant familial periodic fever (FPF) syndrome characterized by recurrent fever associated with abdominal pain. The clinical features are similar to the disorder previously described as familial Hibernian fever, and they differ from familial Mediterranean fever (FMF) in that FPF episodes usually do not respond to colchicine and FPF is not associated with amyloidosis. Frequent recombination with the marker D16S2622,  $<1$  Mb from FMF, at 16p13.3, excluded allelism between these clinically similar conditions. Subsequently, a semiautomated genome search

detected linkage of FMF to a cluster of markers at 12p13, with a multipoint LOD score of 6.14 at D12S356. If penetrance of 90% is assumed, the FPF gene maps to a 19-cM interval between D12S314 and D12S364; however, if complete penetrance is assumed, then FPF maps to a 9-cM region between D12S314 and D12S1695. This interval includes the dentatorubropallidoluysian atrophy locus, which, with FPF, gave a maximum two-point LOD score of 3.7 at a recombination fraction of 0. This is the first of the periodic-fever genes, other than FMF, to be mapped.

Positional candidate genes may now be selected for mutation analysis to determine the molecular basis for FPF. Together with the recent identification of the defective gene in FMF, identification of a gene for FPF might provide new insights into the regulation of inflammatory responses.

DOI: 10.1086/301793

PMCID: PMC1377033

PMID: 9529351 [Indexed for MEDLINE]

5008. Lancet. 1998 May 30;351(9116):1658-9.

Familial Mediterranean fever.

Rajput V, Bromley SM.

Comment on

Lancet. 1998 Feb 28;351(9103):659-64.

DOI: 10.1016/S0140-6736(05)77714-X

PMID: 9620740 [Indexed for MEDLINE]

5009. Lancet. 1998 May 30;351(9116):1658.

Familial Mediterranean fever.

Bosch X, Pomares M.

Comment on

Lancet. 1998 Feb 28;351(9103):659-64.

DOI: 10.1016/S0140-6736(05)77713-8

PMID: 9620739 [Indexed for MEDLINE]

5010. J Med Genet. 1998 May;35(5):432-4.

Exclusion of the familial Mediterranean fever locus as a susceptibility region for autosomal dominant familial Hibernian fever.

McDermott MF(1), McDermott EM, Quane KA, Jones LC, Ogunkolade BW, Curtis D, Waldron-Lynch F, Phelan M, Hitman GA, Molloy MG, Powell RJ.

Author information:

(1)Department of Psychiatry, St Bartholomew's and the Royal London Hospital School of Medicine and Dentistry, Whitechapel, UK.

Autosomal dominant periodic fevers constitute a range of syndromes characterised by recurrent attacks of fever and abdominal pain. Familial Hibernian fever (FHF) has been described in only one United Kingdom based family, but two other Irish families have been found with similar clinical features. FHF resembles familial Mediterranean fever (FMF) in several clinical features, but the mode of inheritance of FHF is dominant whereas FMF is recessive. We have investigated whether autosomal dominant periodic fevers, in particular FHF, map to the FMF susceptibility locus (MEFV) on chromosome 16p13.3. We have used informative microsatellite markers flanking this locus to genotype members of the three families mentioned above. Two point and multipoint lod scores definitively excluded linkage to MEFV in the two larger families. A haplotype study confirmed these findings, indicating that FHF is genotypically as well as phenotypically distinct from FMF.

PMCID: PMC1051322

PMID: 9610811 [Indexed for MEDLINE]

5011. Hum Mutat. 1998;11(6):456-60.

Assessment of pyrin gene mutations in Turks with familial Mediterranean fever (FMF).



Chen X(1), Fischel-Ghodsian N, Cercek A, Hamon M, Ogur G, Lotan R, Danon Y, Shohat M.

Author information:

(1)Ahmanson Department of Pediatrics, Steven Spielberg Pediatric Research Center, Cedars-Sinai Medical Center and UCLA School of Medicine, Los Angeles, California 90048, USA.

Familial Mediterranean fever (FMF) is an autosomal recessive disease clinically characterized by recurrent short self-limited attacks of fever accompanied by peritonitis, pleurisy, and arthritis and can lead to amyloidosis and renal failure in the longer term. It is prevalent mainly in non-Ashkenazi Jews, Armenians, Turks, and Arabs. Due to the lack of an accurate diagnostic test, patients often experience years of attacks and invasive diagnostic procedures before the correct diagnosis is made and adequate treatment is begun. Recently, the gene responsible for FMF, denoted pyrin, has been cloned, and three disease mutations have been described (French FMF Consortium, 1997; International FMF Consortium, 1997). In the current study we assessed the spectrum of mutations in this gene in 16 unrelated families of Turkish origin. The three previously reported missense mutations (Met-Ile at codon 680, Met-Val at codon 694, and Val-Ala at codon 726) accounted for 29 of the 34 disease alleles. In one patient in whom no disease mutation was identified, the clinical picture was atypical enough to raise questions regarding the diagnosis. These results imply that the origin of FMF in Turkey is heterogeneous, that molecular diagnosis of FMF is possible in the majority of cases and clinically helpful, and that delineation of the undiscovered disease mutation(s) in the remaining cases remains a high priority.

DOI: 10.1002/(SICI)1098-1004(1998)11:6<456::AID-HUMU6>3.0.CO;2-G  
PMID: 9603438 [Indexed for MEDLINE]

5012. Rev Rhum Engl Ed. 1998 Apr;65(4):217-9.

The gene for familial Mediterranean fever has been identified.

Pouchot J, Vinceneux P, Grateau G, Méry JP.

PMID: 9599788 [Indexed for MEDLINE]

5013. J Rheumatol. 1998 May;25(5):916-9.

Familial Mediterranean fever clinical and genetic features in Druzes and in Iraqi Jews: a preliminary study.

Touitou I(1), Ben-Chetrit E, Notarnicola C, Domingo C, Dewalle M, Dross C, Dupont M, Demaille J, Rosner I, Rozenbaum M.

Author information:

(1)A. de Villeneuve Hospital, Montpellier, France. [touitou@vega.crbm.cnrs-mop.fr](mailto:touitou@vega.crbm.cnrs-mop.fr)

**OBJECTIVE:** A number of differences have been noted in clinical familial Mediterranean fever (FMF) among ethnic groups. Iraqi Jews and Druzes are characterized by less severe disease. The differences in disease expression raise the possibility of background genes peculiar to specific ethnic groups.

**METHODS:** We analyzed a series of FMF linked microsatellite markers and searched for gene mutations in these 2 populations.

**RESULTS:** We observed a conserved haplotype in 46% of the FMF druze chromosomes that was different from the Mediterranean haplotype but identical to the ARM3 haplotype. In contrast, 56% of the FMF chromosomes in Iraqi Jews displayed the same mutation as that found in Jews from North Africa.

**CONCLUSION:** Variable expression in FMF is probably due to both allelic heterogeneity and/or modifier genes as well as environmental factors.

PMID: 9598891 [Indexed for MEDLINE]

5014. Scand J Rheumatol. 1998;27(2):92-7.

Familial Mediterranean fever: from the clinical syndrome to the cloning of the pyrin gene.

Pras M.

Familial Mediterranean fever (FMF) is a genetic disorder, restricted to peoples originating in the Middle East. The clinical syndrome is characterized by shortlived febrile episodes, accompanied by inflammation in one of the serous membranes, resulting in peritonitis pleuritis or synovitis. In many untreated FMF patients, systemic amyloidosis developed. The clinical presentation of amyloidosis in FMF is nephropathic, progressing from proteinuria, nephrosis to renal failure and end stage renal disease. Continuous colchicine treatment, which was introduced in 1972, prevents most febrile-inflammatory attacks of FMF, and inhibits the development of amyloidosis in this otherwise fatal disease. Recently, the gene that causes FMF was cloned. It is called the pyrin gene and encodes the pyrin protein. Five missense mutations were found so far in the gene. These give rise to 5 amino acid substitutions, all of them in the carboxyterminal part of the pyrin protein. The pyrin protein is expressed solely in neutrophils white blood cells which are found in large numbers in the inflammatory sites during FMF attacks. It seems that the role of the wild type of the pyrin protein is to inhibit inflammation that can be provoked by a minor insult. The mutated pyrin protein in FMF is probably unable to inhibit these unnecessary inflammatory events. Preliminary studies of phenotype genotype correlation are reported.

PMID: 9572633 [Indexed for MEDLINE]

5015. Hosp Pract (1995). 1998 Apr 15;33(4):131-4, 139-40, 143-6 passim.

Familial Mediterranean fever: the genetics of inflammation.

Kastner DL(1).

Author information:

(1)National Institutes of Health, Bethesda, Md., USA.

When a patient complains of episodic fever accompanied by unexplained arthritis, peritonitis, pleurisy, or skin rash, this disorder should be considered. The disease-related gene codes for a protein that guides a neutrophil's participation in inflammation; the protein's existence implies an entire regulatory pathway hitherto unknown. At least two other mendelian periodic fever syndromes have also been described.

PMID: 9562837 [Indexed for MEDLINE]

5016. Hum Reprod. 1998 Feb;13(2):360-2.

The effect of colchicine treatment on sperm production and function: a review.

Haimov-Kochman R(1), Ben-Chetrit E.

Author information:

(1)Department of Obstetrics and Gynecology, Hadassah University Hospital, Mount Scopus, Jerusalem, Israel.

Colchicine is used for the treatment of various diseases including gouty arthritis, familial Mediterranean fever (FMF) and Behcet's disease. As a modulator of the microtubules at the cytoskeleton level, it arrests cell division at metaphase and inhibits microtubular-dependent cell motility. Controversy exists as to the adverse effect of colchicine on sperm production and function in healthy subjects as well as in gout, FMF and Behcet's patients. Sperm analysis shows a spectrum of pathology, from oligo- and azoospermia to normospermia with disturbances in sperm motility. These inconsistent sperm pathologies can be explained in part by the variability of the pathophysiology of the underlying disease. Thus, it seems that colchicine by itself may not have a significant direct adverse effect on sperm production and function.

PMID: 9557838 [Indexed for MEDLINE]

5017. Nephrol Dial Transplant. 1998 Mar;13(3):812-3.

Perirenal haematoma as the presenting feature of polyarteritis nodosa: one more case from Turkey.

Bihorac A, Ozener C, Koç M, Akoglu E.

Comment on

Nephrol Dial Transplant. 1997 Mar;12(3):582-4.

PMID: 9550682 [Indexed for MEDLINE]

5018. N Engl J Med. 1998 Apr 2;338(14):993-4.

Familial Mediterranean fever--amyloidosis and the Val726Ala mutation.

Yalçinkaya F, Akar N, Misirlioglu M.

DOI: 10.1056/NEJM199804023381414

PMID: 9527614 [Indexed for MEDLINE]

5019. N Engl J Med. 1998 Apr 2;338(14):992-3.

Familial Mediterranean fever gene.

Holmes AH, Booth DR, Hawkins PN.

Comment on

N Engl J Med. 1997 Nov 20;337(21):1548-9.

DOI: 10.1056/NEJM199804023381413

PMID: 9527613 [Indexed for MEDLINE]

5020. Abdom Imaging. 1998 Mar-Apr;23(2):147-9.

Abdominal CT in familial Mediterranean fever: a case report.

Wikström M(1), Wolf A, Birk D, Brambs HJ.

Author information:

(1)Department of Diagnostic Radiology, University Hospital of Ulm, Germany.

In order to clarify abnormal findings at abdominal ultrasound (suspicion of late abscess subsequent to appendectomy) in a young male patient with known familial

Mediterranean fever (FMF), a helical CT examination of the abdomen was performed. At CT, extensive serositis of the lower abdomen was detected. Findings at CT were verified 2 weeks later at laparoscopy.

PMID: 9516502 [Indexed for MEDLINE]

5021. Curr Opin Hematol. 1998 Jan;5(1):1-2.

Familial Mediterranean fever and the control of inflammation.

Babior BM.

PMID: 9515195 [Indexed for MEDLINE]

5022. Lancet. 1998 Feb 28;351(9103):659-64.

Familial Mediterranean fever.

Ben-Chetrit E(1), Levy M.

Author information:

(1)Familial Mediterranean Fever Clinic, Department of Medicine, Hadassah University Hospital, Jerusalem, Israel.

Comment in

Lancet. 1998 May 30;351(9116):1658.

Lancet. 1998 May 30;351(9116):1658-9.

DOI: 10.1016/S0140-6736(97)09408-7

PMID: 9500348 [Indexed for MEDLINE]

5023. Rev Prat. 1997 Oct 15;47(16):1798-801.

[Can amyloidosis regress?].

[Article in French]

Dray JM(1), Blétry O.

Author information:

(1)Service de médecine interne, Hôpital Foch, Suresnes.

Amyloidosis always worsens in the absence of treatment. Suitable treatments may improve the prognosis, but results depend on the type of amyloidosis. AA amyloidosis can improve according to clinical and biological criteria after the treatment of underlying disease, or after colchicine therapy in familial mediterranean fever. Histological regression is very unusual. A small clinical improvement or at least a stabilisation can be observed in familial amyloidosis with mutation in plasma transthyretin, after liver transplantation. However, the follow-up is short and the mortality is high. In AL amyloidosis, the survival is usually less than 15 months. Some patients have a better survival when they receive chemotherapy similar to that given in multiple myeloma. This could indicate an amyloidosis improvement, or at least a stabilisation.

PMID: 9453206 [Indexed for MEDLINE]

5024. Rev Prat. 1997 Oct 15;47(16):1783-6.

[Hereditary amyloidosis].

[Article in French]

Grateau G(1).

Author information:

(1)Service de médecine interne, L'Hôtel-Dieu, Paris.

Clinical aspects of hereditary amyloidoses are very diverse, and they pose many diagnostic problems to the physician. Biochemical and genetic aspects are also various. Several proteins are implicated in these hereditary diseases: transthyretin, apolipoprotein A1, gelsolin, fibrinogen alpha chain and lysozyme.

Studies on structural changes induced by the mutations in these proteins should bring new data relevant to our understanding of the amyloidogenic process. Familial mediterranean fever is a hereditary disease of the inflammatory reaction which is associated with AA amyloidosis.

PMID: 9453203 [Indexed for MEDLINE]

5025. Semin Arthritis Rheum. 1997 Dec;27(3):169-72.

Chronic massive knee effusion in familial Mediterranean fever.

Salai M(1), Zemmer D, Segal E, Corat A, Heyman Z, Davidson B, Langevitz P, Livneh A.

Author information:

(1)Department of Orthopedic Surgery A, Chaim Sheba Medical Center, Tel Hashomer, Israel.

OBJECTIVE: To document the occurrence of chronic massive knee effusions in patients with familial Mediterranean fever (FMF).

PATIENTS: Three cases of chronic massive knee effusion of young FMF patients requiring open synovectomy are presented.

RESULTS: Open synovectomy necessitated protracted rehabilitation, eventually with good results.

CONCLUSIONS: FMF should be considered in the differential diagnosis of chronic massive knee effusion. Early diagnosis and daily colchicine treatment generally result in a good clinical outcome and may eliminate the need for open synovectomy in favor of arthroscopic surgery.

PMID: 9431588 [Indexed for MEDLINE]

5026. Am J Med Genet. 1998 Jan 13;75(2):216-9.

Clinical differences between North African and Iraqi Jews with familial Mediterranean fever.



Pras E(1), Livneh A, Balow JE Jr, Pras E, Kastner DL, Pras M, Langevitz P.

Author information:

(1)Department of Medicine F, Sheba Medical Center, Tel-Hashomer, Israel.

Comment in

Am J Med Genet. 1999 Feb 19;82(5):442.

Familial Mediterranean fever (FMF) is an autosomal recessive disease causing attacks of fever and serositis. The gene causing this disease, designated MEFV, was mapped to the short arm of chromosome 16, but has not yet been cloned. North African and Iraqi Jews constitute the two largest population groups suffering from the disease in Israel. In this report we compared the severity of the disease between these two populations. North African Jews were found to have a more severe disease manifested by an earlier age of onset, an increase in frequency and severity of joint involvement, a higher incidence of erysipelas-like erythema, and a higher dose of colchicine required to control symptoms. The involvement of additional genes, environmental factors, and different mutations in MEFV, may explain the clinical variation in disease severity between these two population groups.

PMID: 9450890 [Indexed for MEDLINE]

5027. QJM. 1997 Oct;90(10):643-7.

Attacks of pericarditis as a manifestation of familial Mediterranean fever (FMF).

Kees S(1), Langevitz P, Zemer D, Padeh S, Pras M, Livneh A.

Author information:

(1)Heller Institute of Medical Research, Sheba Medical Center, Tel-Hashomer, Israel.

Familial Mediterranean fever (FMF) is characterized by recurrent attacks of febrile serositis. While arthritis, pleuritis and peritonitis are common in FMF, no association of pericarditis with FMF has been described in detail. We

retrospectively studied about 4000 FMF patients, using a computer chart review. Pericarditis was diagnosed when patients sustained attacks of pleuritic retrosternal chest pain and had typical findings in the electrocardiogram, echocardiogram or chest radiogram. The incidence and features of pericarditis in FMF were compared to published data. Over a period of 20 years, one or more episodes of pericarditis were recorded in 27 patients, a significantly higher incidence than in the general population (68 vs. 6 per 10(5) per year,  $p < 0.001$ ). Each patient experienced 1-3 pericarditis attacks, lasting a mean of 4.2 days, accompanied by high temperature and symptoms of FMF attack at another site. The pericarditis attack resolved spontaneously and left no sequelae. FMF patients with pericarditis were comparable to other FMF patients in most demographic and clinical parameters. Pericarditis may be considered another rare manifestation of FMF.

PMID: 9415347 [Indexed for MEDLINE]

5028. Harefuah. 1997 Nov 2;133(9):372-4.

[Ancient mutations in the Sons of Shem cause familial Mediterranean fever].

[Article in Hebrew]

Migdal A, Langevitz P, Padeh S, Pras E, Zemer D, Zaks N, Livneh A, Pras M.

PMID: 9418342 [Indexed for MEDLINE]

5029. Arch Esp Urol. 1997 Sep;50(7):800-1.

[Recurrent hydrocele in a patient with familial mediterranean fever].

[Article in Spanish]

Ferrero Doria R(1), Guzmán Martínez-Valls P, López Alba J, Tomás Ros M, Rico Galiano JL, Rodríguez de Ledesma JM, Fontana Compiano LO.

Author information:

(1)Servicio de Urología, Hospital General Universitario de Murcia, España.

**OBJECTIVE:** To report an uncommon case of familial Mediterranean fever with urological manifestations.

**METHODS/RESULTS:** A case of recurrent hydrocele in a patient with familial Mediterranean fever is described.

**CONCLUSIONS:** Although familial Mediterranean fever is characterized by an acute febrile stage and involvement of the serosa, it may manifest as recurrent hydrocele due to involvement of the urological serosa, as in the case described herein.

PMID: 9412388 [Indexed for MEDLINE]

5030. Br J Rheumatol. 1997 Oct;36(10):1118-21.

An unusual case of familial Mediterranean fever.

Steuer A(1), Leonard N, Ahmed FB, Price AB, Gumpel JM.

Author information:

(1)Department of Rheumatology, Northwick Park and St Mark's Hospital, Harrow.

Familial Mediterranean fever (FMF) is an inherited disorder characterized by recurrent self-limiting attacks of joint, chest and abdominal pain associated with fever. The most serious complication in FMF is the development of amyloidosis, which usually leads to death from renal failure within a year. The use of colchicine has dramatically reduced this complication. We describe a 56-yr-old female patient with FMF in whom the arthropathy became the dominant clinical feature, resulting in the development of an erosive large and small joint arthritis during the course of the disease. The patient was treated with colchicine, but despite this, later developed amyloidosis confirmed on rectal biopsy, and chlorambucil was added to her treatment. For 10 yr, she also suffered intermittent abdominal pain and had terminal ileal changes suggestive of Crohn's disease. However, she was found to have ischaemic colitis at post mortem secondary to amyloidosis. Ischaemic bowel disease is an extremely unusual event in FMF. Other factors which may have contributed to the terminal ischaemia in

this patient include anaemia secondary to blood loss and a drug-induced myelodysplasia, as well as hypotension during the final septicaemic illness. Clinicians should consider an ischaemic colitis as a possible differential diagnosis of abdominal pain in patients with FMF even in the absence of other clinical evidence of systemic amyloidosis.

PMID: 9374932 [Indexed for MEDLINE]

5031. Anaesthesia. 1997 Nov;52(11):1116-7.

Pain relief in familial Mediterranean fever.

Tunca M.

Comment on

Anaesthesia. 1997 May;52(5):483-6.

PMID: 9404182 [Indexed for MEDLINE]

5032. Hum Genet. 1997 Dec;101(2):238-42.

Familial Mediterranean fever: clastogenic plasma factors correlated with increased O<sub>2</sub>(-)-production by neutrophils.

Sarkisian T(1), Emerit I, Arutyunyan R, Levy A, Cernjavski L, Filipe P.

Author information:

(1)Department of Genetics, Yerevan State University, Armenia.

Familial Mediterranean fever (FMF) is an autosomal recessive disease predominantly affecting Armenians and non-Ashkenazi Jews. The disease begins in childhood with paroxysmal attacks of pain and fever accompanied by peritonitis, pleuritis, and synovitis. During the acute phase, there is a massive influx of polymorphonuclear leukocytes into the serosal membranes, connected with degranulation of the neutrophils and with secretion of lysosomal enzymes and

pyrogenic substances. An increase in the lipoxygenase product, leukotriene B<sub>4</sub>, a chemotactic agent, and a decrease in the activity of the inhibitor of chemotaxis, C5a, in serosal fluids have been considered responsible. Previous work from our laboratories had shown that the chromosomal instability observed in blood cultures of patients with FMF is secondary to circulating clastogenic factors (CFs), and that the antioxidant enzyme superoxide dismutase, as well as lipoxygenase inhibitors, reduce the chromosome damaging effects. CFs are observed in chronic inflammatory diseases and in various other pathological conditions accompanied by oxidative stress. Similar clastogenic materials were found in supernatants of neutrophils and monocytes after a respiratory burst and were shown to contain lipid peroxidation products and cytokines. In the present study we compared the clastogenic effects exerted by plasma ultrafiltrates from 20 adult patients with FMF to the unstimulated O<sub>2</sub>- production of their neutrophils. In comparison to 20 age- and sex-matched controls, which were studied simultaneously, the O<sub>2</sub>- production by patient's neutrophils was routinely higher than that of controls. The clastogenic effects of patient's plasma, expressed as the number of chromosomal aberrations induced in test cultures of healthy donors, were correlated with the importance of O<sub>2</sub>- production by their neutrophils ( $r = 0.5235$ ). Even if the relative contribution of disturbance in arachidonic acid metabolism, neutrophil activation, and CF formation in the disease process remains unclear, the demonstration of oxidative stress in this genetic disorder suggests the use of antioxidants and free radical scavengers, in particular during acute attacks, when the classical colchicine treatment is without effect.

PMID: 9402978 [Indexed for MEDLINE]

5033. Br J Rheumatol. 1997 Nov;36(11):1228-30.

Protracted arthritis of familial Mediterranean fever (an unusual complication).

Yalçinkaya F(1), Tekin M, Tümer N, Ozkaya N.

Author information:

(1)Department of Paediatric Nephrology, Faculty of Medicine, Ankara University, Turkey.

An unusual case of familial Mediterranean fever and vasculitis in which the

patient developed amyloidosis and had protracted arthritis persisting for years is presented. The long-standing arthritis did not respond to corticosteroid and colchicine therapy, but an excellent response to synovectomy was achieved.

PMID: 9402871 [Indexed for MEDLINE]

5034. N Engl J Med. 1997 Nov 20;337(21):1548-9.

The familial Mediterranean fever gene--cloned at last.

Babior BM(1), Matzner Y.

Author information:

(1)Scripps Research Institute, La Jolla, CA 92037, USA.

Comment in

N Engl J Med. 1998 Apr 2;338(14):992-3.

DOI: 10.1056/NEJM199711203372112

PMID: 9366590 [Indexed for MEDLINE]

5035. Semin Arthritis Rheum. 1997 Oct;27(2):67-72.

Seronegative spondyloarthropathy in familial Mediterranean fever.

Langevitz P(1), Livneh A, Zemer D, Shemer J, Pras M.

Author information:

(1)Heller Institute of Medical Research, Sheba Medical Center, Tel-Hashomer, Israel.

To define a possible association between familial Mediterranean fever (FMF) and seronegative spondyloarthropathy (SNSA) and to study features of SNSA in FMF patients, we screened for the presence and manifestations of SNSA in 3,000 FMF patients attending the National Center for FMF in our institution. This population included 160 patients with chronic arthritis, most who suffered from

SNSA. Patients were considered to suffer from SNSA if they had chronic arthritis, inflammatory back/neck pain, and sacroiliitis. Patients who had other diseases associated with SNSA were excluded. Eleven patients, nine men and two women, with chronic monoarthritis or oligoarthritis, grade 2 (four patients) or grades 3 to 4 (seven patients), sacroiliitis, and inflammatory back pain met the criteria for diagnosis of SNSA of FMF. These patients were rheumatoid factor (RF) and HLA-B27 negative. In seven patients, spondyloarthropathy developed while they received colchicine, and in four before colchicine. Most patients responded to treatment with nonsteroidal antiinflammatory drugs, but three required second-line agents. These findings suggest that SNSA is one of the musculoskeletal manifestations of FMF that may occur despite colchicine therapy and requires specific treatment.

PMID: 9355205 [Indexed for MEDLINE]

5036. Genomics. 1997 Sep 15;44(3):280-91.

A high-resolution genetic map of the familial Mediterranean fever candidate region allows identification of haplotype-sharing among ethnic groups.

Balow JE Jr(1), Shelton DA, Orsborn A, Mangelsdorf M, Aksentijevich I, Blake T, Sood R, Gardner D, Liu R, Pras E, Levy EN, Centola M, Deng Z, Zaks N, Wood G, Chen X, Richards N, Shohat M, Livneh A, Pras M, Doggett NA, Collins FS, Liu PP, Rotter JI, Kastner DL, et al.

Author information:

(1)Arthritis and Rheumatism Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, Maryland 20892-1820, USA.

Familial Mediterranean fever (FMF) is a recessive disorder of inflammation caused by mutations in a gene (designated MEFV) on chromosome 16p13.3. We have recently constructed a 1-Mb cosmid contig that includes the FMF critical region. Here we show genotype data for 12 markers from our physical map, including 5 newly identified microsatellites, in FMF families. Intrafamilial recombinations placed MEFV in the approximately 285 kb between D16S468/D16S3070 and D16S3376. We observed significant linkage disequilibrium in the North African Jewish population, and historical recombinants in the founder haplotype placed MEFV between D16S3082 and D16S3373 (approximately 200 kb). In smaller panels of Iraqi

Jewish, Arab, and Armenian families, there were significant allelic associations only for D16S3370 and D16S2617 among the Armenians. A sizable minority of Iraqi Jewish and Armenian carrier chromosomes appeared to be derived from the North African Jewish ancestral haplotype. We observed a unique FMF haplotype common to Iraqi Jews, Arabs, and Armenians and two other haplotypes restricted to either the Iraqi Jewish or the Armenian population. These data support the view that a few major mutations account for a large percentage of the cases of FMF and suggest that some of these mutations arose before the affected Middle Eastern populations diverged from one another.

PMID: 9325049 [Indexed for MEDLINE]

5037. Br J Rheumatol. 1997 Sep;36(9):1005-8.

The efficacy of interferon alpha on colchicine-resistant familial Mediterranean fever attacks: a pilot study.

Tunca M(1), Tankurt E, Akbaylar Akpinar H, Akar S, Hizli N, Gönen O.

Author information:

(1)Department of Internal Medicine, Dokuz Eylül University School of Medicine, Balçova, Izmir, Turkey.

About a quarter of familial Mediterranean fever (FMF) patients have recurrent painful attacks of polyserositis despite regular colchicine treatment. There is no known alternative drug for colchicine-resistant cases. We had previously observed a patient with FMF whose painful attacks disappeared during the 6 month period of interferon alpha (IFN) treatment for his chronic hepatitis B. The objective of the present study was to investigate the possible beneficial effect of IFN on these episodes. Twenty-one consecutive attacks in seven adult patients with FMF were treated at early onset with IFN, the dosage being 3-10 million I U s.c. Eighteen of the 21 attacks could be halted in a mean time of 3.05 h, while the intensity of abdominal pain remained very low. Observed side-effects were generally mild and acceptable. IFN may be a useful adjunct for the treatment of colchicine-resistant attacks in FMF patients.



PMID: 9376975 [Indexed for MEDLINE]

5038. Arthritis Rheum. 1997 Oct;40(10):1879-85.

Criteria for the diagnosis of familial Mediterranean fever.

Livneh A(1), Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, Migdal A, Padeh S, Pras M.

Author information:

(1)Sheba Medical Center, Tel-Hashomer, Israel.

Comment in

Arthritis Rheum. 1998 Aug;41(8):1516-7.

**OBJECTIVE:** To establish a new set of criteria for the diagnosis of familial Mediterranean fever (FMF).

**METHODS:** Twenty-seven features and manifestations typical of FMF were studied to determine their prevalence in 105 patients with FMF and 106 controls. Diagnosis of FMF in the study group was based on clinical judgment. Controls were patients with a variety of other diseases who presented to the emergency room or outpatient clinics with recurrent episodes of pain in body sites usually involved in FMF attacks. Manifestations observed to be significantly more common in FMF patients than in controls were incorporated into the rule proposed for diagnosis of FMF, based on a model of major, minor, and supportive criteria.

**RESULTS:** Two sets of diagnostic criteria were established. A conservative criteria set for diagnosis of FMF was based on the presence of 1 major or 2 minor criteria, or 1 minor plus 5 supportive criteria, and a simple criteria set for diagnosis of FMF required 1 major or 2 minor criteria. The sensitivity and specificity of these 2 criteria sets were >95% and >97%, respectively.

**CONCLUSION:** The proposed new sets of criteria were highly sensitive and specific, and could be used to readily diagnose FMF and to distinguish FMF from other periodic febrile diseases.

DOI: 10.1002/1529-0131(199710)40:10<1879::AID-ART23>3.0.CO;2-M

PMID: 9336425 [Indexed for MEDLINE]

5039. Dig Dis Sci. 1997 Sep;42(9):1959-63.

Colchicine is an effective treatment for patients with chronic constipation: an open-label trial.

Verne GN(1), Eaker EY, Davis RH, Sninsky CA.

Author information:

(1)Gainesville Veterans Affairs Medical Center, and Department of Medicine, University of Florida College of Medicine, 32610, USA.

Chronic constipation is a common clinical condition that frequently does not respond to routine therapeutic measures. We hypothesized that colchicine would be effective in this condition because we reported that it stimulates intestinal motility in rats and commonly causes diarrhea in patients taking the drug for either gouty arthritis or Familial Mediterranean fever. We prospectively studied seven patients with chronic constipation who were refractory to medical therapy and treated them with oral colchicine 0.6 mg per os three times a day for eight weeks in an open-label pilot study. During the study, the mean number of spontaneous bowel movements significantly increased ( $P < 0.05$ ) from  $1.7 \pm 0.5$  noted during routine therapy of constipation with laxatives and enemas to  $6.4 \pm 0.7$  per week; mean colonic transit time significantly ( $P < 0.05$ ) decreased from  $58.1 \pm 2.5$  to  $47.1 \pm 5.0$  hr; and symptoms of abdominal pain, nausea, and bloating significantly ( $P < 0.05$ ) improved during therapy with colchicine. Oral colchicine (0.6 mg three times a day) therapy appears to be an a promising treatment for chronic constipation and a placebo-controlled trial is indicated to confirm these findings.

PMID: 9331162 [Indexed for MEDLINE]

5040. Nat Genet. 1997 Sep;17(1):25-31.

A candidate gene for familial Mediterranean fever.

French FMF Consortium.

Collaborators: Bernot A, Clepet C, Dasilva C, Devaud C, Petit JL, Caloustian C,

Cruaud C, Samson D, Pulcini F, Weissenbach J, Heilig R, Notanicola C, Domingo C, Rozenbaum M, Benchetrit E, Topaloglu R, Dewalle M, Dross C, Hadjari P, Dupont M, Demaille J, Touitou I, Smaoui N, Nedelec B, Méry JP, Chaabouni H, Delpech M, Grateau G.

Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by attacks of fever and serositis. In this paper, we define a minimal co-segregating region of 60 kb containing the FMF gene (MEFV) and identify four different transcript units within this region. One of these transcripts encodes a new protein (marenostrin) related to the ret-finger protein and to butyrophilin. Four conservative missense variations co-segregating with FMF have been found within the MEFV candidate gene in 85% of the carrier chromosomes. These variations, which cluster at the carboxy terminal domain of the protein, were not present in 308 control chromosomes, including 162 validated non-carriers. We therefore propose that the sequence alterations in the marenostrin protein are responsible for the FMF disease.

DOI: 10.1038/ng0997-25

PMID: 9288094 [Indexed for MEDLINE]

5041. Cell. 1997 Aug 22;90(4):797-807.

Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. The International FMF Consortium.

[No authors listed]

Familial Mediterranean fever (FMF) is a recessively inherited disorder characterized by dramatic episodes of fever and serosal inflammation. This report describes the cloning of the gene likely to cause FMF from a 115-kb candidate interval on chromosome 16p. Three different missense mutations were identified in affected individuals, but not in normals. Haplotype and mutational analyses disclosed ancestral relationships among carrier chromosomes in populations that have been separated for centuries. The novel gene encodes a 3.7-kb transcript that is almost exclusively expressed in granulocytes. The predicted protein, pyrin, is a member of a family of nuclear factors homologous to the Ro52 autoantigen. The cloning of the FMF gene promises to shed light on the regulation of acute inflammatory responses.

PMID: 9288758 [Indexed for MEDLINE]

5042. Harefuah. 1997 Aug;133(3-4):100-2.

[Colchicine as therapy for recurrent pericarditis].

[Article in Hebrew]

Adler Y, Shoenfeld Y.

PMID: 9332074 [Indexed for MEDLINE]

5043. J Neurol. 1997 Aug;244(8):510-4.

Familial Mediterranean fever and multiple sclerosis.

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Author information:

(1)Department of Neurology, Hacettepe University Hospitals, Ankara, Turkey.  
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Central nervous system (CNS) manifestations of familial Mediterranean fever (FMF) are extremely rare. These include pseudotumor cerebri, optic neuritis, CNS complications of polyarteritis nodosa type vasculitis, or hypercoagulable states secondary to renal amyloidosis, recurrent aseptic meningitis, and amyloid ophthalmoplegia. We present three patients with FMF whose neurological findings and magnetic resonance imaging (MRI) abnormalities resembled multiple sclerosis (MS). These two conditions in the same patient could arise from either coincidence or an unknown pathophysiological relationship. Both explanations are equally speculative and this matter needs further study, especially to investigate MRI features in FMF patients without CNS symptoms.

PMID: 9309558 [Indexed for MEDLINE]

5044. Arch Dis Child. 1997 Aug;77(2):155-7.

Serum prolactin in coeliac disease: a marker for disease activity.

Reifen R(1), Buskila D, Maislos M, Press J, Lerner A.

Author information:

(1)School of Nutritional Sciences, Hebrew University of Jerusalem, Rehovot.

Prolactin, a polypeptide hormone of anterior pituitary origin, has pronounced physiological effects on growth, reproduction, and osmoregulation. Increasing evidence indicates that prolactin also has an immunomodulatory influence on the immune system. The status of prolactin in patients with coeliac disease was investigated by obtaining serum samples from 48 patients with active and non-active coeliac disease. These were compared with samples from 20 children with familial Mediterranean fever and 65 normal controls. Serum prolactin in patients with active coeliac disease was significantly higher than in the other groups studied and reference values. Serum prolactin correlated well with the degree of mucosal atrophy and with the serum concentration of antiendomysial antibodies. Prolactin may play a part in immune modulation in the intestinal damage of coeliac disease and serve as a potential marker for disease activity.

PMCID: PMC1717265

PMID: 9301358 [Indexed for MEDLINE]

5045. Eur J Pediatr. 1997 Aug;156(8):619-23.

Familial Mediterranean fever in children: report of a large series and discussion of the risk and prognostic factors of amyloidosis.

Saatçi U(1), Ozen S, Ozdemir S, Bakkaloglu A, Besbas N, Topaloglu R, Arslan S.

Author information:

(1)Hacettepe University Medical Faculty, Department of Paediatric Nephrology and

Rheumatology, Ankara, Turkey.

Familial Mediterranean fever (FMF) is a genetically transmitted disease characterized by recurrent attacks of fever and serositis. The most important complication of this disease is the development of amyloidosis. We present our analysis of 425 FMF patients without and 180 with amyloidosis (123 FMF having amyloidosis type I and 57 FMF having amyloidosis type II). The male female ratio was higher in the amyloidosis population (111/69) when compared to the FMF population (225/200) ( $P = 0.048$ ). Consanguinity rate was the same among FMF and amyloidosis groups. However, a family history of amyloidosis was significantly more frequent in the amyloidosis group ( $P = 0.00001$ ). Multivariate analysis has revealed that in FMF patients, the presence of a family history of amyloidosis plus consanguinity has a 6.04 fold increased risk of amyloidosis ( $P < 0.0001$ ). The 5-year chronic renal failure free survival was 43.1% and 18.7% in type I and type II amyloidosis, respectively. The time interval to develop chronic renal failure after the development of amyloidosis was 4.8 in type I and 3.0 years in type II, respectively. We found ten cases of Henoch-Schönlein Purpura and nine of polyarteritis nodosa among our patients. The significance of the association between FMF and vasculitis awaits to be clarified. Among the FMF patients put on colchicine therapy (435), only 10 (2.3%) have developed amyloidosis confirming that this drug protects from amyloidosis. **CONCLUSION:** Since the presence of a familial history of amyloidosis has been defined as the most important risk factor in the development of amyloidosis, we suggest that additional genetic factors may be operative in the development of amyloidosis.

PMID: 9266193 [Indexed for MEDLINE]

5046. J Rheumatol. 1997 Aug;24(8):1558-63.

Familial Mediterranean fever and hyperimmunoglobulinemia D syndrome: two diseases with distinct clinical, serologic, and genetic features.

Livneh A(1), Drenth JP, Klasen IS, Langevitz P, George J, Shelton DA, Gumucio DL, Pras E, Kastner DL, Pras M, van der Meer JW.

Author information:

(1)Heller Institute of Medical Research, Sheba Medical Center, Tel-Hashomer,

Israel.

**OBJECTIVE:** To determine whether the 2 periodic febrile syndromes familial Mediterranean fever (FMF) and hyperimmunoglobulinemia D syndrome (HIDS) are distinct diseases.

**METHODS:** Clinical manifestations of the diseases were analyzed by physicians experienced with FMF and HIDS. Serum immunoglobulin (Ig) levels were studied in 70 patients with FMF using nephelometry or ELISA and compared with Ig levels in 50 patients with HIDS. Genetic linkage of HIDS with the chromosome 16 polymorphic locus RT70, currently used for refined localization of the FMF susceptibility gene (MEFV), was studied in 9 HIDS families (18 patients) using polymerase chain reaction amplification and gel electrophoresis.

**RESULTS:** The main clinical features distinguishing FMF from HIDS were lymphadenectomy, skin eruption, and symmetrical oligoarthritis in HIDS, and monoarthritis, peritonitis, and pleuritis in FMF. Increased IgG levels were found in 12 patients with FMF (17%), IgA in 16 (23%), IgM in 9 (13%), and IgD in 9 (13%), significantly lower than the prevalence reported for HIDS. We found no evidence for genetic linkage between HIDS and the chromosome 16 marker RT70.

**CONCLUSION:** HIDS and FMF are different entities, clinically, immunologically, and genetically.

PMID: 9263151 [Indexed for MEDLINE]

5047. Clin Exp Rheumatol. 1997 Jul-Aug;15(4):355-60.

Quality of life of patients with familial Mediterranean fever.

Buskila D(1), Zaks N, Neumann L, Livneh A, Greenberg S, Pras M, Langevitz P.

Author information:

(1)Rheumatic Unit, Soroka Medical Center, Ben-Gurion University of the Negev, Beer Sheva, Israel.

**OBJECTIVE:** The aim of the present study was to assess the quality of life (QOL) of patients with Familial Mediterranean Fever (FMF) and to explore its possible contributing factors.

**METHODS:** One hundred and two FMF patients were evaluated using a QOL Scale, and

were compared to 124 healthy controls. The QOL scale includes 16 items, each measured on a 7-point scale (7 indicating maximal satisfaction).

RESULTS: The total QOL score of FMF patients was significantly lower than that of the controls: 81.6 +/- 19.2 vs 88.0 +/- 12.8 ( $p < 0.01$ ). Male and female patients reported similar QOL scores. QOL was inversely correlated with the number of FMF attacks in the last year ( $r = -0.302$ ,  $p = 0.002$ ), and with the number of FMF hospitalizations ( $r = -0.238$ ,  $p = 0.017$ ). Patients with widespread pain, sleep disturbances and headaches had significantly lower QOL scores than patients without them.

CONCLUSIONS: The QOL of FMF patients was found to be impaired compared to healthy controls. Further studies are needed to determine the exact factors affecting the quality of life of FMF patients.

PMID: 9272294 [Indexed for MEDLINE]

5048. J Med Genet. 1997 Jul;34(7):573-8.

Genetic linkage study of familial Mediterranean fever (FMF) to 16p13.3 and evidence for genetic heterogeneity in the Turkish population.

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Author information:

(1)Department of Surgery, University of Connecticut Health Center, Farmington 06030-1110, USA.

Familial Mediterranean fever (FMF) is an autosomal recessive condition that is almost entirely restricted to the non-Askhenazi Jews, Arabs, Armenians, and Turks. Genetic linkage study of a large group of non-Turkish families has previously mapped the FMF locus to the 16p13.3 region and shown that this locus resides 0.305 cM distal to D16S246. Furthermore, allelic association has also been shown with D16S3070 (75%) and D16S3275 (66%). However, no genetic heterogeneity has been described for any of the three major reported groups of FMF families. Here, we describe the genetic linkage relationship of the fourth major group of Turkish families and report the first evidence for genetic heterogeneity of this condition. Two point linkage analysis and haplotype inspection of 15 DNA markers from the reported region of the FMF locus identified



tight linkage in a group of six Turkish FMF families. A maximum lod score of 9.115 at  $\theta = 0.00$  was observed for D16S3024. Nine other DNA markers provided similar evidence of linkage with lod score values of above 5.21. However, two other FMF families were completely unlinked to this region of chromosome 16. Haplotype construction of DNA markers in five consanguineous linked families showed that a segment of homozygosity has been conserved for D16S3070 and D16S2617. No other DNA markers showed any such conservation. Therefore, we suggested that these two markers reside in close proximity to the FMF locus. Furthermore, we observed 80% allelic association with D16S2617 but no association with D16S3070 or any other DNA markers from the FMF critical region. In summary, we conclude that our Turkish families are also linked to the reported FMF locus at 16p13.3, there is a genetic heterogeneity for this condition at least in our group of Turkish families, and D16S2617 is in linkage disequilibrium in the Turkish FMF families. Combination of this study with previously published observations suggests that the FMF locus resides between D16S246 and D16S3070/D16S2617 and within a region of about 250-300 kb.

PMCID: PMC1050998

PMID: 9222966 [Indexed for MEDLINE]

5049. J Clin Gastroenterol. 1997 Jun;24(4):276-9.

Peritoneal mesothelioma in recurrent familial peritonitis.

Gentiloni N(1), Febbraro S, Barone C, Lemmo G, Neri G, Zannoni G, Capelli A, Gasbarrini G.

Author information:

(1)Institute of Internal Medicine and Geriatrics, Catholic University of the Sacred Heart, Rome, Italy.

A 39-year-old man had a 2-year history of fatigue, weight loss, drug-resistant ascites, and decreased intestinal motility. During adolescence he began to suffer frequent episodes of acute benign peritonitis that spontaneously subsided at age 35. The fact that his younger brother was taking colchicine for the same symptoms led us to diagnose familial Mediterranean fever (FMF). The medical workup revealed uniform thickening of the intestinal wall with no signs of amyloidosis.

Exploratory laparotomy revealed diffuse peritoneal mesothelioma that proved to be unresponsive to chemotherapy. There was no history of asbestos exposure. It is probable that the chronic peritoneal inflammation was responsible for the development of this tumor, although in almost all cases of FMF this phenomenon causes only limited peritoneal fibrosis or, less commonly, encapsulating peritonitis. A computerized search of the literature indicates that this is the second report of peritoneal mesothelioma associated with FMF.

PMID: 9252860 [Indexed for MEDLINE]

5050. Eur J Pediatr. 1997 Jun;156(6):505-6.

Familial Mediterranean fever and polyarteritis nodosa: experience of five paediatric cases. A causal relationship or coincidence?

Tinaztepe K, Güçer S, Bakkaloğlu A, Tinaztepe B.

PMID: 9208253 [Indexed for MEDLINE]

5051. Am J Kidney Dis. 1997 Jun;29(6):942-6.

Light chain deposition disease complicating familial Mediterranean fever.

Vella JP(1), Doyle GD, Campbell E, Walshe JJ.

Author information:

(1)Division of Nephrology, Beaumont Hospital, Dublin, Ireland.

Familial Mediterranean fever (fMf) is an inherited condition characterized by polyserositis and is sometimes complicated by AA renal amyloidosis leading to nephrotic syndrome and renal failure. We present a case of a man with fMf who presented with rapidly progressive renal failure caused by light chain deposition disease. This disease association has not previously been described in the medical literature.

PMID: 9186082 [Indexed for MEDLINE]

5052. Ned Tijdschr Geneeskd. 1997 May 31;141(22):1106-9.

[Medicine in Turkey, with special reference to nephrology].

[Article in Dutch]

Dorhout Mees EJ(1).

Author information:

(1)Ege Universitesi Lojmanlari, Izmit, Turkije.

The stormy development of Turkey in this century resulted in a drastic decrease of illiteracy and in a craving for knowledge among the younger generations. Qualitatively good students are admitted to universities. In the last 25 years, 47 new universities were founded (8 of them private ones), partly for political reasons. Teachers of medicine are underpaid, so that many earn extra money by working in a private practice. The results of medical teaching are adequate, owing in part to quality and motivation of students and interns. Much research is being subsidized by the Turkish Institute for Scientific and Technical Research, Tübitak, but bureaucracy inhibits originality. Research and postgraduate training are increasingly controlled by the pharmaceutical industry. Primary medical care is underdeveloped. The quality of medical treatment is technically adequate; modern diagnostic and surgical methods are available in all major centres. There is much private enterprise in health care (private clinics, private laboratories, research centres, universities and pharmacies). The latest drugs are available and given preference in prescribing. In Southeast Turkey, populated by Kurds, however, the economy has come to a complete standstill and there is an enormous shortage of physicians and hospitals. The prevalence of renal diseases differs from that in the Netherlands: fewer cystic kidneys, less diabetic nephropathy and nephropathy due to analgetics, but more acute glomerulonephritis and amyloidosis due to familial Mediterranean fever. Haemodialysis, is one of the fastest-growing methods of treatment; peritoneal dialysis is rapidly gaining ground. Kidney transplantations have been performed regularly since 1975.

PMID: 9380139 [Indexed for MEDLINE]

5053. Praxis (Bern 1994). 1997 May 28;86(22):952-6.

[Follow-up and therapy of acute colchicine poisoning].

[Article in German]

Stern N(1), Kupferschmidt H, Meier-Abt PJ.

Author information:

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Colchicine poisoning is a rare event. Its outcome is, compared to other drug intoxications, often serious or even fatal. Intoxications with colchicine may occur by ingestion of tablets as well as by consumption of meadow saffron leaves (*Colchicum autumnale*) that are often mistakenly collected instead of the leaves of ramson herb (*Allium ursinum*). Colchicine poisoning typically shows three phases: initially gastrointestinal symptoms predominate, in the second phase multiorgan failure may occur possibly leading to death. In case the patient survives, the third phase of recovery follows during which the patients often present with hair loss. The fatal dose of acute colchicine poisoning is estimated at about 0.9 mg/kg. Since hemodialysis and hemoperfusion are not effective measures because of the high volume of distribution, an aggressive primary decontamination with gastric lavage and activated charcoal is required as early as possible. A promising new aspect in the treatment of heavy colchicine overdose is the immunotherapy with colchicine-specific fab-fragments. At present this treatment is still in an experimental stage and has been applied so far to one patient with beneficial effects. Unfortunately colchicine-specific antibodies are not yet commercially available.

PMID: 9289794 [Indexed for MEDLINE]

5054. Genomics. 1997 May 15;42(1):83-95.

Construction of a 1-Mb restriction-mapped cosmid contig containing the candidate

region for the familial Mediterranean fever locus (MEFV) on chromosome 16p 13.3.

Sood R(1), Blake T, Aksentijevich I, Wood G, Chen X, Gardner D, Shelton DA, Mangelsdorf M, Orsborn A, Pras E, Balow JE Jr, Centola M, Deng Z, Zaks N, Chen X, Richards N, Fischel-Ghodsian N, Rotter JJ, Pras M, Shohat M, Deaven LL, Gumucio DL, Callen DF, Richards RI, Doggett NA, et al.

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In this paper we describe the assembly and restriction map of a 1.05-Mb cosmid contig spanning the candidate region for familial Mediterranean fever (FMF), a recessively inherited disorder of inflammation localized to 16p13.3. Using a combination of cosmid walking and screening for P1, PAC, BAC, and YAC clones, we have generated a contig of genomic clones spanning approximately 1050 kb that contains the FMF critical region. The map consists of 179 cosmid, 15 P1, 10 PAC, 3 BAC, and 17 YAC clones, anchored by 27 STS markers. Eight additional STSs have been developed from the approximately 700 kb immediately centromeric to this genomic region. Five of the 35 STSs are microsatellites that have not been previously reported. NotI and EcoRI mapping of the overlapping cosmids, hybridization of restriction fragments from cosmids to one another, and STS analyses have been used to validate the assembly of the contig. Our contig totally subsumes the 250-kb interval recently reported, by founder haplotype analysis, to contain the FMF gene. Thus, our high-resolution clone map provides an ideal resource for transcriptional mapping toward the eventual identification of this disease gene.

PMID: 9177779 [Indexed for MEDLINE]

5055. Baillieres Clin Rheumatol. 1997 May;11(2):335-55.

Other forms of vasculitis and pseudovasculitis.

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Author information:

(1)Department of Internal Medicine, University of Istanbul, Cerrahpaşa Medical Faculty, Cerrahpaşa, Turkey.

Behçet's syndrome can involve all sizes and kinds of blood vessels. There is an association between arterial involvement and venous thrombosis. Pulmonary arterial aneurysms and neurological involvement have a definite influence on mortality. Male sex and young age are indicators of a more severe disease course. Immunosuppressive treatment early in the disease may affect the long term prognosis favourably. Patients with familial Mediterranean fever may develop manifestations of vasculitis. The most common associations are with Schönlein-Henoch purpura and polyarteritis nodosa. In some patients the diagnosis of vasculitis precedes that of familial Mediterranean fever. Kawasaki disease, although rare, can be seen in adults. The coronary sequela of childhood disease can affect the prognosis later in life. Many conditions, like myxoma, cholesterol embolism, calciphylaxis may mimic vasculitic syndromes. These conditions should always be kept in mind because their pathophysiology and treatment are different from true vasculitides.

PMID: 9220081 [Indexed for MEDLINE]

5056. Anaesthesia. 1997 May;52(5):483-6.

Pain relief with oral cannabinoids in familial Mediterranean fever.

Holdcroft A(1), Smith M, Jacklin A, Hodgson H, Smith B, Newton M, Evans F.

Author information:

(1)Hammersmith Hospital, London, UK.

Comment in

Anaesthesia. 1997 Nov;52(11):1116-7.

Cannabinoids have analgesic and, possibly, anti-inflammatory properties but their clinical use has been restricted by legislation. This is the first United Kingdom report of the controlled use of a standardised pharmaceutical preparation of cannabinoids in capsular form. The therapy was assessed in a patient with

familial Mediterranean fever, who presented with chronic relapsing pain and inflammation of gastrointestinal origin. After determining a suitable analgesic dosage, a double-blind placebo-controlled cross-over trial was conducted using 50 mg tetrahydrocannabinol daily in five doses in the active weeks and measuring effects on parameters of inflammation and pain. Although no anti-inflammatory effects of tetrahydrocannabinol were detected during the trial, a highly significant reduction ( $p < 0.001$ ) in additional analgesic requirements was achieved. Future study designs can now incorporate prescribable forms of cannabinoids but the choice of previous cannabis users only as patients has clinical limitations. Cannabis naive patients would tolerate controlled investigations but may generate medicolegal problems.

PMID: 9165969 [Indexed for MEDLINE]

5057. J Med Genet. 1997 May;34(5):375-81.

Genotypic diagnosis of familial Mediterranean fever (FMF) using new microsatellite markers: example of two extensive non-Ashkenazi Jewish pedigrees.

Dupont M(1), Dross C, Smaoui N, Nedelec B, Grateau G, Clépet C, Gourdier I, Koné-Paut I, Delpech M, Demaille J, Touitou I.

Author information:

(1)Laboratoire de Génétique Moléculaire et Chromosomique, Hôpital A de Villeneuve, Montpellier, France.

Familial Mediterranean fever is an autosomal recessive disease characterised by multiple attacks of serosal inflammation in the absence of treatment. In the absence of timely diagnosis, renal amyloidosis is a life threatening complication. The diagnosis is often missed because no specific test is available. Early colchicine treatment prevents attacks and renal complications. The FMF gene (MEF) has been mapped to chromosome 16p 13.3 but has not yet been identified. We compared the suitability of a series of microsatellite markers (four of them were new) and propose the routine use of seven of these markers, exhibiting alleles in strong linkage disequilibrium with the disease and informative in 100% of diagnosed patients. Moreover, the discovery of a homozygous status for the 3-3-9 (or 3-3-18) haplotype at the core loci (D16S3070,

D16S3082, and D16S3275), which was found in 73% non-Ashkenazi Jewish patients, points to a diagnosis of FMF, even in sporadic cases, with a risk of error of only  $2.10(-5)$ . Two extensive pedigrees covering most indications for genetic counselling are presented, showing that it is now possible both prospectively and retrospectively to identify members likely to have MEF mutations. With the help of this accurate test, colchicine treatment can be better targeted, especially where the symptomatology is mild or atypical.

PMCID: PMC1050944

PMID: 9152834 [Indexed for MEDLINE]

5058. Ann Med. 1997 Apr;29(2):175-9.

Rare vasculitic syndromes.

Dillon MJ(1).

Author information:

(1)Great Ormond Street Hospital for Children, London, UK. M.Dillon@ich.ucl.ac.uk

Vasculitis can and does occur in childhood. Apart from the common vasculitides (Henoch-Schönlein purpura, hypersensitivity angiitis and Kawasaki disease) there are a number of important but comparatively rare disorders affecting children. These include macroscopic and microscopic polyarteritis, cutaneous polyarteritis, Wegener's granulomatosis, Churg-Strauss syndrome, primary angiitis of the central nervous system, hypocomplementaemic urticarial vasculitis, vasculitis associated with various connective tissue disorders, Takayasu's disease and vasculitis associated with conditions such as Behcet's syndrome, familial Mediterranean fever and Cogan's syndrome. Distinguishing these conditions from other disorders is often difficult and requires clinical acumen and appropriate investigative procedures. With modern therapeutic agents it is possible to implement appropriate therapy but in spite of this, there remains a not inconsequential morbidity and mortality.

PMID: 9187236 [Indexed for MEDLINE]



5059. *Pediatr Nephrol*. 1997 Apr;11(2):210-2.

Renal, gastric and thyroidal amyloidosis due to familial Mediterranean fever.

Kavukçu S(1), Türkmen M, Eroğlu Y, Canda T, Yörükoğlu K, Iğci E, Büyükgebiz A.

Author information:

(1)Department of Pediatrics, Faculty of Medicine, Dokuz Eylül University, Izmir, Turkey.

Chronic renal failure developed in a 10-year-old girl due to renal amyloidosis secondary to familial Mediterranean fever (FMF). During management of the chronic renal failure by hemodialysis and of FMF with colchicine, goiter and hypothyroidism were observed. Thyroid fine-needle aspiration and gastric endoscopic biopsies, performed when recurrent abdominal pain could not be controlled, revealed amyloid deposits in both thyroid and gastric tissues. After 6 months' therapy with colchicine and levothyroxine, there was no significant change in the thyroid volume. This is the first case in which gastric amyloidosis secondary to FMF in childhood has been demonstrated. Patients with amyloidosis secondary to FMF who have thyroid enlargement and unexplained gastrointestinal symptoms despite adequate therapy should be evaluated with imaging studies and biopsy examinations.

PMID: 9090667 [Indexed for MEDLINE]

5060. *Clin Exp Immunol*. 1997 Mar;107(3):574-7.

Colchicine derivatives inhibit neopterin production in human peripheral blood mononuclear cells (PBMC).

Altindag ZZ(1), Werner-Felmayer G, Sahin G, Wachter H, Fuchs D.

Author information:

(1)Institute for Medical Chemistry and Biochemistry, University of Innsbruck, Austria.

Colchicine is a microtubule disrupting agent, mostly used as treatment in various kinds of inflammatory diseases such as acute familial Mediterranean fever and Behcet's disease, as well as gout. In patients with familial Mediterranean fever treatment with colchicine induces a decline of urinary neopterin concentrations which indicates a decrease of cell-mediated immune activation. In this study, we investigated a potential effect of colchicine on the T cell/macrophage system in vitro. The human myelomonocytic cell line THP-1 and PBMC were treated with colchicine or the colchicine derivative, colcemide, in the presence or absence of 250 U/ml interferon-gamma (IFN-gamma) or 10 microg/ml lipopolysaccharide (LPS) for 48 h or 96 h. Colchicine and colcemide increased neopterin/protein production in unstimulated THP-1 cells, but no such effect was apparent in cells stimulated with IFN-gamma. By contrast, when PBMC were treated with colchicine or colcemide a significant reduction in neopterin formation was evident in cells without and with prestimulation by IFN-gamma or LPS. In parallel, reduced production of IFN-gamma was observed in PBMC. These data suggest that colchicine and colcemide are able to inhibit T cell activation within the cellular immune response.

PMCID: PMC1904601

PMID: 9067535 [Indexed for MEDLINE]

5061. J Rheumatol. 1997 Feb;24(2):323-7.

Vasculitis in familial Mediterranean fever.

Ozdogan H(1), Arisoy N, Kasapçapur O, Sever L, Calışkan S, Tuzuner N, Mat C, Yazici H.

Author information:

(1)Department of Rheumatology, Cerrahpaşa Medical Faculty, University of Istanbul, Turkey.

**OBJECTIVE:** To evaluate the frequency of vasculitis, mainly in the forms of Henoch-Schönlein purpura and polyarteritis nodosa (PAN), and to investigate the presence of occult blood in the first stool specimens after an abdominal attack in Turkish patients with familial Mediterranean fever (FMF).

**METHODS:** Review of the charts of 207 patients with FMF seen between 1983 and 1993 with respect to clinical vasculitis. A prospective study designed to test the

presence of occult blood in the first stool specimens obtained after abdominal attack and at least one week later in 36 patients with FMF compared with healthy and diseased controls.

RESULTS: There were 15 patients with Henoch-Schönlein purpura (7%), 2 with definite and one with probable PAN (1%), one of whom developed perirenal hematoma. The diagnosis of FMF was made after the onset of Henoch-Schönlein purpura in 9 and subsequent to the development of PAN in one patient. Occult blood was positive in the first stool specimens obtained after an attack in 17 of the 36 patients with FMF (47%), a finding not reported previously.

CONCLUSION: Vasculitis seems to be an important but not a widely recognized feature of FMF.

PMID: 9034991 [Indexed for MEDLINE]

5062. Klin Med (Mosk). 1997;75(12):14-7.

[Contemporary trends in the studies of pathogenesis of a periodic disease].

[Article in Russian]

Arutiunian VM(1), Akopian GS, Grigorian EG.

Author information:

(1)Kafedra vnutrennikh boleznei No. 2 Erevanskogo gosudarstvennogo meditsinskogo universiteta.

PMID: 9503804 [Indexed for MEDLINE]

5063. Adv Pediatr. 1997;44:389-428.

Periodic syndromes of childhood.

Arav-Boger R(1), Spier Z.

Author information:

(1) Dana Children Hospital, Tel-Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Israel.

Periodic syndromes of childhood comprise a large group of disorders that require long-term follow-up to be diagnosed. Several disorders have fixed rhythmicity and are therefore identified more easily. Other disorders are usually diagnosed after a prolonged follow-up and exclusion of other more common childhood diseases. In general, most of the periodic fever syndromes have a benign prognosis, and their symptomatology tends to improve in the long term. Periodic syndromes without fever or chronic pain syndromes constitute not only a diagnostic dilemma but also a therapeutic challenge. A general diagnostic approach to the periodic syndromes is outlined in Figure 1.

PMID: 9265977 [Indexed for MEDLINE]

5064. Z Rheumatol. 1997 Jan-Feb;56(1):40-2.

[Hyper-IgD-syndrome].

[Article in German]

Suschke J(1), Walther JU.

Author information:

(1) Kinderpoliklinik der Universität München.

We report on a 6-year-old Romanian girl with recently diagnosed hyper-IgD-syndrome. The leading symptom of this rare disease are periodic pyrexia, joint involvements (arthralgias/arthritis) and swollen lymph nodes. A permanent increase of alpha 1-acid glycoprotein fucosylation indicates persisting inflammation. Most important in differential diagnosis is familial Mediterranean fever. Therapy is merely supportive as yet, the long-term outlook seems good despite duration of the illness. CONCLUSION: the hyper-IgD-syndrome must be considered in cases of otherwise unexplained periodic fever.

PMID: 9173750 [Indexed for MEDLINE]

5065. Eur J Clin Pharmacol. 1997;52(1):27-30.

Chronic colchicine treatment does not impair glucose tolerance in familial Mediterranean fever patients.

Burstein R(1), Seidman DS, Zemer D, Shpilberg O, Arnon R, Epstein Y, Pras M.

Author information:

(1)Heller Institute of Medical Research, Sheba Medical Center, Tel Hashomer, Israel.

**OBJECTIVE:** To investigate a long-term colchicine treatment in inhibiting normal release of insulin, in response to a glucose load.

**SETTING:** The Heller Institute of Medical Research, Sheba Medical Center, Tel-Hashomer.

**PATIENTS:** Thirty-one familial Mediterranean fever (FMF) patients, treated continuously with colchicine (1.0-2.0 mg.day<sup>-1</sup>) for 2-13 years.

**METHODS:** A standard oral glucose tolerance test (OGTT) was performed to study the effect of long-term colchicine treatment on glucose-induced insulin response. An intravenous glucose tolerance test (IVGTT) was then performed on randomly chosen FMF patients (n = 9) and age-matched controls (n = 5). Glucose was administered 30 min after intravenous colchicine (2 mg) infusion. The sum of 1st- and 3rd-min insulin levels served as an index of early-phase insulin release.

**RESULTS:** Based on the Office Guide to Diagnosis of Glucose Intolerance [13], one subject exhibited impaired glucose tolerance and two others had abnormal dynamics of glucose during the test but normal values at 120 min. Insulin values were normal in all participants. No significant differences were found in maximal glucose and insulin concentration, nor in the insulin release index between FMF colchicine-treated and healthy controls.

**CONCLUSIONS:** Based on these findings, no impairment in glucose dynamics could be demonstrated in chronically colchicine treated patients, compared to untreated controls.

PMID: 9143863 [Indexed for MEDLINE]

5066. Z Gastroenterol. 1997 Jan;35(1):XVIII.

[Case report: secondary amyloidosis in ulcerative colitis--successful treatment with colchicine].

[Article in German]

Swarowsky B.

PMID: 9123952 [Indexed for MEDLINE]

5067. QJM. 1997 Jan;90(1):37-43.

The clinical patterns of arthritis in children with familial Mediterranean fever.

Majeed HA(1), Rawashdeh M.

Author information:

(1)Department of Pediatrics, Faculty of Medicine, University of Jordan, Jordan.

We studied the clinical patterns of arthritis in 133 children with familial Mediterranean fever (FMF) over 5.5 years. Six clinical patterns were noted. The commonest was recurrent monoarticular arthritis as seen in 95 children (71%), mainly affecting the knee and ankle joints. This type followed two different courses: acute (< 1 month) and chronic (> 1 month). In 18 (14%) children, both knee or ankle joints were simultaneously and symmetrically involved: here too the course was either acute or chronic. Five (4%) children developed symmetric polyarthritis similar to juvenile rheumatoid arthritis (JRA). Six (4%) children developed asymmetric oligoarticular arthritis similar to acute rheumatic fever (ARF). The small joints of the hands (SJH) were involved in seven (5%) children, and the small joints of the feet in one. One child developed sacroiliitis similar to ankylosing spondylitis (AS). Between attacks, the joints were normal. Overall, outcome was good: residual damage of the hip joint occurred in one patient and of the shoulder in another. Although the clinical presentation and course of FMF arthritis are diverse, delineating these clinical patterns may help with earlier recognition and treatment. The low incidence of residual articular damage in this study may be related to the use of colchicine prophylaxis.

PMID: 9093587 [Indexed for MEDLINE]

5068. Semin Arthritis Rheum. 1996 Dec;26(3):612-27.

The changing face of familial Mediterranean fever.

Livneh A(1), Langevitz P, Zemer D, Padeh S, Migdal A, Sohar E, Pras M.

Author information:

(1)Heller Institute of Medical Research, Sheba Medical Center, Tel-Hashomer, Israel.

Familial Mediterranean fever (FMF) is a genetic disease characterized by painful febrile "attacks" of serositis and the development of amyloidosis. Although FMF has been extensively studied and described, new data have accumulated during the last decade. This report gives an update, focusing specifically on (1) newly characterized manifestations, such as acute scrotal "attacks," protracted febrile myalgia, and spondyloarthropathy; (2) progress made in the diagnosis and treatment of FMF-amyloidosis; (3) experience acquired with colchicine, establishing its safety in common practice, childhood, conception, and pregnancy; (4) colchicine's role in the prevention and treatment of FMF-amyloidosis; (5) new laboratory findings; and (6) new considerations in the differential diagnosis. The most important achievement in recent years, however, is the mapping of the FMF susceptibility gene to chromosome 16p, a finding that raises hopes for prompt cloning of the gene and elucidation of the mechanisms involved in FMF expression.

PMID: 8989806 [Indexed for MEDLINE]

5069. Lancet. 1996 Nov 9;348(9037):1321-2.

Familial Mediterranean fever crisis and lupus anticoagulant.

Disdier P, Swiader L, Aillaud MF, Harlé JR, Weiller PJ.

PMID: 8909414 [Indexed for MEDLINE]

5070. Ann Rheum Dis. 1996 Nov;55(11):852-5.

Serum soluble interleukin-2 receptor levels in familial Mediterranean fever.

Erken E(1), Güneşçar R, Ozbek S, Konca K.

Author information:

(1)Department of Rheumatology, Faculty of Medicine, Cukurova University, Balcal, Adana, Turkey.

**OBJECTIVE:** To investigate serum soluble interleukin-2 receptor (sIL-2R) in familial Mediterranean fever (FMF) and assess its role in acute FMF crisis.

**METHODS:** Serum sIL-2R concentrations were measured in patients with FMF during acute crises and during inactive periods of the disease, using an immunoenzymatic assay kit. Twenty four FMF patients during acute crisis (active FMF), 17 patients with inactive FMF, 24 healthy controls, and 20 active patients with rheumatoid arthritis (as a disease control group) were studied.

**RESULTS:** Serum sIL-2R concentrations were increased during an acute FMF crisis compared with the values in inactive FMF patients and healthy controls ( $P = 0.0105$  and  $P = 0.0012$  respectively), while there was no significant difference between the mean values in active FMF and rheumatoid arthritis patients ( $P = 0.7325$ ). In 14 of the FMF group whose blood samples were available in both active and inactive phases, sIL-2R concentrations were significantly higher in an acute attack than in an attack-free period ( $P = 0.027$ ).

**CONCLUSIONS:** An increase in sIL-2R may be a result of hyperreactivity of IL-2R-expressing cells during an acute inflammatory attack of FMF.

PMCID: PMC1010325

PMID: 8976646 [Indexed for MEDLINE]

5071. Clin Rheumatol. 1996 Nov;15(6):610-2.

Atypical hypergammaglobulinaemia D syndrome with amyloidosis: an overlap with



familial Mediterranean fever?

Ostuni P(1), Vertolli U, Marson P.

Author information:

(1)Division of Rheumatology, University of Padova, Italy.

A case of hypergammaglobulinaemia D and periodic fever syndrome, developing an amyloidosis-related nephrotic syndrome, is reported. Since such a complication represents a typical feature of another disease characterized by recurrent febrile attacks, i.e., familial Mediterranean fever, an overlap syndrome between these two rare clinical disorders can be suggested.

PMID: 8973873 [Indexed for MEDLINE]

5072. Aust Fam Physician. 1996 Nov;25(11):1717-9.

When doctors lack knowledge and deal with uncertainty.

Glasgow NJ(1).

Author information:

(1)Department of Family Medicine, Faculty of Medicine and Health Sciences, United Arab Emirates University.

General practitioners are often confronted with problems, where their knowledge base may be lacking and/or diagnostic uncertainty exists, but competent management is still needed. Sometimes a case brings these issues very much to the fore, and in this case study the problem of familial Mediterranean fever is used to highlight some of the issues involved. This article also summarises this unusual condition which, with recent immigration patterns, may become more frequent in Australasia.

PMID: 8952106 [Indexed for MEDLINE]

5073. Br J Rheumatol. 1996 Nov;35(11):1188-9.

Resolving familial Mediterranean fever attacks with interferon alpha.

Tankurt E, Tunca M, Akbaylar H, Gönen O.

PMID: 8948315 [Indexed for MEDLINE]

5074. J Rheumatol. 1996 Nov;23(11):2003.

Migrating monopredominant arthritis in children of Assyrian ancestry.

Gül A, Aral O, Koniçe M.

Comment in

J Rheumatol. 1999 Jun;26(6):1415.

PMID: 8923387 [Indexed for MEDLINE]

5075. J Rheumatol. 1996 Nov;23(11):2002-3; author reply 2003-4.

Migrating monopredominant arthritis in children of Assyrian ancestry.

Arisoy N, Kasapçopur O, Sever L.

Comment in

J Rheumatol. 1999 Jun;26(6):1415.

Comment on

J Rheumatol. 1996 Jan;23(1):178-80.

PMID: 8923386 [Indexed for MEDLINE]

5076. J Rheumatol. 1996 Nov;23(11):2002.

Migrating monopredominant arthritis in children of Assyrian ancestry.

Gedalia A, Shetty AK.

Comment in

J Rheumatol. 1999 Jun;26(6):1415.

Comment on

J Rheumatol. 1996 Jan;23(1):178-80.

PMID: 8923385 [Indexed for MEDLINE]

5077. J Rheumatol. 1996 Nov;23(11):2002.

Migrating monopredominant arthritis in children of Assyrian ancestry.

Fomberstein B, Barakat F.

Comment in

J Rheumatol. 1999 Jun;26(6):1415.

Comment on

J Rheumatol. 1996 Jan;23(1):178-80.

PMID: 8923384 [Indexed for MEDLINE]

5078. Dtsch Med Wochenschr. 1996 Oct 18;121(42):1299-300.

[The hyper-IgD syndrome].

[Article in German]

Drenth JP(1), Endres S, Belohradsky BH, van der Meer JW.

Author information:

(1)Klinikum für Innere Medizin, Universitätsspital St. Radboud, Nimwegen.

DOI: 10.1055/s-2008-1043143

PMID: 8964204 [Indexed for MEDLINE]

5079. Harefuah. 1996 Oct;131(7-8):283-4.

[Hyperimmunoglobulinemia D--a new periodic syndrome with features simulating familial Mediterranean fever].

[Article in Hebrew]

Livneh A, Langevitz P.

PMID: 8940530 [Indexed for MEDLINE]

5080. J Clin Pharmacol. 1996 Oct;36(10):874-83.

Oral absorption characteristics and pharmacokinetics of colchicine in healthy volunteers after single and multiple doses.

Ferron GM(1), Rochdi M, Jusko WJ, Scherrmann JM.

Author information:

(1)Department of Pharmaceutics, State University of New York at Buffalo, USA.

Colchicine is an antimitotic drug used to treat gout and familial Mediterranean fever. Absolute bioavailability, pharmacokinetics, and absorption characteristics of colchicine after single 1.0-mg doses in oral solution or tablet form or 0.5-mg intravenous doses were compared in 6 subjects. This study was combined with 14 days of multiple-dose administration of 1.0-mg colchicine tablets in 6 subjects. Serial blood samples were collected for 48 hours after administration of single doses and for 120 hours after the last dose in the multiple-dose regimen. Plasma colchicine profiles as measured by radioimmunoassay were analyzed using

deconvolution and compartmental methods. After intravenous bolus injection of colchicine, the area under the concentration-time curve (AUC) was  $61.2 \pm 12.7$  ng.hr/mL, steady-state volume of distribution ( $V_{ss}$ ) was  $419 \pm 95$  L, systemic clearance (Cl) was  $8.5 \pm 1.8$  L/hr, and the terminal half-life ( $t_{1/2}$ ) was  $57.8 \pm 10.7$  hours. After oral administration in solution form, peak plasma concentrations ( $C_{max}$ ) of  $6.50 \pm 1.03$  ng/mL were reached at time ( $t_{max}$ )  $1.07 \pm 0.55$  hours, with a rate of  $0.109 \pm 0.024$  hr<sup>-1</sup> ( $C_{max}/AUC$ ); bioavailability was  $47 \pm 14\%$ . Oral tablets yielded similar  $C_{max}$ ,  $t_{max}$ , and  $C_{max}/AUC$  values, but AUC was significantly lower. Most participants exhibited a secondary peak within 6 hours of administration, possibly in relation to a second absorption site or enterohepatic recirculation. This second absorption process was significantly longer than the first one, and accounted for a similar amount of colchicine absorbed. From the multiple-dose study, a model including an alteration of colchicine absorption due to possible drug-induced gastrointestinal modifications allowed better determination of steady-state plasma concentrations of colchicine.

PMID: 8930773 [Indexed for MEDLINE]

5081. *Pediatr Nephrol.* 1996 Oct;10(5):631-3.

The coexistence of familial Mediterranean fever and polyarteritis nodosa; report of a case.

Koçak H(1), Cakar N, Hekimoglu B, Atakan C, Akkök N, Unal S.

Author information:

(1)Department of Pediatric Nephrology, Social Security Hospital, Ankara, Turkey.

We describe a 14-year-old boy with a 5-year history of familial Mediterranean fever (FMF), treated with colchicine, who developed polyarteritis nodosa (PAN). He was admitted to our hospital with fever, general weakness, arthritis, and purpura. Five weeks after admission, hypertension was noted. Skin biopsy showed perivascular leukocyte infiltration in the epidermis. An aortography revealed multiple aneurysms of the renal, common hepatic, and intercostal arteries. He was treated with intravenous methylprednisolone, oral cyclophosphamide, and azathioprine. The known rare association of FMF and PAN is discussed.

PMID: 8897571 [Indexed for MEDLINE]

5082. *Pediatr Infect Dis J.* 1996 Oct;15(10):924-5.

First patients with hyperimmunoglobulinemia D syndrome from the United States.

Drenth JP, Weemaes CM.

Comment on

*Pediatr Infect Dis J.* 1996 Jan;15(1):72-7.

PMID: 8895936 [Indexed for MEDLINE]

5083. *J Assist Reprod Genet.* 1996 Sep;13(8):684-5.

Successful pregnancy in a familial Mediterranean fever patient following assisted reproduction.

Ditkoff EC(1), Sauer MV.

Author information:

(1)Department of Obstetrics and Gynecology, Columbia-Presbyterian Medical Center, Columbia University, New York, New York 10032, USA.

We conclude that untreated women with FMF have up to a 30% incidence of infertility due to ovulatory dysfunction and peritoneal adhesions. Some of these women conceive during ovulation induction with or without insemination. We have described the first case of a successful and normal pregnancy in a patient with FMF following in vitro fertilization (IVF) while on prophylaxis colchicine therapy after other treatments for infertility were unsuccessful.

PMID: 8897132 [Indexed for MEDLINE]

5084. Clin Rheumatol. 1996 Sep;15(5):517-8.

Hyperactive polymorphonuclear leucocytes migration in patients with Familial Mediterranean Fever.

Disdier P, Fossat C, Veit V, David M, Swiader L, Harle JR, Juhan-Vague I, Weiller PJ.

PMID: 8894373 [Indexed for MEDLINE]

5085. Eur J Pediatr. 1996 Sep;155(9):787-90.

Autosomal dominant familial Mediterranean fever--like syndrome.

Mache CJ(1), Goriup U, Fischel-Ghodsian N, Chen X, Schwingshandl J.

Author information:

(1)University Children's Hospital, Graz, Austria.

We report a syndrome characterized by recurrent episodes of fever and serositis in an Austrian family. Three family members over two successive generations were affected. The febrile episodes had their onset at the age of 11-12 years, lasted 1-5 weeks, and occurred in intervals of 6-24 months. While the disorder resembles familial Mediterranean fever (FMF) clinically, ethnic distribution and other features suggest a distinct entity. Clinically, the attacks last longer than the usual FMF attacks, and in the male patients are associated with scrotal inflammation. Genetically, the disorder appears to be inherited as an autosomal dominant syndrome, whereas FMF is autosomal recessive. Molecular analysis made the involvement of a gene in the FMF region of chromosome 16p13.3 highly unlikely. CONCLUSION: An Austrian family with recurrent fever syndrome is reported. Ethnicity, clinical features, and molecular studies point to a distinct clinical entity.

PMID: 8874113 [Indexed for MEDLINE]

5086. Am J Hum Genet. 1996 Sep;59(3):603-12.

Localization of the familial Mediterranean fever gene (FMF) to a 250-kb interval in non-Ashkenazi Jewish founder haplotypes. The French FMF Consortium.

[No authors listed]

Chromosome 16p13.3 harbors a gene (MEF) associated with familial Mediterranean fever (FMF), a recessive disease very common in populations of Mediterranean ancestry. In the course of positional cloning of MEF, we genotyped 26 non-Ashkenazi Jewish FMF pedigrees (310 meioses) with 15 microsatellite markers, most of which were recently developed by Généthon. Identification of recombination events in the haplotypes allowed narrowing of the MEF interval to a region between D16S3124 (telomeric) and D16S475 (centromeric). Two markers, D16S3070 and D16S3275, a microsatellite marker isolated from a YAC that also contains D16S3070, showed no recombination with the disease. Linkage disequilibrium and haplotype analysis highlighted the existence of a founder haplotype in our population. The core ancestral alleles were present in 71% of MEF-bearing chromosomes at loci D16S3070 and D16S3275. Furthermore, identification of historical crossing-over events in these pedigrees indicated that MEF is located between these two loci, which are both contained in a 250-kb genomic fragment.

PMCID: PMC1914916

PMID: 8751861 [Indexed for MEDLINE]

5087. Lancet. 1996 Aug 24;348(9026):554; author reply 555.

Familial Mediterranean fever.

Matzner Y.

Comment on

Lancet. 1996 Jun 29;347(9018):1779-80.

DOI: 10.1016/S0140-6736(05)64719-8

PMID: 8786687 [Indexed for MEDLINE]



5088. Lancet. 1996 Aug 24;348(9026):554-5.

Familial Mediterranean fever.

McDermott EM, Drenth JP, Powell RJ.

Comment on

Lancet. 1996 Jun 29;347(9018):1779-80.

PMID: 8757177 [Indexed for MEDLINE]

5089. J Am Dent Assoc. 1996 Aug;127(8):1202-13.

Recurrent aphthous ulcers: a review of diagnosis and treatment.

Woo SB(1), Sonis ST.

Author information:

(1)Harvard School of Dental Medicine, Boston, USA.

Recurrent aphthous ulcers, or RAU--also called canker sores--are among the oral mucosal conditions that dentists and physicians see most commonly in their patients. Several systemic conditions are associated with oral aphthouslike ulcers, and aphthae themselves often are mistaken for recrudescant oral herpes simplex virus, or HSV, infections. This article will review RAU, describe systemic conditions associated with aphthous-like ulcerations and discuss the differences between RAU and recrudescant oral HSV infections.

PMID: 8803396 [Indexed for MEDLINE]

5090. BMJ. 1996 Jul 27;313(7051):233.

Efficacy of colchicine in familial Mediterranean fever is well established.

Drenth JP.

Comment on

BMJ. 1996 Apr 27;312(7038):1087-9.

PMCID: PMC2351620

PMID: 8696225 [Indexed for MEDLINE]

5091. Clin Exp Rheumatol. 1996 Jul-Aug;14(4):407-12.

Increased prevalence of joint manifestations in patients with recurrent aphthous stomatitis (RAS)

Livneh A(1), Zaks N, Katz J, Langevitz P, Shemer J, Pras M.

Author information:

(1)Department of Medicine F and Oral Medicine Clinic, Sheba Medical Center, Tel Hashomer, Israel.

Comment in

Clin Exp Rheumatol. 1996 Jul-Aug;14(4):355-8.

Clin Exp Rheumatol. 1997 Jan-Feb;15(1):118-9.

**OBJECTIVE:** To characterize the systemic manifestations and joint disease in patients with recurrent aphthous stomatitis (RAS).

**METHODS:** The presence and features of extra-oral manifestations were determined by a rheumatologist, who examined and interviewed 64 patients, referred during 1993 to the oral medicine clinic for treatment of RAS. Controls were 65 medical staff members of a military clinic associated with the hospital.

**RESULTS:** Based on the rheumatologist's findings and published criteria, the patients were diagnosed as suffering from RAS alone (24 patients), Reiter's syndrome (8), Behçet disease (8), familial Mediterranean fever (1), or RAS with undiagnosable extra oral manifestations (23). Thirteen patients in the last group had joint disease ( $p < 0.01$  compared to the controls), characterized by recurrent mono- or oligoarthritis/arthritis of short duration, affecting mostly the large joints. Conjunctivitis, pustular rash, lower back pain and urethritis/cervicitis

were also common in RAS patients, but only the latter was significantly more frequent in RAS patients than in controls ( $p < 0.02$ ).

CONCLUSION: These findings suggest that patients with RAS have an increased frequency of a palindromic type joint disease.

PMID: 8871840 [Indexed for MEDLINE]

5092. Eur J Pediatr. 1996 Jul;155(7):540-4.

Familial Mediterranean fever in Arab children: the high prevalence and gene frequency.

Rawashdeh MO(1), Majeed HA.

Author information:

(1)Department of Paediatrics, Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan.

Over a period of 3 years, 192 children with familial Mediterranean fever were prospectively studied. Of these, 106 (55%) were girls and 86 (45%) were boys. The prevalence was 1:2600 children with a gene frequency of 1:50. The age at onset ranged between 4 months and 16 years. Of these patients 24% started their illness below the age of 2 years and 88% were symptomatic before the age of 10 years: 82% had recurrent abdominal pain, 43% had pleurisy, 37% had arthritis, 15% had cutaneous manifestations, 12% had splenomegaly and 4% had hepatomegaly. The presenting symptoms were abdominal pain in 51%, unilateral chest pain in 23% and arthritis in 26%. The family history was positive in 62%. Of 12 affected families 19 members had/have renal failure and amyloidosis was confirmed in 7 patients. CONCLUSIONS: Our data show a high prevalence of familial Mediterranean fever and a high gene frequency in Arab children similar to that reported in Jews and Americans.

PMID: 8831074 [Indexed for MEDLINE]

5093. J Immunol. 1996 Jul 1;157(1):400-4.

Unstimulated peripheral blood mononuclear cells from patients with the hyper-IgD syndrome produce cytokines capable of potent induction of C-reactive protein and serum amyloid A in Hep3B cells.

Drenth JP(1), van der Meer JW, Kushner I.

Author information:

(1)Department of Medicine, MetroHealth Medical Center, Cleveland, OH 44109, USA.

The hyper-IgD and periodic fever syndrome (HIDS) and familial Mediterranean fever (FMF) are both characterized by attacks of periodic fever accompanied by acute phase responses that are substantially higher in HIDS than in FMF. To determine whether this difference could be due to differences in production of acute phase protein-inducing mediators, we studied PBMC from HIDS and FMF patients in the inactive phase of disease. Unstimulated PBMC from patients with inactive HIDS released significantly more IL-1 beta, IL-6, and TNF-alpha than did PBMC from patients with FMF, but unstimulated PBMC from the latter group released significantly more IL-1 beta and IL-6 compared with controls. Conditioned medium (CM) derived from PBMC of patients with inactive HIDS induced significantly greater CRP production and significantly higher mRNAs for CRP and SAA in Hep3B cells than did CM derived from the PBMC of patients with inactive FMF. Stimulation of PBMC with LPS led to further increases in cytokine production and in acute phase protein-inducing ability in both patient groups and in controls. These findings suggest that the greater acute phase response seen in HIDS compared with FMF reflects greater production of acute phase protein-inducing cytokines in the former patients and indicates that PBMC from inactive HIDS patients are already activated in vivo. Finally, the finding of both quantitative and qualitative differences in cytokine production by unstimulated PBMC from HIDS and FMF patients supports the likelihood of different pathogeneses of these diseases.

PMID: 8683144 [Indexed for MEDLINE]

5094. Arthritis Rheum. 1996 Jul;39(7):1213-7.

Colchicine in breast milk of patients with familial Mediterranean fever.

Ben-Chetrit E(1), Scherrmann JM, Levy M.

Author information:

(1)Hadassah University Hospital, Jerusalem, Israel.

**OBJECTIVE:** To clarify whether colchicine is excreted in breast milk, and to compare its concentrations in the serum and breast milk of lactating women who have familial Mediterranean fever (FMF).

**METHODS:** Using a specific radioimmunoassay, we determined colchicine concentrations in the serum and breast milk of 4 patients at various time points, following oral administration of the drug. The study evaluated 4 patients with FMF who had been taking colchicine on a long-term basis.

**RESULTS:** Colchicine was found to be excreted in breast milk. Its levels ranged between 1.9 and 8.6 ng/ml, which were similar to those found in the serum (parallel concentration time curves). However, there appeared to be a considerable variation in colchicine milk concentration among the different patients, which might be related to individual breast milk composition and, possibly, to other nutritional or metabolic factors.

**CONCLUSION:** The extensive peripheral tissue binding and relatively low concentration of colchicine in breast milk suggests that the amount ingested by the infant is small. Furthermore, based on our clinical experience, nursing appears to be safe for lactating women with FMF who continue to take colchicine.

PMID: 8670333 [Indexed for MEDLINE]

5095. Lancet. 1996 Jun 29;347(9018):1779-80.

Familial Mediterranean fever: underlying defect clearer, but diagnostic problems persist.

Cook GC(1).

Author information:

(1)Hospital for Tropical Diseases, London, UK.

Comment in

Lancet. 1996 Aug 24;348(9026):554-5.

Lancet. 1996 Aug 24;348(9026):554; author reply 555.

PMID: 8667917 [Indexed for MEDLINE]

5096. J Clin Pathol. 1996 Jun;49(6):453-5.

Evidence of oxidative stress in erythrocyte phospholipid composition in the pathogenesis of familial Mediterranean fever (periodical disease).

Karaguezyan KG(1), Haroutjunian VM, Mamiconyan RS, Hakobian GS, Nazaretian EE, Hovsepyan LM, Hoveyan GA, Gevorkian EM, Hovakimyan SS, Zakarian AE, Quinn PJ.

Author information:

(1)Department of Bioinorganic Chemistry, Yerevan State Medical University, Republic of Armenia.

**BACKGROUND:** Familial Mediterranean fever (FMF) is a genetically linked disorder common amongst races of the Eastern Mediterranean region. Typical symptoms include episodic pain syndrome extending throughout the chest or abdomen associated with histopathological signs of amyloidosis of the kidney.

**AIM:** To investigate possible connections between the aseptic inflammation that occurs during pain crises and cell membrane structural and functional integrity in patients with FMF.

**METHODS:** Oxidative stress parameters in 42 patients in remission and during a pain crisis were compared with 21 normal subjects.

**RESULTS:** The patient group had significantly greater concentrations of chemiluminescent and thiobarbituric acid-reactive substances in the blood plasma and lower concentrations of alpha-tocopherol than the control group while in remission; these changes were exacerbated during pain crises. Analyses of the phospholipid composition of erythrocyte membranes showed significant increases in amounts of acidic phospholipids (phosphatidic acid, monophosphatidylinositol and cardiolipin) and lysophosphatidylcholine compared with healthy subjects.

**CONCLUSIONS:** The pattern of differences in membrane phospholipid composition was consistent with increased oxidative stress in patients with FMF.

PMCID: PMC500532

PMID: 8763256 [Indexed for MEDLINE]

5097. J Pediatr Hematol Oncol. 1996 May;18(2):159-61.

Atypical PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, adenitis) in a young girl with Fanconi anemia.

Scimeca PG(1), James-Herry AG, Weinblatt ME.

Author information:

(1)Division of Pediatric Hematology/Oncology, North Shore University Hospital-Cornell University Medical College, Manhasset, New York 11030, USA.

**PURPOSE:** To describe a case of atypical, severe, periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome (PFAPA syndrome) in a patient with Fanconi anemia. Important aspects about the PFAPA syndrome and Fanconi anemia are reviewed.

**PATIENTS AND METHODS:** An 8-year-old girl with Fanconi anemia was noted to have a pattern of periodic fever, stomatitis, and pharyngitis consistent with the diagnosis of PFAPA syndrome, a generally benign disorder. After prednisone treatment for the syndrome, life-threatening intestinal ulceration and perforation developed, which was successfully treated.

**CONCLUSION:** In patients with underlying hematologic disease such as Fanconi anemia, PFAPA syndrome may be associated with severe clinical problems in contrast to otherwise normal children with the disorder.

PMID: 8846129 [Indexed for MEDLINE]

5098. Clin Nephrol. 1996 May;45(5):361-2.

Goitre and severe autonomic neuropathy due to secondary amyloidosis in a renal transplant patient.

Ok E, Akcicek F, Toz H, Coker A, Kursat S, Tokat Y, Arac N.

PMID: 8738674 [Indexed for MEDLINE]

5099. Clin Infect Dis. 1996 May;22(5):881-2.

Recurrent erysipelas or erysipelas-like rash?

van der Meer JW, Drenth JP, Schellekens PT.

Comment on

Clin Infect Dis. 1995 Jun;20(6):1491, 1547.

PMID: 8722969 [Indexed for MEDLINE]

5100. Eur J Haematol. 1996 May;56(5):283-6.

The effect of desmopressin on platelet aggregation defect in systemic amyloidosis: a preliminary report.

Demiroğlu H(1), Barişta I, Gürsoy M, Oymak O, Dündar S.

Author information:

(1)Department of Hematology, Hacettepe University Medical School, Ankara, Turkey.

Systemic amyloidosis may often be complicated with haemorrhagic tendency. The causes of this manifestation are factor deficiencies, hyperfibrinolysis and vasculopathy. In order to investigate the role of platelets, if any, we performed platelet aggregation tests with different aggregants in 10 patients with systemic amyloidosis due to familial Mediterranean fever and 10 healthy controls. Platelet aggregation was defective with different aggregants (ADP, epinephrine, collagen) in patients compared with controls. Platelet aggregation tests repeated after desmopressin (DDAVP) administration were normalized. These findings may suggest a role of a platelet aggregation defect in haemorrhagic diathesis complicating systemic amyloidosis. DDAVP may benefit patients with this disease in case of bleeding and before surgical interventions.



PMID: 8641401 [Indexed for MEDLINE]

5101. Int J Gynaecol Obstet. 1996 Apr;53(1):59-60.

Nephrotic syndrome and periodic fever in pregnancy.

Ersan F, Toppare MF, Seckin N.

PMID: 8737307 [Indexed for MEDLINE]

5102. Clin Rheumatol. 1996 Mar;15(2):216-8.

Anti-neutrophil cytoplasmic antibodies in familial Mediterranean fever.

Simsek H, Kadayifci A, Kirazli S.

PMID: 8777864 [Indexed for MEDLINE]

5103. Clin Exp Rheumatol. 1996 Mar-Apr;14(2):224-5.

High urinary neopterin levels in Familial Mediterranean Fever.

Simsek H, Kadayifci A, Altindag ZZ, Sahin G.

PMID: 8737737 [Indexed for MEDLINE]

5104. QJM. 1996 Mar;89(3):205-10.

Induced TNF production in vitro as a test for familial Mediterranean fever.

Schattner A(1), Gurevitz A, Zemer D, Hahn T.

Author information:

(1)Department of Medicine 'A', Hebrew University, Jerusalem.

We have previously demonstrated an altered pattern of tumor necrosis factor (TNF) secretion in patients with familial Mediterranean fever (FMF). To examine whether TNF determination could assist in diagnosing FMF, we stimulated heparinized blood of 51 asymptomatic FMF patients with lipopolysaccharide (LPS) and then measured TNF production in response to inducers, compared to unstimulated blood cells and to cells from a control group of 12 matched healthy subjects. Following LPS pretreatment, which induced TNF release, FMF patients produced significantly less TNF than controls, whether production was 'spontaneous' or induced by either LPS or phytohaemagglutinin ( $p < \text{or} = 0.003$ ). Such 'exhaustion' did not occur in untreated cells. We then used these results to classify a further group of 29 FMF patients and 10 matched healthy controls ('validation' group) who underwent the same studies. The test correctly identified 25/29 patients as having FMF and 7/10 controls as not having FMF; a sensitivity of 86% and a specificity of 70% (likelihood ratios 2.9 (positive test) and 0.2 (negative)). Identification of a blunted TNF response following previous stimulation by a simple assay, may help the diagnosis of FMF in asymptomatic patients, provided it is interpreted in conjunction with supportive clinical data.

PMID: 8731564 [Indexed for MEDLINE]

5105. Ann Rheum Dis. 1996 Mar;55(3):208-10.

Gastrointestinal involvement in Behçet's syndrome: a controlled study.

Yurdakul S(1), Tüzüner N, Yurdakul I, Hamuryudan V, Yazici H.

Author information:

(1)Department of Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Turkey.

**OBJECTIVE:** To make a retrospective and prospective analysis of the frequency of symptomatic inflammatory bowel disease in patients with Behçet's syndrome (BS).

**METHODS:** The medical records of the first 1000 patients with BS were reviewed

retrospectively for past or present history of diarrhoea. The past and present history of diarrhoea was also elicited prospectively among 147 consecutive patients with BS and 78 diseased controls (42 with rheumatoid arthritis, 17 with systemic lupus erythematosus, seven with seronegative spondylarthropathy, and 12 with miscellaneous rheumatic diseases). Inflammatory mucosal changes were sought in rectal biopsy specimens from 75 patients with BS, 47 diseased controls (29 with nephrotic syndrome, eight with rheumatoid arthritis, six with familial Mediterranean fever, and four with ankylosing spondylitis), and 14 patients with ulcerative colitis.

**RESULTS:** In chart review there were only seven Behçet's patients with diarrhoea; none of them had inflammatory bowel disease. In the prospective survey there were no significant differences between the BS and control groups in the past and present history of diarrhoea. There were no significant differences in the rectal mucosal histology between patients with BS and controls, while patients with ulcerative colitis showed pronounced differences.

**CONCLUSION:** Symptomatic inflammatory bowel disease is not common in BS patients from Turkey.

PMCID: PMC1010133

PMID: 8712889 [Indexed for MEDLINE]

5106. Am J Hum Genet. 1996 Mar;58(3):523-34.

Linkage disequilibrium mapping places the gene causing familial Mediterranean fever close to D16S246.

Levy EN(1), Shen Y, Kupelian A, Kruglyak L, Aksentijevich I, Pras E, Balow JE Jr, Linzer B, Chen X, Shelton DA, Gumucio D, Pras M, Shohat M, Rotter JI, Fischel-Ghodsian N, Richards RI, Kastner DL.

Author information:

(1)Arthritis and Rheumatism Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD 20892-1820, USA.

This report presents refined genetic mapping data for the gene causing familial Mediterranean fever (FMF), a recessively inherited disorder of inflammation. We sampled 65 Jewish, Armenian, and Arab families and typed them for eight markers

from chromosome 16p. Using a new algorithm that permits multipoint calculations for a dense map of markers in consanguineous families, we obtained a maximal LOD score of 49.2 at a location 1.6 cM centromeric to D16S246. A specific haplotype at D16S283-D16S94-D16S246 was found in 76% of Moroccan and 32% of non-Moroccan Jewish carrier chromosomes, but this haplotype was not overrepresented in Armenian or Arab FMF carriers. Moreover, the 2.5-kb allele at D16S246 was significantly associated with FMF in Moroccan and non-Moroccan Jews but not in Armenians or Arabs. Since the Moroccan Jewish community represents a relatively recently established and genetically isolated founder population, we analyzed the Moroccan linkage-disequilibrium data by using Luria-Delbrück formulas and simulations based on a Poisson branching process. These methods place the FMF susceptibility gene within 0.305 cM of D16S246 (2-LOD-unit range 0.02-0.64 cM).

PMCID: PMC1914560

PMID: 8644712 [Indexed for MEDLINE]

5107. Drugs Aging. 1996 Feb;8(2):75-83.

Anti-amyloid drugs: potential in the treatment of diseases associated with aging.

Kisilevsky R(1).

Author information:

(1)Department of Pathology, Queen's University, Kingston, Ontario, Canada.

The requirements for amyloidogenesis, as it is currently understood, include an adequate amyloid precursor pool, a nidus for fibrillogenesis, interactions with a set of common components (most of which are involved in basement membrane structure) and amyloid turnover. These factors serve as the basis for therapeutic attack. General strategies focusing on each of these factors are presented with examples from the experimental and clinical literature. These include reducing the amyloid precursor protein pool in familial amyloid polyneuropathy by liver transplantation, inhibiting nidus formation in familial Mediterranean fever by the use of colchicine, inhibiting amyloid precursor protein/heparan sulphate interaction in experimental inflammation-associated amyloidosis by the use of novel small molecule anionic sulphates and sulphonates, and the use of new analogues of doxorubicin in light chain amyloidosis to accelerate amyloid

removal. The potential significance of local and systemic amyloid deposits is discussed in the light of new information on the genetics of Alzheimer's disease, observations made in patients receiving long term dialysis for renal failure, and the potential involvement of amyloid deposits in the pathogenesis of non-insulin-dependent diabetes mellitus.

DOI: 10.2165/00002512-199608020-00001

PMID: 8845588 [Indexed for MEDLINE]

5108. Ann Med Interne (Paris). 1996;147(5):373.

[Use of colchicine in periodic disease].

[Article in French]

Bouchon JP.

Comment on

Ann Med Interne (Paris). 1996;147(3):185-211.

PMID: 9033743 [Indexed for MEDLINE]

5109. Eur J Clin Pharmacol. 1996;51(3-4):241-5.

Colchicine enhances intestinal permeability in patients with familial Mediterranean fever.

Fradkin A(1), Yahav J, Diver-Haber A, Zemer D, Jonas A.

Author information:

(1)Pediatric Gastrointestinal Unit, Chaim Sheba Medical Center, Tel Hashomer, Israel.

OBJECTIVE: Colchicine therapy is complicated by frequent gastrointestinal adverse effects.

METHODS: We compared intestinal permeability in 21 patients with familial

Mediterranean fever on long-standing colchicine therapy (mean 5.8 years) and significant gastrointestinal complaints and 12 untreated patients and 14 healthy volunteers. The double probe (lactulose/mannitol) permeability test was performed using a hyperosmolar test solution (1580 mosmol) and the differential urinary recovery ratios were calculated.

**RESULTS:** Familial Mediterranean fever patients on colchicine therapy had significantly higher lactulose/mannitol urinary excretion ratios (0.073) compared to untreated patients (0.035) and to healthy controls (0.021). Untreated familial Mediterranean fever patients had significantly greater urinary lactulose/mannitol recovery ratios than controls ( $P < 0.02$ ). No correlation was found between the degree of enhanced permeability and the length of exposure to the drug or the severity of clinical symptoms.

**CONCLUSIONS:** Intestinal permeability was significantly enhanced in patients with familial Mediterranean fever treated with colchicine.

PMID: 9010692 [Indexed for MEDLINE]

5110. Curr Opin Rheumatol. 1996 Jan;8(1):62-71.

Amyloidosis.

Friman C(1), Pettersson T.

Author information:

(1)Department of Medicine, Helsinki University Central Hospital, Finland.

Developments concerning amyloidosis associated with rheumatic diseases or often causing musculoskeletal symptoms are reviewed. The pathogenesis, clinical manifestations, diagnosis, and therapy of amyloid A, amyloid light-chain, and amyloid beta 2-microglobulin amyloidosis are discussed from the standpoint of a clinical rheumatologist. The biology of the precursor protein serum amyloid A (SAA) has been extensively studied, and a new assay for SAA has been developed. In amyloid beta 2-microglobulin amyloidosis, modified beta 2-microglobulin may function as a pathogenic factor that initiates an inflammatory reaction in which macrophages produce cytokines that induce osteoclastogenesis and bone resorption. Further experience with serum amyloid P component scintigraphy in the diagnosis and monitoring of amyloidosis has accumulated. Guidelines for the dosage of

colchicine in the treatment of amyloidosis associated with familial Mediterranean fever have been published. In amyloid light-chain amyloidosis, intensive chemotherapy in combination with bone marrow transplantation or autologous stem-cell infusion has potential therapeutic significance.

PMID: 8867542 [Indexed for MEDLINE]

5111. Clin Infect Dis. 1996 Jan;22(1):22-7.

Periodic illness associated with Epstein-Barr virus infection.

Lekstrom-Himes JA(1), Dale JK, Kingma DW, Diaz PS, Jaffe ES, Straus SE.

Author information:

(1)NIAID, Bethesda, Maryland 20892, USA.

Comment in

Clin Infect Dis. 1996 Jan;22(1):28-9.

A 15-year-old boy with a 13-year history of periodic fevers, lymphadenopathy, and leukocytosis showed virological, serological, immunohistologic, and molecular evidence of persistent, active, Epstein-Barr virus (EBV) infection. Acyclovir and several other agents failed to alter his clinical course. Comprehensive immunological studies could not identify a defined immune deficiency syndrome to explain the persistent infection, although he does continue to have circulating polymeric EBV-specific immunoglobulin type A, as is seen in individuals during acute EBV infections. In vitro work suggests that this polymeric antibody prevents B cell infection by EBV. Cumulative data suggest that this patient suffers from a novel form of EBV infection.

PMID: 8824960 [Indexed for MEDLINE]

5112. Ann Dermatol Venereol. 1996;123(5):314-21.

[Hyperimmunoglobulinemia D or periodic fever syndrome. Cutaneous manifestations

in 3 cases].

[Article in French]

Cartier H(1), Guillet MH, Lemoigne E, Sassolas B, Leroy JP, Mottier D, Guillet G.

Author information:

(1)Service de Dermatologie, CHRU, Brest.

INTRODUCTION: We describe 3 cases of hyperimmunoglobulinemia D syndrome (hyper-IgD syndrome).

CASES REPORT: As the 2 first cases are conventional with an onset in childhood, the third one appeared later suggesting possibility of acquired syndrome. The 3 cases presented with one or several skin eruptions during febrile attacks.

COMMENTS: Up to now, 64 cases of this syndrome have been described. Skin lesions are observed in 80 p. 100 of patients. In this particular clinical context, they must lead to the diagnosis. This 3 cases and the review of literature show that skin manifestations are polymorphic, transient, not very symptomatic and not correlated to IgD rates. Histological examination may reveal urticarial reaction with leucocytoclastic vasculitis, where IgD could directly or not interact.

PMID: 8761083 [Indexed for MEDLINE]

5113. Pediatr Infect Dis J. 1996 Jan;15(1):72-7.

Children with hyperimmunoglobulinemia D and periodic fever syndrome.

Grose C(1), Schnetzer JR, Ferrante A, Vladutiu AO.

Author information:

(1)Department of Pediatrics, University of Iowa College of Medicine, Iowa City 52242-1083, USA.

Comment in

Pediatr Infect Dis J. 1996 Oct;15(10):924-5.



PMID: 8684881 [Indexed for MEDLINE]

5114. Acta Med Port. 1995 Dec;8(12):671-5.

[Neuro-brucellosis. Report of 8 cases].

[Article in Portuguese]

Dias MS(1), Morganho A, Passão V, Aguiar T, Pedrosa R.

Author information:

(1)Serviço de Neurologia do Hospital Santo António dos Capuchos Lisboa.

Brucellosis is an endemic disease in Portugal. There was an increase in incidence in 1994. Neurobrucellosis (NB), although only occurring in 5 to 10% of cases of cases of chronic infection, has heterogeneous forms of presentation which makes differential diagnosis difficult. By reviewing four years of in-patient clinical files in the neurology Ward of St. António dos Capuchos Hospital, the authors study the clinical features, complementary tests, therapy and evolution of differential diagnosis of eight patients with neurobrucellosis.

PMID: 8669316 [Indexed for MEDLINE]

5115. Harefuah. 1995 Nov 15;129(10):413-6.

[Colchicine in familial Mediterranean fever: practical problems and their solutions].

[Article in Hebrew]

Ben-Chetrit E, Levi M.

PMID: 8647547 [Indexed for MEDLINE]

5116. JAMA. 1995 Nov 15;274(19):1509.

Human foamy virus and familial Mediterranean fever in Japan.

Tamura N, Kira S.

PMID: 7474216 [Indexed for MEDLINE]

5117. J La State Med Soc. 1995 Nov;147(11):493-9.

A 38-year-old man with nephrotic syndrome, episodic fever and abdominal pain.

Gadallah MF, Vasquez F, Abreo F, Abreo K.

The differential diagnosis for a 38-year-old white man with a chronic fever associated with nephrotic syndrome is discussed in the setting of a clinicopathological conference at Louisiana State University Medical Center in Shreveport, Louisiana. The etiology and pathophysiology of fever-associated nephrotic syndrome are discussed.

PMID: 8522900 [Indexed for MEDLINE]

5118. J Pediatr Surg. 1995 Oct;30(10):1517-8.

Acute orchitis in recurrent polyserositis.

Moskovitz B(1), Bolkier M, Nativ O.

Author information:

(1)Department of Urology, Bnai Zion Medical Center, Haifa, Israel.

The authors report an unusual case of bilateral short term acute orchitis in a patient with recurrent polyserositis (familial Mediterranean fever).

5119. Turk J Pediatr. 1995 Oct-Dec;37(4):357-73.

Renal amyloidosis in childhood. An overview of the topic with 25 years experience.

Tinaztepe K(1).

Author information:

(1)Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey.

Amyloidosis is a heterogeneous group of diseases characterized by extracellular accumulation of an eosinophilic, hyalin and proteinaceous material containing mucopolysaccharide substance in various tissues and organs. Knowledge about the chemical structure of amyloid fibril proteins has led to the recognition of various forms of amyloidosis including Amyloid-A (AA), Amyloid-L (AL), hereditary, senile, dialysis-related, localized and cerebral amyloidosis. It is now recognized that all types of amyloid contain amyloid P (AP) component which is derived from the serum amyloid P component, a normal circulating glycoprotein and a member of the pentraxin family. A recent classification proposed by WHO-IUIS (Nomenclature Subcommittee) is based on the chemical nature of amyloid fibrils rather than their clinical and pathologic features. The kidneys are frequently involved, and renal failure is the major cause of death. Childhood renal amyloidosis is almost always secondary (reactive, AA type) and usually associated with chronic inflammatory, infectious and hereditary diseases. In developed countries, rheumatoid arthritis is the most common cause of renal amyloidosis, while in developing countries patients with familial Mediterranean fever (FMF) (untreated) and chronic suppurative infections constitute a large proportion of renal amyloidosis cases. No specific therapy is currently available for amyloidosis. Once renal amyloidosis develops, progress to end-stage renal failure is almost inevitable within 2-13 years. The aim of treatment is to give effective supportive therapy and to control the underlying diseases by colchicine, alkylating agents and appropriate antibiotics. The prognosis of patients with end-stage renal failure can be improved by maintenance dialysis and renal transplantation. The growing knowledge about the pathogenesis and chemical nature of amyloid fibrils may open up further avenues for the discovery of

specific therapeutic modalities against amyloidosis.

PMID: 8560604 [Indexed for MEDLINE]

5120. Isr J Med Sci. 1995 Oct;31(10):616-20.

Colchicine-induced lactose malabsorption in patients with familial Mediterranean fever.

Fradkin A(1), Yahav J, Zemer D, Jonas A.

Author information:

(1)Pediatric Gastrointestinal Unit, Chaim Sheba Medical Center, Tel-Hashomer, Israel.

Abdominal pain and diarrhea are frequent side effects of chronic colchicine therapy. Drug-induced lactose deficiency has been demonstrated in the experimental animal. Lactose malabsorption was assessed by the lactose breath test in 23 patients with familial Mediterranean fever (FMF) receiving colchicine for 0.25-15 years (mean 3.16). Twenty FMF patients not receiving colchicine and 38 non-FMF lactose malabsorbers served as controls. Patients receiving colchicine had a significantly higher percentage of lactose malabsorption (20/23, 87%) versus nontreated FMF patients (13/20, 65%;  $P < 0.05$ ). Lactose intolerance was also more prevalent in colchicine-treated patients (17/23, 74%) versus nontreated FMF (5/20, 25%;  $P < 0.0005$ ) and control lactose malabsorbers (16/38, 42%;  $P < 0.01$ ). Of the 12 patients investigated before and 3 months after colchicine administration, 7 showed induction or aggravation of lactose malabsorption. The lactose-free diet resulted in partial improvement of symptoms. Colchicine induces significant lactose malabsorption in FMF patients and this is partially responsible for the gastrointestinal side effects of the drug.

PMID: 7591685 [Indexed for MEDLINE]

5121. Presse Med. 1995 Sep 16;24(26):1211-3.

[Hyperimmunoglobulin D syndrome].

[Article in French]

Drenth JP(1), Denecker NE, Prieur AM, Van der Meer JW.

Author information:

(1)Département de Médecine interne, Hôpital Universitaire St Radboud, Nimègue, Pays-Bas.

The hyper-IgD syndrome is a rare entity characterized by early onset of attacks of periodic fever. All patients have an elevated serum IgD (> 100 U/ml). Symptoms during attacks include joint involvements (arthralgias/arthritis), abdominal complaints (vomiting, pain, diarrhoea), skin lesions, swollen lymph nodes, and headache. In 1992 an International hyper-IgD study group was established, and to date the diagnosis has been made in 60, mainly European patients; 14 come from France. The disorder occurs in families and is transmitted by autosomal recessive inheritance. Linkage studies indicate that the gene encoding for familial Mediterranean fever is different from the gene for the hyper-IgD syndrome. In children the hyper-IgD syndrome should be distinguished from two other periodic febrile disorders. CINCA (chronic inflammatory, neurological, cutaneous and articular syndrome) and FAPA (periodic fever, adenopathies, pharyngitis, and aphthous stomatitis) share some symptoms with the hyper-IgD syndrome but in these syndromes serum IgD is normal. The pathogenesis remains to be elucidated but during attacks all patients have an acute-phase response with elevated C-reactive protein concentrations. During the febrile episodes, the inflammatory cytokines such as IL-6 TNF alpha, IFN gamma are increased together with natural occurring inhibitors such as IL-1ra and sTNFr. There is no therapy for the syndrome and patients will experience attacks during their entire life although frequency and severity tend to diminish with age.

PMID: 7567850 [Indexed for MEDLINE]

5122. FEBS Lett. 1995 Sep 4;371(2):110-4.

Apolipoprotein E increases the fibrillogenic potential of synthetic peptides derived from Alzheimer's, gelsolin and AA amyloids.

Soto C(1), Castaño EM, Prelli F, Kumar RA, Baumann M.

Author information:

(1)Department of Neurology, New York University Medical Center, NY 10016, USA.

Apolipoprotein E (apoE) has been found in association with several different types of systemic and cerebral amyloid deposits and the presence of the epsilon 4 allele constitutes a risk factor for Alzheimer's disease. It has been shown that apoE binds and promotes the fibrillogenesis in vitro of Alzheimer's amyloid beta-peptide, suggesting an important role for apoE in the modulation of amyloidogenesis. Due to the co-localization of apoE with several biochemically distinct amyloid deposits, it has been proposed that apoE plays a general role modulating and/or participating in amyloidosis. In the present study, we show for the first time that apoE, isolated from human plasma, increases fibril formation of synthetic peptides comprising the amyloidogenic sequences of gelsolin amyloid related to familial amyloidosis Finnish type, and amyloid A found in secondary amyloidosis and familial Mediterranean fever. Our results suggest that apoE acts as a general pathological chaperone in various amyloidoses by enhancing the transition from soluble peptides into amyloid-forming, pathological molecules.

PMID: 7672107 [Indexed for MEDLINE]

5123. Angiology. 1995 Sep;46(9):859-61.

Familial Mediterranean fever and primary antiphospholipid syndrome, a rare association. A case report.

Halabe-Cherem J(1), Nellen-Hummel H, Flores-Padilla G, Mercado-Atri M, Pizutto-Chavez J.

Author information:

(1)Department of Medicine, Hospital de Especialidades, Centro Medico Nacional Siglo XXI, I.M.S.S., Mexico City, Mexico.

The authors present the case of a twenty-one-year-old woman with familial Mediterranean fever who during her first pregnancy developed a primary

antiphospholipid syndrome. This is an association not reported previously.

DOI: 10.1177/000331979504600915

PMID: 7661392 [Indexed for MEDLINE]

5124. Clin Immunol Immunopathol. 1995 Sep;76(3 Pt 1):279-84.

Elevated serum level and altered glycosylation of alpha 1-acid glycoprotein in hyperimmunoglobulinemia D and periodic fever syndrome: evidence for persistent inflammation.

Havenaar EC(1), Drenth JP, van Ommen EC, van der Meer JW, van Dijk W.

Author information:

(1)Department of Medical Chemistry, Faculty of Medicine, Vrije Universiteit, Amsterdam, The Netherlands.

Crossed affinoimmunoelectrophoresis using concanavalin A and Aleuria aurantia lectin as diantennary glycan- and fucose-specific affinocomponents, respectively, was applied to study changes in the concentration and glycosylation of the acute phase protein alpha 1-acid glycoprotein (AGP) in sera obtained from patients with hyperimmunoglobulinemia D and periodic fever syndrome. Increases in concentration of AGP compared to control values were found not only during attacks, but also during remissions. Compared to healthy controls, the presence of diantennary glycan-containing glycoforms of AGP also increased during febrile attacks, while no changes were found during remissions. A continuous high degree of alpha 1-->3 fucosylation was accompanied by a continuous high expression of sialyl Lewisx on AGP. Despite the clinical picture of recurrent febrile attacks with asymptomatic intervals, these studies indicate that hyperimmunoglobulinemia D should be considered a condition of persistent inflammation.

PMID: 7554449 [Indexed for MEDLINE]

5125. Isr J Med Sci. 1995 Aug;31(8):503-4.

The origin of the FMF gene.

Pras M, Pras E, Kastner D.

Comment on

Isr J Med Sci. 1995 Aug;31(8):497-9.

PMID: 7635702 [Indexed for MEDLINE]

5126. Isr J Med Sci. 1995 Aug;31(8):497-9.

Familial Mediterranean fever in the "Chuetas" of Mallorca--origin in inquisition?

Buades J(1), Ben-Chetrit E, Levy M.

Author information:

(1)Division of Medicine, Hospital Joan March, Mallorca, Spain.

Comment in

Isr J Med Sci. 1995 Aug;31(8):503-4.

The aim of our study was to compare the features of familial Mediterranean fever (FMF) in Mallorcan "Chuetas" with those in non-Ashkenazi Jews in Israel. The clinical and laboratory data of FMF were evaluated in a recently identified cluster of 50 FMF patients from Mallorca (the Chuetas) and 45 patients from Israel. We found that the prevalence and clinical manifestations of FMF were similar among the Chuetas and the Israeli group. Furthermore, in contrast to other ethnic groups with FMF, joint involvement was quite common in both the Chuetas (70%) and the Israeli group (75%). The Chuetas are descendants of Mallorcan Jews who emigrated from Spain to the island in the 12th century. The non-Ashkenazi Jews originated mainly in North Africa and are descendants of refugees who escaped from Spain as a result of the Inquisition in the 15th century. We suggest that the non-Ashkenazi Jews and the Chuetas may have a common gene defect for FMF.

PMID: 7635700 [Indexed for MEDLINE]



5127. J Intern Med. 1995 Aug;238(2):185-6.

Absence of circulating antineutrophil cytoplasmic antibodies in familial Mediterranean fever.

Simsek H, Kadayifci A.

PMID: 7629490 [Indexed for MEDLINE]

5128. J Biol Chem. 1995 Jul 21;270(29):17610-5.

Apolipoprotein E carboxyl-terminal fragments are complexed to amyloids A and L. Implications for amyloidogenesis and Alzheimer's disease.

Castaño EM(1), Prelli F, Pras M, Frangione B.

Author information:

(1)Department of Pathology, New York University Medical Center, New York 10016, USA.

Apolipoprotein E (ApoE) immunoreactivity is consistently present in the senile plaques and neurofibrillary tangles of Alzheimer's disease (AD) brain. In vitro, apoE, and in particular its apoE4 isoform, can bind to and promote fibrillogenesis of the amyloid A beta peptide, the main constituent of senile plaques. These findings, together with the strong genetic association between late onset AD and the E4 allele of apoE, have strengthened the hypothesis that apoE may have a central role in the pathogenesis of AD by modulating A beta cerebral accumulation. However, apoE immunoreactivity is present in all cerebral and systemic amyloidoses tested, and tryptic apoE fragments have been identified in association with amyloid A (AA). In order to further elucidate the interaction between apoE and amyloids, we purified AA and amyloid L (AL) fibrils from patients with familial Mediterranean fever and primary amyloidosis, respectively, and studied the association of apoE with AA and AL proteins. In each case, apoE fragments, detected by Western blot, co-purified with the amyloid fibrils. Microsequencing analysis identified COOH-terminal fragments of apoE, similar to the 10-kDa fragment produced by thrombin digestion that contains the purported

binding region to A beta. In vitro co-incubation of AA with purified human apoE resulted in the formation of an SDS-resistant AA.apoE complex and a higher degree of polymerization of the AA peptide. These findings and similar results obtained from AD senile plaques suggest that 1) the carboxyl-terminal fragment of apoE is complexed to amyloid fibrils and resists proteolysis in vivo and 2) apoE may promote amyloidogenesis through a conformation-dependent interaction regardless of the primary structure of the amyloid precursors.

PMID: 7615568 [Indexed for MEDLINE]

5129. Ugeskr Laeger. 1995 Jul 10;157(28):4035-7.

[Nephrotic syndrome in familial Mediterranean fever--effect of colchicine therapy].

[Article in Danish]

Højberg AS(1), Mertz H.

Author information:

(1)Børneafdelingen og patologisk institut, Aalborg Sygehus.

Familial Mediterranean fever (FMF) is a genetic disorder virtually restricted to people originating from the Middle East. It is characterized by short, self-limiting, febrile attacks of peritonitis, synovitis, pleuritis or an erysipelas-like erythema. Without treatment systemic amyloidosis often develops and causes death in renal failure, usually at an early age. Two siblings with FMF and renal amyloidosis are presented. One had nephrotic syndrome, the other severe proteinuria. Continuous colchicine treatment reverse the nephrotic syndrome and in both patients the proteinuria was reduced. It is concluded, that even though colchicine can improve severe renal amyloidosis, early diagnosis of FMF is crucial because continuous colchicine treatment prevents both the febrile attacks and the amyloidosis.

PMID: 7645081 [Indexed for MEDLINE]

5130. Am J Med Genet. 1995 Jul 3;57(3):455-7.

Dominant inheritance in two families with familial Mediterranean fever (FMF).

Yuval Y(1), Hemo-Zisser M, Zemer D, Sohar E, Pras M.

Author information:

(1)Heller Institute of Medical Research, Sheba Medical Center, Tel-Aviv  
University Medical School, Tel-Hashomer, Israel.

Familial Mediterranean fever (FMF) is an autosomal-recessive disease which affects almost exclusively people of Mediterranean and Middle Eastern origin. We examined the possibility of a dominant inheritance of FMF among our 3,000 patients in Israel. Two hundred forty FMF patients were members of 77 families in which the disease affected more than one generation. In 75 of these families the occurrence of FMF in more than one generation was found to be consistent with a recessive mode of inheritance due to a high gene frequency (q) and consanguinity among parents of the patients. In 2 families, one of Ashkenazi and the other of Georgian Iraqi origin, in which FMF occurred in 4 consecutive generations, the mode of inheritance could be explained only by autosomal-dominant inheritance.

DOI: 10.1002/ajmg.1320570319

PMID: 7677151 [Indexed for MEDLINE]

5131. Rev Med Univ Navarra. 1995 Jul-Sep;39(3):153-63.

[Update on familial Mediterranean fever].

[Article in Spanish]

Zaglio A.

PMID: 8552918 [Indexed for MEDLINE]

5132. Blood. 1995 Jun 15;85(12):3586-93.

Cytokine activation during attacks of the hyperimmunoglobulinemia D and periodic fever syndrome.

Drenth JP(1), van Deuren M, van der Ven-Jongekrijg J, Schalkwijk CG, van der Meer JW.

Author information:

(1)Department of Medicine, University Hospital St. Radboud, Nijmegen, The Netherlands.

The hyperimmunoglobulinemia D and periodic fever (hyper-IgD) syndrome is typified by recurrent febrile attacks with abdominal distress, joint involvement (arthralgias/arthritis), headache, skin lesions, and an elevated serum IgD level (> 100 U/mL). This familial disorder has been diagnosed in 59 patients, mainly from Europe. The pathogenesis of this febrile disorder is unknown, but attacks are joined by an acute-phase response. Because this response is considered to be mediated by cytokines, we measured the acute-phase proteins C-reactive protein (CRP) and soluble type-II phospholipase A2 (PLA2) together with circulating concentrations and ex vivo production of the proinflammatory cytokines interleukin-1 alpha (IL-1 alpha), IL-1 beta, IL-6, and tumor necrosis factor alpha (TNF alpha) and the inhibitory compounds IL-1 receptor antagonist (IL-1ra), IL-10, and the soluble TNF receptors p55 (sTNFr p55) and p75 (sTNFr p75) in 22 patients with the hyper-IgD syndrome during attacks and remission. Serum CRP and PLA2 concentrations were elevated during attacks (mean, 213 mg/L and 1,452 ng/mL, respectively) and decreased between attacks. Plasma concentrations of IL-1 alpha, IL-1 beta, or IL-10 were not increased during attacks. TNF alpha concentrations were slightly, but significantly, higher with attacks (104 v 117 pg/mL). Circulating IL-6 values increased with attacks (19.7 v 147.9 pg/mL) and correlated with CRP and PLA2 values during the febrile attacks. The values of the antiinflammatory compounds IL-1ra, sTNFr p55, and sTNFr p75 were significantly higher with attacks than between attacks, and there was a significant positive correlation between each. The ex-vivo production of TNF alpha, IL-1 beta, and IL-1ra was significantly higher with attacks, suggesting that the monocytes/macrophages were already primed in vivo to produce increased amounts of these cytokines. These findings point to an activation of the cytokine network, and this suggests that these inflammatory mediators may contribute to the symptoms of the hyper-IgD syndrome.

PMID: 7780142 [Indexed for MEDLINE]

5133. Blood. 1995 Jun 15;85(12):3503-9.

Purification and characterization of a C5a-inactivating enzyme from human peritoneal fluid.

Ayesh SK(1), Azar Y, Barghouti II, Ruedi JM, Babior BM, Matzner Y.

Author information:

(1)Hematology Unit, Hadassah University Hospital, Mount Scopus, Jerusalem, Israel.

Earlier work has suggested that familial Mediterranean fever, an inherited disorder characterized by sporadic episodes of inflammation involving the pleural and peritoneal cavities and the joints, is caused by the lack of a C5a inactivator normally found in serosal fluid. We have purified this inactivator from ascites fluid and obtained a protein of molecular weight 53 to 56 kD with a specific activity 10,000-fold greater than the crude material. On Western blot, an inhibitory antibody recognized a single antigenic species at the same molecular weight. The enzyme had no activity against denatured bovine serum albumin. With recombinant C5a as substrate, the  $K_m$  and  $V_m$  were 3.4  $\mu\text{mol/L}$  and 52 nmol C5a/min/mg protein, respectively.

PMID: 7780136 [Indexed for MEDLINE]

5134. Recenti Prog Med. 1995 Jun;86(6):243-7.

[Hyper-IgD syndrome (HIDS)].

[Article in Italian]

Scolozzi R.

In 1984, Van der Meer first reported six patients with a long history of

recurrent attacks of fever of unknown cause and a constantly elevated polyclonal IgD (> 100 U/mL); he suggested the acronym of "hyper-IgD syndrome" (HIDS). A recent literature review identified 60 cases (59 from Europe and 1 from Japan). The mean age was 27 years (range: 3-69 years). The family studies have shown a positive family history for periodic fever (40% out of the patients) but not for hyper-IgD. The median age at onset was 0.5 years (range from the first weeks of life to 53 years). The length of the febrile attacks, though variable, lasted from 3 to 7 days. The frequency of the attacks varied among the individual patients, but in general it was once a month or bimonthly. The fever was sustained in all 60 patients (from 38 degrees C to 41 degrees C), with a rapid rise, a plateau and a slow decline to normal values over 5 days. The associated clinical findings involve abdominal symptoms (pain, vomiting, diarrhea), recurrent peritonitis, lymphadenopathy, splenomegaly, articular manifestations (non-destructive recurrent arthritis) and skin lesions (vasculitis). The prognosis is benign. The aetiopathogenesis of HIDS is unknown. The role of IgD in the pathogenesis remains to be elucidated. The therapy is only supportive.

PMID: 7624586 [Indexed for MEDLINE]

5135. Clin Infect Dis. 1995 Jun;20(6):1491, 1547.

Photo quiz. Familial Mediterranean fever (FMF)

Jones SR.

Comment in

Clin Infect Dis. 1996 May;22(5):881-2.

PMID: 7548497 [Indexed for MEDLINE]

5136. Harefuah. 1995 May 15;128(10):611-2, 672.

[Recurrent pericarditis in familial Mediterranean fever].

[Article in Hebrew]

Tauber T(1), Zimand S, Kotzer E.

Author information:

(1)Pediatrics Dept., Assaf Harofeh Medical Center, Z'rifin.

The diagnosis of familial Mediterranean fever (FMF) is based on clinical evidence, since there is no specific diagnostic test. Manifestations are recurrent attacks of fever accompanied by serositis, mainly involving the peritoneum, pleura and joints. Although pericardial inflammation has been considered rare, when echocardiography is used to detect it, an incidence of 27% has been reported. We describe a boy of 11 and a girl of 15 years who developed recurrent pericarditis despite treatment with steroids, nonsteroidal anti-inflammatory drugs and pericardiocentesis. A few months after the first episode, both patients were admitted with typical bouts of FMF. Continuous prophylaxis with colchicine was initiated, and there were no further attacks during 18 and 10 month follow-ups, respectively. We conclude that acute or recurrent pericarditis in children or young adults of Mediterranean origin may be due to FMF.

PMID: 7601373 [Indexed for MEDLINE]

5137. Presse Med. 1995 Apr 8;24(14):691-4.

[Testicular localization of systemic diseases].

[Article in French]

Gillot JM(1), Brouillard M, Hatron PY, Devulder B.

Author information:

(1)Service de Médecine interne A, Hôpital Claude Huriez, CHRU de Lille.

Comment in

Presse Med. 1995 Nov 18;24(35):1666.

Acute orchitis or a mass in testis usually evokes a neoplasm, a torsion or

infectious disease for the clinician. Rarely, a systemic disease is involved. Nevertheless, testicular involvement occurs during vasculitis, Behçet or granulomatous diseases, but is uncommonly the first manifestation. Histologic changes after biopsy or orchiectomy usually give the diagnosis. Testicular localization of systemic disease does not change the general treatment.

PMID: 7770418 [Indexed for MEDLINE]

5138. J Pediatr Surg. 1995 Apr;30(4):577-9.

Adhesive small bowel obstruction caused by familial Mediterranean fever: the incidence and outcome.

Ciftci AO(1), Tanyel FC, Büyükpamukçu N, Hiçsönmez A.

Author information:

(1)Department of Pediatric Surgery, Hacettepe University, Ankara, Turkey.

Familial Mediterranean fever (FMF) is a disease characterized by recurring and self-limiting attacks of febrile serosal inflammation involving the peritoneal, synovial, and pleural membranes. Peritonitis is the most common clinical picture of FMF, and repeated acute abdominal episodes may result in formation of peritoneal adhesions that may cause adhesive small bowel obstruction (ASBO) requiring surgical intervention. This subject has neither been clarified nor thoroughly evaluated in the literature. The records of 355 pediatric patients diagnosed to have FMF were reviewed in order to clarify the incidence and outcome of ASBO without prior laparotomy during the course of FMF. The incidence rate has been found as 3% with no mortality. This figure shows ASBO to be the most frequent complication of FMF. Therefore this life-threatening surgical emergency should be kept in mind in the differential diagnosis of acute abdominal attacks during the course of FMF.

PMID: 7595838 [Indexed for MEDLINE]

5139. Crit Rev Oncol Hematol. 1995 Mar;18(3):197-205.



Biologic and clinical advances in familial Mediterranean fever.

Matzner Y(1).

Author information:

(1)Hematology Unit, Hadassah University Hospital, Mount Scopus, Jerusalem, Israel.

PMID: 7695832 [Indexed for MEDLINE]

5140. Am J Hum Genet. 1995 Feb;56(2):519-27.

Rapid multipoint linkage analysis of recessive traits in nuclear families, including homozygosity mapping.

Kruglyak L(1), Daly MJ, Lander ES.

Author information:

(1)Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology, Cambridge 02142.

Homozygosity mapping is a powerful strategy for mapping rare recessive traits in children of consanguineous marriages. Practical applications of this strategy are currently limited by the inability of conventional linkage analysis software to compute, in reasonable time, multipoint LOD scores for pedigrees with inbreeding loops. We have developed a new algorithm for rapid multipoint likelihood calculations in small pedigrees, including those with inbreeding loops. The running time of the algorithm grows, at most, linearly with the number of loci considered simultaneously. The running time is not sensitive to the presence of inbreeding loops, missing genotype information, and highly polymorphic loci. We have incorporated this algorithm into a software package, MAPMAKER/HOMOZ, that allows very rapid multipoint mapping of disease genes in nuclear families, including homozygosity mapping. Multipoint analysis with dozens of markers can be carried out in minutes on a personal workstation.

PMCID: PMC1801139

PMID: 7847388 [Indexed for MEDLINE]

5141. J Rheumatol. 1995 Feb;22(2):376-7.

Absence of antineutrophil cytoplasmic autoantibodies in familial Mediterranean fever.

Rozenbaum M, Rosner I, Naschitz Y, Golan TD.

PMID: 7738973 [Indexed for MEDLINE]

5142. Am J Med Genet. 1995 Jan 30;55(3):311-4.

Familial Mediterranean fever: high gene frequency among the non-Ashkenazic and Ashkenazic Jewish populations in Israel.

Daniels M(1), Shohat T, Brenner-Ullman A, Shohat M.

Author information:

(1)Institute of Medical Genetics, FMRC, Beilinson Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Petah Tiqva, Israel.

Familial Mediterranean fever (FMF) is an autosomal recessive recurrent episodic inflammatory disorder that occurs with high frequency in certain populations in the Mediterranean area. Using extended pedigree data of 90 FMF probands, we calculated the FMF gene frequency in various ethnic groups in Israel by analyzing the frequency in a total of 2,312 first cousins. The heterozygote frequencies were as follows: 1:4.9 (0.2 +/- 0.06) for the Libyan subgroup, 1:6.4 (0.16 +/- 0.03) for the other North African countries subgroup, 1:13.3 (0.07 +/- 0.04) for the Iraqi subgroup, 1:11.4 (0.09 +/- 0.06) for the Ashkenazic subgroup, and 1:29.4 (0.03 +/- 0.03) for the remaining ethnic groups. The observed number of affected parents and offspring of the probands was in agreement with the estimated gene frequency. Thus, the FMF gene frequency is very high in all Jewish ethnic groups in Israel, especially those originating in North African countries. This also explains the parent-to-off-spring transmission of FMF reported in

North-African Jews.

DOI: 10.1002/ajmg.1320550313

PMID: 7726228 [Indexed for MEDLINE]

5143. J Med. 1995;26(3-4):133-8.

HLA-B5 in the diagnosis of Behcet's disease.

Augarten A(1), Yahav Y, Szeinberg A, Fradkin A, Gazit E, Laufer J.

Author information:

(1)Department of Pediatrics B, Chaim Sheba Medical Center, Tel Hashomer, Israel.

Behçet's disease, a multisystem disease is, by its nature, difficult to diagnose. The first manifestation of the disease may precede the appearance of other symptoms and signs essential for diagnosis by many years. In patients of Mediterranean origin, the early manifestations of the disease, may be confused with those of familial Mediterranean fever (FMF). Determination of HLA-B5 may, however, contribute to the diagnosis in children with partial manifestations of Behçet syndrome.

PMID: 8558094 [Indexed for MEDLINE]

5144. Rev Med Interne. 1995;16(10):782-9.

[Colchicine: recent data on pharmacokinetics and clinical pharmacology].

[Article in French]

Chappey O(1), Scherrmann JM.

Author information:

(1)Laboratoire de pharmacocinétique, faculté de pharmacie, université Paris V, France.

Colchicine is widely used in the treatment of acute gouty arthritis. Recently, colchicine was shown to be effective in inflammatory diseases such as familial Mediterranean fever. Two proteins can modulate its pharmacokinetics: tubulin, the specific intracellular receptor for colchicine which determines the plasma half-life, and P-glycoprotein, an active efflux pump towards some anticancer drugs which regulates colchicine absorption, distribution, and elimination. Therapeutic dosage is monitored empirically, by the control of the balance between the occurrence of side effects and the clinical efficacy. Recently, using a specific and sensitive radioimmunoassay, the investigation of plasma concentrations during single and multiple dose studies has allowed to define the colchicine pharmacokinetic parameters. Following oral route, colchicine bioavailability is extremely variable (from 24 to 88% of the administered dose), the distribution volume is elevated (7 l/kg) but the binding to albumin is moderate. Colchicine elimination occurred mainly via hepatic pathways and the elimination half-life ranged from 20 to 40 hours. In multiple dose study (1 mg/d), the steady-state is reached 8 days after the first oral administration and plasma concentrations ranged from 0.3 to 2.5 ng/ml. Pharmacokinetic/pharmacodynamic studies show that the biological effects of colchicine were not related to plasma concentrations but with intraleukocyte concentrations. Drug interactions may occur when colchicine is associated to drugs which interact with cytochrome P450 and/or P-glycoprotein and modify renal and/or hepatic clearances. The therapeutic drug monitoring of colchicine during these circumstances could allow to prevent the observation of side effects.

PMID: 8525161 [Indexed for MEDLINE]

5145. Nephron. 1995;69(1):124.

Pattern of proteinuria in patients with renal amyloidosis secondary to familial Mediterranean fever.

Colakoglu M, Sungur C, Sungur A, Akpolat T, Kansu E, Yasavul U, Turgan C, Caglar S.

DOI: 10.1159/000188388

PMID: 7891791 [Indexed for MEDLINE]

5146. Clin Exp Rheumatol. 1995 Jan-Feb;13(1):126.

Regression of amyloidosis with colchicine in familial Mediterranean fever in an Ashkenazi patient.

Rozenbaum M, Rosner I.

PMID: 7774093 [Indexed for MEDLINE]

5147. Curr Opin Rheumatol. 1995 Jan;7(1):58-64.

Cryoglobulinemia and other dysproteinemias, familial Mediterranean fever, and POEMS syndrome.

Cuéllar ML(1), García C, Molina JF.

Author information:

(1)Louisiana State University School of Medicine, Department of Medicine, New Orleans 70112, USA.

The introduction of newer technology in the past few years, especially the use of second-generation enzyme-linked immunosorbent assays, recombinant immunoblot assays, reverse transcriptase, and DNA amplification, have clearly defined the role of hepatitis C virus as the most important etiologic factor in the development of mixed cryoglobulinemia. This has led to a better understanding of the pathogenic mechanisms involved in disease expression, particularly vasculitis, and also has provided a rationale for the use of interferon alfa and other antiviral drugs in the therapy of these disorders. The clinical manifestations of the syndrome also have been well characterized, as well as some of the risk factors. There also has been an improvement in our understanding of the pathogenic mechanisms involved in multiple myeloma and related monoclonal gammopathies, as well as several attempts to improve early recognition of bone disease with magnetic resonance imaging. The susceptibility gene for familial Mediterranean fever has been better characterized, as have risk factors for colchicine toxicity. The role of cytokines has been better delineated for both monoclonal gammopathies and POEMS (polyneuropathy, organomegaly, endocrinopathy,

M protein, and skin changes) syndrome.

PMID: 7718425 [Indexed for MEDLINE]

5148. Ter Arkh. 1995;67(5):83-4.

[A rare case of a combination of hereditary amyloidosis and sarcoidosis].

[Article in Russian]

Androsova SS, Kornev BM, Miroshnichenko NG, Privezentseva ND.

PMID: 7638791 [Indexed for MEDLINE]

5149. Adv Exp Med Biol. 1995;371B:901-3.

The gene for familial Mediterranean fever is mapped to 16p 13.3- p13.1 with evidence for homogeneity.

Shohat M(1), Fischel-Ghodsian N, Rotter JI, Danon YL.

Author information:

(1)Children's Medical Center of Israel Petah-Tikva.

PMID: 7502922 [Indexed for MEDLINE]

5150. Nihon Naibunpi Gakkai Zasshi. 1994 Dec 20;70(10):1075-82.

[A case of familial Mediterranean fever with obvious family history].

[Article in Japanese]

Takenaka K(1), Yanase T, Nagatomo H, Tanaka A, Nawata H.

Author information:

(1)Third Department of Internal Medicine, Faculty of Medicine, Kyusyu University.

A 26-year-old female was admitted to our hospital on December 4, 1992, because of recurrent fever. She had experienced recurrent fever of over 38 degrees C, occurring at irregular intervals 4-6 times a year with chest or abdominal pain, since the age of 19. After delivery of a baby at the age of 25, her symptoms had increased to once a week. In the febrile phase, leukocytosis, an increased erythrocyte sedimentation rate and positive CRP were recognized. These symptoms and laboratory findings spontaneously disappeared within a few days. Despite systemic and careful examinations, no evidence of infectious diseases, collagen diseases or malignant diseases were found. There were no significant differences of serum and urine catecholamines, and urine etiocholanolone between the febrile phase and the afebrile phase. An intravenous infusion of metaraminol induced symptoms similar to a spontaneous attack, and the metaraminol rechallenge test became negative after she was treated with oral colchicine. Based on these findings, she was diagnosed as having familial Mediterranean fever. Since she was treated with colchicine, the febrile attacks have decreased. Significantly, her elder brother has had similar recurrent fever with abdominal pain. He was diagnosed as having familial Mediterranean fever due to a positive metaraminol provocative test, and his febrile attacks have also been suppressed by colchicine. This is the first case of familial Mediterranean fever with obvious family history in Japan.

PMID: 7859887 [Indexed for MEDLINE]

5151. Hum Genet. 1994 Dec;94(6):616-20.

Location of the gene causing hyperimmunoglobulinemia D and periodic fever syndrome differs from that for familial Mediterranean fever. International Hyper-IgD Study Group.

Drenth JP(1), Mariman EC, Van der Velde-Visser SD, Ropers HH, Van der Meer JW.

Author information:

(1)Department of Medicine, University Hospital St Radboud, Nijmegen, The

Netherlands.

The hyperimmunoglobulinemia D and periodic fever (hyper-IgD) syndrome is typified by recurrent febrile attacks with abdominal distress, joint involvement (arthralgias/arthritis), headache, skin lesions, and an elevated serum IgD level ( $> 100$  U/ml). This familial disorder has been diagnosed in 56 subjects worldwide. As the hyper-IgD syndrome resembles familial Mediterranean fever, one could speculate that both result from mutations in the same gene. The gene causing familial Mediterranean fever (MEF) has been located on chromosome 16p. We have studied 10 families with 19 affected and 28 non-affected subjects. The clinical findings and IgD determinations from these families are compatible with autosomal recessive inheritance. Using highly polymorphic markers surrounding the MEF gene, only negative Lod scores were obtained, whereas haplotype analysis excluded this locus as the cause of the hyper-IgD syndrome. In addition, no indication for linkage was obtained with markers from other candidate gene regions on chromosomes 17q and 14q.

PMID: 7989036 [Indexed for MEDLINE]

5152. Arthritis Rheum. 1994 Dec;37(12):1804-11.

Colchicine treatment of AA amyloidosis of familial Mediterranean fever. An analysis of factors affecting outcome.

Livneh A(1), Zemer D, Langevitz P, Laor A, Sohar E, Pras M.

Author information:

(1)Sheba Medical Center, Tel-Hashomer, Israel.

**OBJECTIVE:** To elucidate factors possibly influencing the outcome of colchicine therapy in patients with amyloidosis of familial Mediterranean fever (FMF).

**METHODS:** Retrospective analysis of data abstracted from the charts of all 68 FMF patients with amyloidosis who presented during the study period (1974-1992) with proteinuria ( $\geq 0.5$  gm/24 hours) and creatinine values  $\leq 2.5$  mg/dl, received colchicine, and were followed up for  $\geq 5$  years.

**RESULTS:** At the end of the study period, kidney disease had worsened in 31 patients and remained stable in 22. Proteinuria had regressed in 15 patients.



Deterioration was related to initial serum creatinine values  $\geq 1.5$  mg/dl ( $P < 0.01$ ) and to mean colchicine dosage  $\leq 1.5$  mg/day ( $P < 0.001$ ). The 3 groups were comparable in terms of initial urinary protein levels, duration of proteinuria, presence of hypertension, occurrence of febrile attacks, sex distribution, and proportion of non-compliant patients.

**CONCLUSION:** The therapeutic dosage of colchicine for amyloidosis of FMF is  $> 1.5$  mg/day. This dosage is effective only in patients with initial serum creatinine levels  $< 1.5$  mg/dl.

PMID: 7986228 [Indexed for MEDLINE]

5153. Acta Neurol Scand. 1994 Dec;90(6):412-6.

Risk factors of aseptic intracranial venous occlusive disease.

Najim al-Din AS(1), Mubaidin A, Wriekat AL, Alqam M.

Author information:

(1)Jordan University Hospital, Medical Centre, Amman.

**INTRODUCTION:** Risk factors for aseptic intracranial venous occlusive disease are varied but only few epidemiologic studies were performed to verify the relative importance of particular factors.

**PATIENTS AND METHODS:** A 2-year hospital-based prospective study was conducted in two hospitals to identify the clinical characteristics and risk factors of patients with confirmed aseptic intracranial venous occlusive disease.

**RESULTS:** 21 patients were identified, representing 0.9% of the total neurological admissions. Men were more commonly affected than women; 81% of the patients presented in a clinical picture indistinguishable from idiopathic intracranial hypertension. Risk factors included Behçet's disease in 4, the puerperium in 3, thrombophilia in 3, familial Mediterranean fever in 2, malignancies in 1, lupus anticoagulant in 1, and the contraceptive pill in 1.

**CONCLUSION:** Aseptic intracranial venous occlusive disease proved to be not rare in Arabs. It should be considered seriously in the differential diagnosis of idiopathic intracranial hypertension, particularly in males. Several risk factors were incriminated.

PMID: 7892760 [Indexed for MEDLINE]

5154. Hum Genet. 1994 Nov;94(5):576-7.

The gene causing familial Mediterranean fever maps to the short arm of chromosome 16 in Druze and Moslem Arab families.

Pras E(1), Aksentijevich I, Levy E, Gruberg L, Prosen L, Dean M, Pras M, Kastner DL.

Author information:

(1)Arthritis and Rheumatism Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD 20892.

PMID: 7959700 [Indexed for MEDLINE]

5155. Am J Med Genet. 1994 Nov 1;53(2):172-5.

Possible protection against asthma in heterozygotes for familial Mediterranean fever.

Brenner-Ullman A(1), Melzer-Ofir H, Daniels M, Shohat M.

Author information:

(1)Department of Medical Genetics, FMRC, Beilinson Medical Center, Petah Tiqva, Israel.

To identify a specific heterozygote advantage in familial Mediterranean fever (FMF), responsible for the high carrier rate of 1/6 in North African Jews, we studied the morbidity and mortality of 148 parents of affected patients and of 148 ethnically matched control persons. Our data demonstrate an apparently reduced prevalence of asthma in the heterozygotes compared with the control persons (3 vs. 6). There were no significant differences between the 2 groups in fertility rate, number of pregnancies and deliveries, or the prevalence of common

diseases. Our data are in agreement with previous studies which demonstrated decreased asthma prevalence in FMF patients. It further confirmed, these findings suggest that identification of the FMF gene on 16p may provide an insight into asthma.

DOI: 10.1002/ajmg.1320530210

PMID: 7856643 [Indexed for MEDLINE]

5156. N Engl J Med. 1994 Oct 6;331(14):934-8.

Clinical problem-solving. Still hazy after all these years.

Ben-Chetrit E(1), Putterman C.

Author information:

(1)Rheumatology Unit, Hadassah University Hospital, Jerusalem, Israel.

Comment in

N Engl J Med. 1995 Feb 2;332(5):332; author reply 333.

N Engl J Med. 1995 Feb 2;332(5):332-3.

N Engl J Med. 1995 Feb 2;332(5):333.

DOI: 10.1056/NEJM199410063311409

PMID: 7888006 [Indexed for MEDLINE]

5157. Br J Rheumatol. 1994 Oct;33(10):995-6.

Muscle ultrasound evaluation of patients with familial Mediterranean fever complicated by myalgia.

Saatci U, Topaloglu R, Bakkaloglu A, Topaloglu H.

PMID: 7921772 [Indexed for MEDLINE]

5158. Semin Arthritis Rheum. 1994 Oct;24(2):124-38.

Amyloidosis: prognosis and treatment.

Gertz MA(1), Kyle RA.

Author information:

(1)Division of Hematology and Internal Medicine, Mayo Clinic, Rochester, MN 55905.

The objective of this study was to review (1) the factors that have been linked to prediction of clinical outcome and survival in amyloidosis and (2) the available studies on the therapy for localized and systemic forms of amyloidosis. We made a retrospective review of the relevant literature on treatment and prognosis in localized and systemic amyloidosis dating back to 1975. The most important prognostic factors in amyloidosis are the presence of congestive heart failure, beta 2-microglobulin, and whether peripheral neuropathy dominates the presentation. The presence of a monoclonal light chain in serum or urine, multiple myeloma, and hepatic involvement are also important adverse factors. Colchicine is beneficial in treating familial Mediterranean fever and may play a role in managing secondary amyloidosis in inflammatory bowel disease. Chlorambucil is particularly useful in juvenile rheumatoid arthritis with amyloidosis. Dimethyl sulfoxide provides benefit in bladder and lichen amyloidosis. A trial of alkylating agent-based chemotherapy is reasonable in symptomatic primary systemic amyloidosis. Advances have been made in the treatment of amyloidosis and include chemotherapy, dialysis, transplantation, and improved supportive care. Definite disease regressions with long-term survival (> 10 years) are seen. Unfortunately, alternatives still need to be developed: Of 859 patients with primary systemic amyloidosis seen at the Mayo Clinic from 1982 to 1992, the median survival was 2.1 years.

PMID: 7839154 [Indexed for MEDLINE]

5159. J Pediatr Endocrinol. 1994 Oct-Dec;7(4):371-2.

Amyloid goiter in a child with familial Mediterranean fever.

Mache CJ(1), Schwingshandl J, Ring E, Pflieger A, Borkenstein MH.

Author information:

(1)Department of Pediatrics, University of Graz, Austria.

A 7 year-old Turkish boy presented with a euthyroid goiter, which was noted during evaluation of familial Mediterranean fever. Amyloid deposits in the thyroid were found on fine-needle aspiration biopsy. Slight involution of the goiter within seven months may be attributed either to colchicine therapy or to treatment with levothyroxine and iodide.

PMID: 7735378 [Indexed for MEDLINE]

5160. J Rheumatol. 1994 Sep;21(9):1708-9.

Protracted febrile myalgia in patients with familial Mediterranean fever.

Langevitz P(1), Zemer D, Livneh A, Shemer J, Pras M.

Author information:

(1)Heller Institute of Medical Research, Sheba Medical Center, Tel-Aviv  
University Medical School, Tel-Hashomer, Israel.

**OBJECTIVE:** We describe a newly defined syndrome of protracted febrile myalgia in patients with familial Mediterranean fever (FMF).

**METHODS:** Fourteen patients with FMF were admitted with an attack of severe disabling myalgia accompanied by fever, high erythrocyte sedimentation rate, and hyperglobulinemia, lasting up to 6 weeks.

**RESULTS:** Unlike in the classical manifestations of FMF response to corticosteroids therapy was prompt.

**CONCLUSION:** Protracted febrile myalgia is an uncommon dramatic manifestation of FMF that may occur despite colchicine therapy and requires treatment with corticosteroids.

PMID: 7799354 [Indexed for MEDLINE]

5161. Baillieres Clin Rheumatol. 1994 Aug;8(3):691-7.

Amyloidosis in children.

Woo P(1).

Author information:

(1)Section of Molecular Rheumatology, MRC Clinical Research Centre, Northwick Park Hospital, Harrow, Middlesex, UK.

PMID: 7954869 [Indexed for MEDLINE]

5162. J Trop Pediatr. 1994 Aug;40(4):243-5. doi: 10.1093/tropej/40.4.243.

Acute hepatitis in recurrent hereditary polyserositis (familial Mediterranean fever).

Neequaye J(1), Jelly AE.

Author information:

(1)Department of Paediatrics, North West Armed Forces Hospital, Tabuk, Saudi Arabia.

The clinical features of two cases of Hereditary Recurrent Polyserositis HRP (Familial Mediterranean Fever) in related Yemeni children resident in Saudi Arabia are described. One presented with recurrent acute hepatitis, which has not been previously documented. These are the first cases of HRP reported in Arabs originating from the Arabian Peninsula.

DOI: 10.1093/tropej/40.4.243

PMID: 7932940 [Indexed for MEDLINE]

5163. Schweiz Rundsch Med Prax. 1994 Jul 5;83(27-28):809-13.

[Acute abdomen].

[Article in German]

Schmid PA(1), Suter S, Greminger P.

Author information:

(1)Departement für Innere Medizin, Universitätsspital Zürich.

A 28-year-old turkish patient was admitted to hospital several times within the last years because of acute abdominal and thoracic pain. On each admission laboratory parameters indicative of an acute inflammatory process were initially found to be slightly increased; however, the cause for the complaints remained undetected. During a recent episode of acute abdominal pain a short increase of these laboratory parameters (particularly of CRP) could be documented, and since no other diagnostic sign indicative of an other disease was found, familial mediterranean fever was diagnosed. A basic therapy with colchicine was initiated, and since five months the patient remained mostly free of symptoms.

PMID: 8047760 [Indexed for MEDLINE]

5164. J Rheumatol. 1994 Jul;21(7):1335-7.

Fibromyalgia in familial Mediterranean fever.

Langevitz P(1), Buskila D, Finkelstein R, Zaks N, Neuman L, Sukenik S, Smythe HA, Pras M.

Author information:

(1)Heller Institute of Medical Research, Chaim Sheba Medical Center, Tel Hashomer, Israel.

**OBJECTIVE:** To determine whether chronic lower body pain in a subpopulation of patients with familial Mediterranean fever (FMF) is due directly to the musculoskeletal manifestations of FMF or whether they are connected to mechanical problems in the low back and leg/foot or to other factors operative in fibromyalgia (FM).

**METHODS:** In 93 consecutive patients with FMF a point count of 14 tender points (TP) was conducted by thumb palpation. Tenderness thresholds were assessed in

some of the TP and of control point sites by Chatillon dolorimeter.

RESULTS: In female patients with FMF dolorimeter thresholds of fibrositic and control point sites were significantly lower than in male patients with FMF ( $p < 0.004$ ). Also patients with FMF with back pain and foot/leg pain are more tender than patients with FMF without this characteristic ( $p < 0.001$ ).

CONCLUSION: The detection of FM and definition of tenderness thresholds is relevant to this disease, since musculoskeletal complaints are common in this group of patients but not always explained by objective findings.

PMID: 7966080 [Indexed for MEDLINE]

5165. J Pediatr Gastroenterol Nutr. 1994 Jul;19(1):121-2.

A case of familial Mediterranean fever and Niemann-Pick disease.

Ozen S(1), Saatci U, Bakaloglu A, Besbas N, Kocak N.

Author information:

(1)Department of Pediatric Nephrology, Hacettepe University Children's Hospital, Sıhhiye, Ankara, Turkey.

PMID: 7965463 [Indexed for MEDLINE]

5166. Br J Clin Pharmacol. 1994 Jul;38(1):87-9.

Colchicine concentration in leukocytes of patients with familial Mediterranean fever.

Chappey O(1), Niel E, Dervichian M, Wautier JL, Scherrmann JM, Cattani D.

Author information:

(1)Laboratoire de Biologie Vasculaire et Cellulaire, Université Paris 7, Hôpital Lariboisière, France.

Free and total plasma, granulocyte and mononuclear cell colchicine concentrations



were measured by radioimmunoassay in 30 patients with familial Mediterranean fever treated with colchicine 0.5 to 2 mg day<sup>-1</sup>. Colchicine concentrations showed a large intersubject variability in plasma (0.13-1.75 ng ml<sup>-1</sup>), granulocytes (4 to 64 ng/10<sup>9</sup> cells), and mononuclear cells (11.4 to 57.6 ng/10<sup>9</sup> cells). Whereas unbound and total plasma colchicine concentrations were well correlated, no correlation was found between total or free plasma and granulocyte or mononuclear cell colchicine concentrations and dose of administered colchicine. In contrast, total or free plasma and granulocyte or mononuclear cell colchicine concentrations were correlated using a hyperbolic function indicating saturable colchicine distribution in both leukocyte populations.

PMCID: PMC1364844

PMID: 7946943 [Indexed for MEDLINE]

5167. Transpl Int. 1994 Jul;7(4):292-6.

Polyarteritis nodosa type vasculitis in a patient with familial Mediterranean fever treated with cyclosporin A.

Henckes M(1), Roskams T, Vanneste S, Van Damme B, Vanrenterghem Y.

Author information:

(1)Department of Nephrology, University Hospital, U.Z. Gasthuisberg, Leuven, Belgium.

Patients with amyloidosis secondary to familial Mediterranean fever (FMF) are known to tolerate cyclosporin A poorly. We report a case of severe cyclosporin toxicity in a patient with FMF amyloidosis who underwent kidney transplantation. The clinical syndrome consisted of severe gastrointestinal, neuromuscular, and psychiatric disturbances. Histological examination of the transplanted kidney revealed vasculitis of the polyarteritis nodosa type. We hypothesize that FMF patients are more vulnerable to the acute vascular toxicity of cyclosporin due to defective inhibition of complement activation, leading to a widespread vasculitis of the polyarteritis nodosa type.

PMID: 7916931 [Indexed for MEDLINE]

5168. Therapie. 1994 Jul-Aug;49(4):339-42.

[Colchicine poisoning apropos of a pediatric case].

[Article in French]

Dubois V(1), Rey N, Constant H, Scherrmann JM, Berthier JC, Aulagner G.

Author information:

(1)Service de Pharmacie, Hôpital Debrousse, Lyon.

Colchicine has been widely used in the treatment of gout and familial mediterranean fever. Overdose is rare mostly in childhood. Colchicine overdose always causes gastrointestinal side effects, bone marrow depression and sometimes neuropathy. The mechanism of colchicine upon the microtubules, provides a better understanding of the pharmacology and also of the multiorgan involvement. We report the case of a ten year old child who ingested 0.6 mg/kg colchicine with a good outcome.

PMID: 7878601 [Indexed for MEDLINE]

5169. Arch Intern Med. 1994 Jun 27;154(12):1411, 1414.

Familial Mediterranean fever in Mexico City: 10-year follow-up.

Cherem JH, Hummel HN, Padilla GF.

PMID: 8002695 [Indexed for MEDLINE]

5170. Br J Surg. 1994 Jun;81(6):894-6.

Acute scrotal pain complicating familial Mediterranean fever in children.

Eshel G(1), Vinograd I, Barr J, Zemer D.

Author information:

(1)Paediatric Intensive Care Unit, Assaf Harofeh Medical Centre, Zerifin, Israel.

Twenty-nine children with familial Mediterranean fever presented with 39 attacks of acute scrotal pain. Of these, 25 patients had an acute scrotum complicating familial Mediterranean fever and only four had testicular torsion. Scrotal pain was the only manifestation of a familial Mediterranean fever crisis in 36 episodes and in 15 boys scrotal involvement was the first manifestation of the condition. Fourteen patients were treated medically. Of 15 patients who underwent scrotal exploration there were no definite diagnostic findings in 11 and four had testicular torsion. Three cardinal features strongly suggest the diagnosis of acute scrotum in familial Mediterranean fever in a boy of Mediterranean origin with a relevant family history: recurrent scrotal pain or swelling; body temperature above 37.5 degrees C; and gradual onset of pain, usually of more than 12 h duration. Conservative management can safely be undertaken in these boys without fear of losing a salvageable testis.

PMID: 8044614 [Indexed for MEDLINE]

5171. Medicine (Baltimore). 1994 May;73(3):133-44.

Hyperimmunoglobulinemia D and periodic fever syndrome. The clinical spectrum in a series of 50 patients. International Hyper-IgD Study Group.

Drenth JP(1), Haagsma CJ, van der Meer JW.

Author information:

(1)Department of Medicine, University Hospital St Radboud, Nijmegen, The Netherlands.

We studied 50 patients (28 male and 22 female) with the hyper-IgD and periodic fever syndrome. Most patients originated from Europe, namely The Netherlands (28 cases; 56%), France (10 cases, 20%), and Italy (3 cases, 6%), but 1 patient was from Japan. A hereditary component is suggested by 18 patients coming from 8 families. The syndrome is typified by a very early age at onset (median, 0.5

years) and life-long persistence of periodic fever. Characteristically, attacks occur every 4-8 weeks and continue for 3-7 days, but the individual variation is large. Attacks feature high spiking fever, preceded by chills in 76% of patients. Lymphadenopathy is commonly present (94% of patients). During attacks, 72% of patients complained of abdominal pains, 56% of vomiting, 82% of diarrhea, and 52% of headache. Joint involvement is common in the hyper-IgD syndrome with poly-arthralgia in 80% and a non-destructive arthritis, mainly of the large joints (knee and ankle), in 68% of patients. Eighty-two percent of patients reported skin lesions with some attacks; these demonstrated vasculitis histologically. Serositis has been seen in only 3 patients (6%), while amyloidosis has not been recorded in any of the patients with this syndrome. Immunizations precipitated attacks in 54% of patients. All patients had a persistently elevated serum IgD level ( $> 100$  U/mL), and in 82% of cases the serum IgA was likewise elevated. During attacks there is an acute-phase response adjudged by leukocytosis, neutrophilia, and increased ESR. The etiology remains to be elucidated, and treatment is supportive. The hyper-IgD syndrome is distinct from other periodic fever syndromes like systemic-onset juvenile rheumatoid arthritis, adult-onset Still disease, and familial Mediterranean fever.

PMID: 8190036 [Indexed for MEDLINE]

5172. Clin Exp Rheumatol. 1994 May-Jun;12(3):347-8.

The clinical features of Familial Mediterranean Fever of elderly onset.

Rozenbaum M, Rosner I.

PMID: 8070176 [Indexed for MEDLINE]

5173. Presse Med. 1994 Apr 16;23(15):718.

Urinary neopterin level in familial Mediterranean fever.

Arat-Altindag Z, Sahin G, Ozyilkan E, Isimer A, Telatar H.

PMID: 8072985 [Indexed for MEDLINE]

5174. J Rheumatol. 1994 Apr;21(4):710-3.

Colchicine disposition in patients with familial Mediterranean fever with renal impairment.

Ben-Chetrit E(1), Scherrmann JM, Zylber-Katz E, Levy M.

Author information:

(1)Division of Medicine, Hadassah University Hospital, Jerusalem, Israel.

**OBJECTIVE:** To assess the pharmacokinetics of serum colchicine in patients with familial Mediterranean fever (FMF) with renal impairment.

**METHODS:** Using a specific radioimmunoassay we determined serum colchicine concentration at various time points following oral administration of a single dose of the drug.

**RESULTS:** Patients with renal insufficiency had a mean  $\pm$  SD apparent total colchicine clearance of  $0.168 \pm 0.063$  l/h/kg, apparent volume of distribution of  $4.56 \pm 1.64$  l/kg and elimination half-life ( $t_{1/2}$ ) of  $18.8 \pm 1.2$  h.

Patients with FMF with normal kidney function had a mean clearance of  $0.726 \pm 0.110$  l/h/kg, volume of distribution of  $4.87 \pm 2.05$  l/kg and terminal  $t_{1/2}$  of  $4.4 \pm 1.0$  h.

**CONCLUSION:** The kidneys have an important role in the clearance of colchicine. Caution should be exercised in the use of colchicine in patients with renal insufficiency.

PMID: 8035398 [Indexed for MEDLINE]

5175. Histopathology. 1994 Mar;24(3):215-21.

Lymphatic amyloidosis, a previously unrecognized form of amyloid deposition in generalized amyloidosis.

Kaiserling E(1), Kröber S.

Author information:

(1)Institute of Pathology, University of Tübingen, Germany.

Comment in

Histopathology. 1994 Dec;25(6):597-8.

Although amyloid deposition in relation to blood vessels is a well-recognized feature of generalized amyloidosis, lymphatic vessel amyloidosis is not mentioned in the literature. Systematic investigation of tissue removed at autopsy from patients with generalized amyloidosis and biopsy specimens from cases of localized amyloidosis and familial Mediterranean fever showed that amyloid deposition around lymphatics is by no means uncommon. The material investigated was mainly large and small bowel, lung, heart and kidney. Amyloid was identified by green birefringence with the Congo red stain on cross-polarization and lymphatics by their lack of immunostaining for CD34. Involvement of lymphatics was noted in 20 of the 42 organs from which specimens were examined, and was always accompanied by involvement of blood vessels and/or the interstitium. In the intestine, lymphatic amyloidosis was found mainly in the submucosa and subserosa, and was also demonstrated by electronmicroscopy in one case. Although lymphatic amyloidosis was equally common in the heart, lung and kidney, it was usually less prominent here than in the intestine. No lymphatic involvement was seen in localized amyloidosis. As the lymphatics play a central role in the resorption of interstitial proteins, they are probably also involved in the resorption of amyloid proteins. Amyloid deposition in the vicinity of lymphatics is probably the result of decompensation of this process.

PMID: 8200623 [Indexed for MEDLINE]

5176. Isr J Med Sci. 1994 Mar;30(3):237-8.

Absence of asthma in patients with familial Mediterranean fever.

Ozyilkan E(1), Simsek H, Telatar H.

Author information:

(1)Hacettepe University Medical Center, Department of Internal Medicine, Ankara,

Turkey.

PMID: 8181925 [Indexed for MEDLINE]

5177. J Med Genet. 1994 Mar;31(3):224-33.

Autosomal recessive disorders among Arabs: an overview from Kuwait.

Teebi AS(1).

Author information:

(1)Department of Genetics, Yale University School of Medicine, New Haven, Connecticut.

Kuwait has a cosmopolitan population of 1.7 million, mostly Arabs. This population is a mosaic of large and small minorities representing most Arab communities. In general, Kuwait's population is characterized by a rapid rate of growth, large family size, high rates of consanguineous marriages within the Arab communities with low frequency of intermarriage between them, and the presence of genetic isolates and semi-isolates in some extended families and Bedouin tribes. Genetic services have been available in Kuwait for over a decade. During this time it has become clear that Arabs have a high frequency of genetic disorders, and in particular autosomal recessive traits. Their pattern is unique and some disorders are relatively common. Examples are Bardet-Biedl and Meckel syndromes, phenylketonuria, and familial Mediterranean fever. A relatively large number of new syndromes and variants have been delineated in Kuwait's population, many being the result of homozygosity for autosomal recessive genes that occurred because of inbreeding. Some of these syndromes have subsequently been found in other parts of the world, negating the concept of the private syndrome. This paper provides an overview of autosomal recessive disorders among the Arabs in Kuwait from a personal perspective and published studies, and highlights the need for genetic services in Arab countries with the goal of prevention and treatment of genetic disorders.

PMCID: PMC1049748

PMID: 8014972 [Indexed for MEDLINE]

5178. Lancet. 1994 Feb 19;343(8895):485.

Familial Mediterranean fever: a misnomer?

Saatci U, Ozen S, Bakkaloglu A, Besbas N.

PMID: 7905983 [Indexed for MEDLINE]

5179. J Urol. 1994 Feb;151(2):431-2.

Recurrent episodes of acute scrotum with ischemic testicular necrosis in a patient with familial Mediterranean fever.

Livneh A(1), Madgar I, Langevitz P, Zemer D.

Author information:

(1)Heller Institute of Medical Research, Sheba Medical Center, Tel-Hashomer, Israel.

The tunica vaginalis is 1 of the sites involved in the recurrent febrile attacks of serositis, which are the hallmark of familial Mediterranean fever. The attacks present clinically as "orchitis." We report on a patient with familial Mediterranean fever in whom recurrent episodes of scrotal attacks were complicated by testicular necrosis requiring orchiectomy. The case emphasizes the challenge of recognizing and differentiating these attacks from other causes of acute scrotum.

PMID: 8283547 [Indexed for MEDLINE]

5180. J Rheumatol. 1994 Feb;21(2):383.

Transplacental passage of colchicine in familial Mediterranean fever.



Amoura Z, Schermann JM, Wechsler B, Zerah X, Goodeau P.

PMID: 8182666 [Indexed for MEDLINE]

5181. World J Surg. 1994 Jan-Feb;18(1):139-41; discussion 141-2.

Elective laparoscopic appendectomy in patients with familial Mediterranean fever.

Reissman P(1), Durst AL, Rivkind A, Szold A, Ben-Chetrit E.

Author information:

(1)Department of General Surgery, Hadassah University Hospital, Jerusalem, Israel.

Familial Mediterranean fever (FMF) also known as hereditary polyserositis, is an inherited disorder commonly found in Armenians, Turks, Arabs, Balkans, and Jews originating from North African countries. The diagnosis of FMF is based on clinical findings and family history, as no specific diagnostic test is yet available. One of its main clinical features is recurrent acute episodes of peritonitis. During such an episode, physical examination and laboratory findings may be similar to those for acute appendicitis. Therefore up to two-thirds of FMF patients undergo emergency appendectomy, with the appendix being normal in most cases. As laparoscopic appendectomy has proved to be safe and advantageous, and to prevent misdiagnosis and unnecessary emergency surgery, we performed elective laparoscopic appendectomy in 13 FMF patients ranging in age from 8 to 32 years. They had been suffering from the disease for 1 to 12 years (mean 3.8) and had had an average of 3.5 yearly episodes of FMF peritonitis. All procedures were concluded by laparoscopy without conversion to open surgery. The average postoperative hospital stay was 3.07 days. The only complication was superficial wound infection in one patient (7.6%), and the mean time to regain full normal activity was 8.5 days. We conclude that elective laparoscopic appendectomy in FMF patients is safe. It helps to exclude appendicitis as a cause for peritonitis in these patients and may prevent unnecessary emergency surgery.

PMID: 8197770 [Indexed for MEDLINE]

5182. Nephrol Dial Transplant. 1994;9(2):218-9.

Late histological recurrence of familial Mediterranean fever amyloidosis after renal transplantation.

Thervet E, Noel LH, Legendre C, Page B, Kreis H.

PMID: 8190345 [Indexed for MEDLINE]

5183. Clin Exp Rheumatol. 1994 Jan-Feb;12(1):96.

Familial Mediterranean fever in an individual of Maltese extraction: history is destiny.

Rosenstein ED, Kramer N.

PMID: 8162654 [Indexed for MEDLINE]

5184. Clin Exp Rheumatol. 1994 Jan-Feb;12(1):67-9.

Familial Mediterranean fever presenting with massive cardiac tamponade.

Zimand S(1), Tauber T, Hegesch T, Aladjem M.

Author information:

(1)Department of Pediatrics, Hssaf Harofeh Medical Center, Tel Aviv, Israel.

A 16-year-old girl, presenting initially with pericarditis and life threatening pericardial tamponade, developed clinical episodes characteristic of FMF few months later. This case report and several others reported previously, suggest that FMF should be considered in patients from certain ethnic groups presenting with pericardial effusion.

PMID: 8162646 [Indexed for MEDLINE]

5185. Arch Dis Child. 1994 Jan;70(1):27-9.

Serum concentration and urinary excretion of beta 2-microglobulin and microalbuminuria in familial Mediterranean fever.

Saatci U(1), Ozdemir S, Ozen S, Bakkaloglu A.

Author information:

(1)Department of Paediatric Nephrology, Hacettepe University, Faculty of Medicine, Ankara, Turkey.

Familial Mediterranean fever is characterised by recurrent and self limited attacks of fever and polyserositis and its devastating complication is the development of renal amyloidosis. In order to detect the presence of early glomerular and tubular damage in patients with familial Mediterranean fever and to assess the possible role of beta 2-microglobulin in the inflammatory attacks of this disease, serum and urine beta 2-microglobulin concentrations and microalbuminuria were evaluated in these patients. A total of 20 patients with familial Mediterranean fever were studied on and off colchicine treatment; seven of these patients developed a familial Mediterranean fever attack when they were off treatment. During the familial Mediterranean fever attacks serum beta 2-microglobulin concentrations decreased, whereas fractional excretion of beta 2-microglobulin, urine beta 2-microglobulin creatinine, and urine albumin/creatinine ratios increased. We conclude that glomerular and tubular functions deteriorate during the attacks. Further studies are needed to discover the effector(s) causing these transient glomerular and tubular disorders.

PMCID: PMC1029677

PMID: 8110003 [Indexed for MEDLINE]

5186. Nephron. 1994;68(1):152.

Beta-2-microglobulin levels of dialysis patients with renal amyloidosis secondary to familial Mediterranean fever.

Sungur C, Ozen S, Ozkuyumcu C, Akpolat T, Yasavul U, Turgan C, Caglar S.

DOI: 10.1159/000188244

PMID: 7991035 [Indexed for MEDLINE]

5187. Nephrol Dial Transplant. 1994;9(6):704-8.

Study of live donor kidney transplantation outcome in recipients with renal amyloidosis.

Sobh M(1), Refaie A, Moustafa F, Shokeir A, Hassan N, Sally S, Ghoneim M.

Author information:

(1)Urology and Nephrology Center, University of Mansoura, Egypt.

We studied the results of renal transplantation in 16 patients with renal amyloidosis and in 46 controls with primary glomerulonephritis. Amyloidosis was primary in five and secondary to familial Mediterranean fever (FMF) in 11. All patients received live related donor kidneys and the majority had one-haplotype HLA match. One- and 5-year graft and patient survival rates were comparable in both groups. Moreover, the frequency of acute rejection episodes and the mean serum creatinine values were not significantly different between members of the two groups. Significant gastrointestinal symptoms in the form of nausea, vomiting, abdominal pains, and diarrhoea occurred in seven of the patients with amyloidosis (43.7%) and in only one of the controls (2%) ( $P = 0.001$ ). All seven recipients with amyloidosis who developed the gastrointestinal manifestations were receiving cyclosporin and six had FMF. Maintenance colchicine treatment prevented recurrence of FMF symptoms. In one patient discontinuation of colchicine was followed by recurrence of FMF symptoms. Recurrence of renal amyloidosis was not observed in five patients subjected to Trucut graft biopsies 1, 2, 3, 18 and 72 months post-transplantation. It is concluded that live-related donor kidney transplantation is a safe procedure in patients with amyloidosis and follows a course similar to glomerulonephritis patients.

PMID: 7970100 [Indexed for MEDLINE]

5188. Semin Arthritis Rheum. 1993 Dec;23(3):206-14.

Colchicine in the treatment of AA and AL amyloidosis.

Livneh A(1), Zemer D, Langevitz P, Shemer J, Sohar E, Pras M.

Author information:

(1)Heller Institute of Medical Research, Sheba Medical Center, Tel Hashomer, Israel.

Colchicine is an effective medication in the prevention and treatment of amyloidosis of familial Mediterranean fever. Its therapeutic effect depends on the stage of renal disease and the drug dose. To evaluate colchicine effect in AA amyloidosis of other diseases and in primary AL amyloidosis, the literature was reviewed. Findings were that (1) the effect of colchicine in reactive amyloidosis has not been methodically studied, but anecdotal reports suggest it may be beneficial; and (2) the results of studies and case reports on the effect of colchicine in primary amyloidosis are conflicting. Because a therapeutic effect of colchicine in primary and reactive amyloidosis has been shown in sporadic cases, a prospective, controlled, multicenter study assessing the effect of colchicine in all types of amyloidosis appears to be justified. Until such a study is available, the addition of colchicine in an appropriate dose to any therapeutic regimen of patients with AA or AL amyloidosis should be considered.

PMID: 8122124 [Indexed for MEDLINE]

5189. Radiographics. 1993 Nov;13(6):1295-308.

CT evaluation of amyloidosis: spectrum of disease.

Urban BA(1), Fishman EK, Goldman SM, Scott WW Jr, Jones B, Humphrey RL, Hruban RH.

Author information:

(1)Department of Radiology and Radiological Science, Johns Hopkins Hospital, Baltimore, MD 21287.

Amyloidosis is a rare systemic disease caused by extracellular deposition of an insoluble protein. Although it is usually seen in a systemic form, 10%-20% of cases can be localized. Systemic amyloidosis is subclassified into an idiopathic primary form and a secondary or reactive form. Patients with primary amyloidosis have no underlying condition or disease. Men are affected more than women, and the mean age at presentation is 55-60 years. Some causes of secondary amyloidosis are multiple myeloma (10%-15%), rheumatoid arthritis (20%-25%), tuberculosis (50%), or familial Mediterranean fever (26%-40%). Radiographic studies of 90 patients with biopsy-proved primary or secondary amyloidosis were reviewed. Computed tomographic (CT) scans demonstrated a wide spectrum of disease in the cardiothoracic, gastrointestinal, genitourinary, and musculoskeletal systems. Amyloid deposition simulated both inflammatory and neoplastic conditions. Amorphous or irregular calcifications were occasionally identified within the amyloid deposit. Definitive diagnosis requires biopsy confirmation, as CT findings are nonspecific.

DOI: 10.1148/radiographics.13.6.8290725

PMID: 8290725 [Indexed for MEDLINE]

5190. J Hered. 1993 Nov-Dec;84(6):438-42.

Inheritance of renal amyloidosis in Chinese Shar-pei dogs.

Rivas AL(1), Tintle L, Meyers-Wallen V, Scarlett JM, van Tassell CP, Quimby FW.

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Renal amyloidosis (RA) and recurrent fever of unknown origin (RFUO) are characteristics of familial Mediterranean fever (FMF), a human disorder inherited as an autosomal-recessive trait. Although no animal model has been established for FMF, a similar syndrome of RFUO and RA has been reported in Chinese Shar-pei (CSP) dogs. This report addresses two questions: (1) Is RA inherited in CSP dogs? (2) If it is, is it possible to hypothesize the type of inheritance involved? Two studies were conducted to answer these questions: a historical cross-sectional comparison, which included CSP and non-CSP dogs with RA; and a prospective study

that included CSP dogs with RA, RFUO, or both. The cross-sectional comparison resulted in an odds ratio of 10 for RA in CSP dogs under 7 years of age. The prospective study of 28 dogs with RA or RFUO identified 20 that had RFUO and RA, three with RA alone, and five with RFUO alone. RFUO preceded RA in all cases with both conditions. The RFUO/RA combination was observed in both sexes. Four dogs with RFUO with or without RA were born to parents that either were alive at age 7 or had died because of conditions other than kidney failure/RA. When one parent was known to express one of these conditions, the prevalence of RA was between 25% and 50% among littermates.(ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 8270767 [Indexed for MEDLINE]

5191. Dig Dis Sci. 1993 Nov;38(11):2017-21.

Effect of long-term colchicine therapy on jejunal mucosa.

Hart J(1), Lewin KJ, Peters RS, Schwabe AD.

Author information:

(1)Department of Pathology, UCLA School of Medicine.

Colchicine is recommended as daily prophylactic therapy in patients with familial Mediterranean fever (FMF) to prevent febrile paroxysms. The drug is known to be a potent inhibitor of mitotic activity and might therefore be expected to have a significant adverse effect on tissues that undergo rapid turnover. We studied small bowel biopsies from nine patients with FMF who were receiving daily low-dose oral colchicine therapy. In each patient the lengths of 20 crypts and villi were measured and the number of mitotic figures in 20 crypts were counted. The data were compared with similar measurements from histologically normal-appearing biopsies obtained from 14 patients with a variety of mild gastrointestinal complaints. The mean crypt length was found to be significantly greater (0.197 mm vs 0.186 mm,  $P < 0.0001$ ) and the mean villous length significantly smaller (0.369 mm vs. 0.442 mm,  $P < 0.0001$ ) in the FMF patients than in the control population. In addition, the mean number of mitotic figures per crypt was significantly higher in the FMF patients (2.58 vs 1.00,  $P < 0.001$ ). The data reveal a pattern of mucosal injury in the colchicine-treated FMF patients characterized by a hyperplastic crypt-villous atrophy pattern with

increased mitotic rate, which is indicative of an increase in cell turnover and opposite to what we anticipated based on colchicine's known effect on mitotic activity.

PMID: 8223075 [Indexed for MEDLINE]

5192. J Formos Med Assoc. 1993 Nov;92(11):1013-6.

Taiwanese patient with recurrent polyserositis: report of a case.

Lee WY(1), Tsai S, Kao JH, Lai MY.

Author information:

(1)Department of Internal Medicine and Emergency Medicine, National Taiwan University Hospital, Taipei, R.O.C.

A 26-year-old man had suffered from recurrent abdominal pain, ascites and arthralgia since childhood. The symptoms occurred usually during the winter, and each attack lasted for two to three days. Initially, the frequency was about once a year, but it had increased to once every one to four months after an exploratory laparotomy carried out four years ago. Leukocytosis accompanied each episode. Many laboratory examinations and imaging studies failed to show pathologic lesions. Laparoscopic examination revealed only yellowish ascites with a hyperemic mesentery and omentum. There were never any sequelae after the attacks. After prophylaxis with colchicine 0.6 mg three times a day, no more attacks occurred. Familial Mediterranean fever (familial paroxysmal polyserositis) was the most likely diagnosis. Recognizing this disease entity in Taiwanese patients may help to avoid unnecessary operations.

PMID: 7910060 [Indexed for MEDLINE]

5193. Monatsschr Kinderheilkd. 1993 Oct;141(10):782-5.

[Monosymptomatic familial Mediterranean fever as the cause of fever of unknown origin].



[Article in German]

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(1)Universitätsklinik für Kinderheilkunde, Wien.

A previously healthy 2 year old female child developed fever of unknown origin recurring in monthly cycles. The periodic fever attacks, family history and ethnologic criteria were in agreement with familial mediterranean fever, although further more major symptoms were missing. It was highly unusual to find repeatedly raised levels of angiotensin I converting enzyme, a finding previously not described in literature. Excluding any other differential diagnosis by intensive investigations, together with a positive metaraminol provocation test, the diagnosis of a rare, monosymptomatic variant of familial mediterranean fever was proposed. Amyloidosis was excluded by rectal biopsy. Monosymptomatic familial mediterranean fever is very seldom. We suggest to measure routinely angiotensin I converting enzyme for further evaluation of our findings.

PMID: 8264679 [Indexed for MEDLINE]

5194. Eur J Pediatr. 1993 Oct;152(10):864-5.

Temporomandibular joint involvement in familial Mediterranean fever.

Mukamel M, Mimouni M.

PMID: 8223794 [Indexed for MEDLINE]

5195. Turk J Pediatr. 1993 Oct-Dec;35(4):249-56.

The association between Henoch-Schönlein syndrome and renal amyloidosis: a proposal of a pathogenic mechanism.

Tinaztepe K(1), Güçer S, Bakkaloğlu A, Tinaztepe B.

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(1)Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.

The clinicopathological analysis of 250 pediatric cases that had been tissue-diagnosed with renal amyloidosis revealed three patients associated with Henoch-Schönlein syndrome (HSS). The renal biopsies revealed AA-type amyloidosis in all three cases. Case 2 displayed focal and segmental proliferative glomerulonephritis in the same renal biopsy. No evidence of well-known diseases and/or conditions for the development of AA-type amyloidosis except for familial Mediterranean fever (FMF) existed in these particular cases. On the other hand, the frequency of the association between FMF and HSS has been reported extensively in the literature; thus, common etiological factors can be considered. The mechanism involved in amyloid deposition in these cases may be related to HSS-associated chronic antigenemia and/or FMF through a mechanism that is, to date, unknown. Further studies are needed to clarify this causal relationship.

PMID: 8160275 [Indexed for MEDLINE]

5196. Kidney Int. 1993 Oct;44(4):834-6.

Diagnostic value of bone marrow biopsy in patients with renal disease secondary to familial Mediterranean fever.

Sungur C(1), Sungur A, Ruacan S, Arik N, Yasavul U, Turgan C, Caglar S.

Author information:

(1)Department of Nephrology, Hacettepe University, School of Medicine, Ankara, Turkey.

Systemic AA type amyloidosis with renal involvement is the major cause of morbidity and mortality in patients with familial Mediterranean fever (FMF). A histopathological examination is essential to achieve a definite diagnosis in systemic amyloidosis. The diagnostic yield of the procedure varies according to the biopsy site and renal biopsy has the highest yield. On the other hand this

procedure has its own complications and requires hospitalization of the patient. Alternative biopsy sites have been proposed with varying degrees of sensitivity and morbidity to reduce the morbidity and mortality of solid organ biopsies. We performed bone marrow biopsies in 39 patients with FMF who had different stages of renal disease. Thirty-one (79.5%) of the 39 specimens showed significant perivascular amyloid infiltration when stained with crystal violet and Congo red. An immunoperoxidase stain with a monoclonal antibody proved that these deposits were AA type amyloid. We suggest that bone marrow biopsy can be utilized for a safe and quick diagnosis of systemic amyloidosis in patients with FMF and renal disease.

PMID: 7505040 [Indexed for MEDLINE]

5197. Ned Tijdschr Geneeskd. 1993 Sep 11;137(37):1898.

[A Dutch family with familial Mediterranean fever].

[Article in Dutch]

Knoers N, Hamel B.

Comment on

Ned Tijdschr Geneeskd. 1993 Jul 31;137(31):1570-3.

PMID: 8413688 [Indexed for MEDLINE]

5198. Free Radic Biol Med. 1993 Sep;15(3):265-71.

Oxyradical-mediated chromosome damage in patients with familial Mediterranean fever.

Emerit I(1), Arutyunyan R, Sarkisian T, Mejlumian H, Torosian E, Panossian AG.

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Increased chromosome breakage is observed in patients with familial mediterranean fever (FMF). Their plasma contains clastogenic material inducing chromosome damage in cells from healthy persons. It is proposed that increased oxyradical generation by activated polymorphonuclear cells in blood and serosal fluids of these patients leads to the formation of a clastogenic factor (CF), as it is observed in other chronic inflammatory diseases. Also similar to these diseases, the clastogenic effects are prevented by superoxide dismutase and partially by inhibitors of arachidonic acid metabolism.

PMID: 8406126 [Indexed for MEDLINE]

5199. Clin Exp Rheumatol. 1993 Sep-Oct;11(5):578-9.

Familial Mediterranean fever is not associated with the antiphospholipid syndrome.

Rozenbaum M, Rosner I.

PMID: 8275598 [Indexed for MEDLINE]

5200. J Rheumatol. 1993 Sep;20(9):1544-9.

Overproduction of monocyte derived tumor necrosis factor alpha, interleukin (IL) 6, IL-8 and increased neutrophil superoxide generation in Behçet's disease. A comparative study with familial Mediterranean fever and healthy subjects.

Mege JL(1), Dilsen N, Sanguedolce V, Gul A, Bongrand P, Roux H, Ocal L, Inanç M, Capo C.

Author information:

(1)Laboratoire d'Immunologie, Hôpital de Sainte-Marguerite, Marseille, France.

OBJECTIVE: The etiopathogenesis of Behçet's disease (BD) has not yet been

clarified but might involve immune dysfunction. As cytokines are involved in the regulation of immune responses and inflammatory reactions, we investigated whether they may play a role in the pathogenesis of BD.

**METHODS:** We investigated spontaneous and lipopolysaccharide (LPS) stimulated production of tumor necrosis factor alpha (TNF alpha), interleukin (IL) 1, IL-6, IL-8 and granulocyte monocyte macrophage colony stimulating factor (GM-CSF) by peripheral blood monocytes from 21 patients with BD, 10 healthy controls and 10 patients with familial Mediterranean fever (FMF), another chronic inflammatory disease. We also studied superoxide generation and surface antigen expression by polymorphonuclear neutrophils (PMN).

**RESULTS:** The spontaneous secretion of TNF alpha, IL-6 and IL-8 by monocytes was significantly increased in patients with active BD. The secretion of TNF alpha, IL-1, IL-6 and IL-8 was found to be in normal range in asymptomatic patients with FMF. The LPS stimulated production of TNF alpha, IL-6, IL-1 and IL-8 was significantly increased in patients with BD, without any correlation with BD activity. In vitro, PMN spontaneously generated significant amounts of superoxide in patients with active BD.

**CONCLUSION:** Taken together, our results suggest that monocyte and PMN dysfunctions may play a role in the pathogenesis of BD.

PMID: 8164212 [Indexed for MEDLINE]

5201. J Rheumatol. 1993 Sep;20(9):1519-23.

Effect of pregnancy on renal function in amyloidosis of familial Mediterranean fever.

Livneh A(1), Cabili S, Zemer D, Rabinovitch O, Pras M.

Author information:

(1)Heller Institute of Medical Research, Sheba Medical Center, Tel-Hashomer, Israel.

**OBJECTIVE:** To study the effect of pregnancy on kidney function in patients with familial Mediterranean fever (FMF) with amyloidosis.

**METHODS:** A retrospective analysis relating kidney function at term to kidney function at conception and to blood pressure and colchicine treatment before and

during pregnancy in 17 patients with 29 pregnancies found among more than 3000 patient files in our FMF clinic.

RESULTS: Following pregnancy, 7 patients (24% of pregnancies) experienced a decline in renal function. Urine protein  $\geq 2$  g/24 h at conception was present in all pregnancies which sustained deterioration in contrast to 6 of 22 which did not ( $p < 0.001$ ). Serum creatinine  $\geq 1.5$  mg/dl at conception was present in 3 patients, all of whom experienced deterioration of renal function during pregnancy ( $p < 0.01$ ). Neither colchicine dose nor elevated blood pressure correlated with status of renal function at term.

CONCLUSION: Our findings suggest a possible deleterious effect of pregnancy on amyloid nephropathy and that this effect may be associated with more advanced renal disease at conception.

PMID: 8164208 [Indexed for MEDLINE]

5202. Sarcoidosis. 1993 Sep;10(2):132-3.

Familial Mediterranean fever. Another cause of raised serum angiotensin converting enzyme; another abortive attempt at masquerading as sarcoidosis.

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PMID: 8140300 [Indexed for MEDLINE]

5203. Am J Hum Genet. 1993 Sep;53(3):644-51.

Familial Mediterranean fever (FMF) in Moroccan Jews: demonstration of a founder effect by extended haplotype analysis.

Aksentijevich I(1), Pras E, Gruberg L, Shen Y, Holman K, Helling S, Prosen L, Sutherland GR, Richards RI, Dean M, et al.

Author information:

(1)Arthritis and Rheumatism Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD 20892.

Familial Mediterranean fever (FMF) is an autosomal recessive disease causing attacks of fever and serositis. The FMF gene (designated "MEF") is on 16p, with the gene order 16cen-D16S80-MEF-D16S94-D16S283-D16S291-++ +16pter. Here we report the association of FMF susceptibility with alleles as D16S94, D16S283, and D16S291 among 31 non-Ashkenazi Jewish families (14 Moroccan, 17 non-Moroccan). We observed highly significant associations at D16S283 and D16S291 among the Moroccan families. For the non-Moroccans, only the allelic association at D16S94 approached statistical significance. Haplotype analysis showed that 18/25 Moroccan FMF chromosomes, versus 0/21 noncarrier chromosomes, bore a specific haplotype for D16S94-D16S283-D16S291. Among non-Moroccans this haplotype was present in 6/26 FMF chromosomes versus 1/28 controls. Both groups of families are largely descended from Jews who fled the Spanish Inquisition. The strong haplotype association seen among the Moroccans is most likely a founder effect, given the recent origin and genetic isolation of the Moroccan Jewish community. The lower haplotype frequency among non-Moroccan carriers may reflect differences both in history and in population genetics.

PMCID: PMC1682431

PMID: 8102507 [Indexed for MEDLINE]

5204. Acta Paediatr. 1993 Aug;82(8):705-6.

Familial Mediterranean fever and amyloidosis in children.

Saatci U(1), Bakkaloglu A, Ozen S, Besbas N.

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(1)Department of Pediatric Nephrology, Hacettepe University Faculty of Medicine, Sıhhiye, Ankara, Türkiye.

PMID: 8374224 [Indexed for MEDLINE]

5205. Am J Hum Genet. 1993 Aug;53(2):451-61.

Refined mapping of the gene causing familial Mediterranean fever, by linkage and homozygosity studies.

Aksentijevich I(1), Pras E, Gruberg L, Shen Y, Holman K, Helling S, Prosen L, Sutherland GR, Richards RI, Ramsburg M, et al.

Author information:

(1)Arthritis and Rheumatism Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD 20892.

Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by attacks of fever and serosal inflammation; the biochemical basis is unknown. We recently reported linkage of the gene causing FMF (designated "MEF") to two markers on chromosome 16p. To map MEF more precisely, we have now tested nine 16p markers. Two-point and multipoint linkage analysis, as well as a study of recombinant haplotypes, placed MEF between D16S94 and D16S80, a genetic interval of about 9 cM. We also examined rates of homozygosity for markers in this region, among offspring of consanguineous marriages. For eight of nine markers, the rate of homozygosity among 26 affected inbred individuals was higher than that among their 20 unaffected sibs. Localizing MEF more precisely on the basis of homozygosity rates alone would be difficult, for two reasons: First, the high FMF carrier frequency increases the chance that inbred offspring could have the disease without being homozygous by descent at MEF. Second, several of the markers in this region are relatively nonpolymorphic, with a high rate of homozygosity, regardless of their chromosomal location.

PMCID: PMC1682355

PMID: 8328461 [Indexed for MEDLINE]

5206. Ned Tijdschr Geneesk. 1993 Jul 31;137(31):1570-3.



[A Dutch family with familial Mediterranean fever].

[Article in Dutch]

Zweers EJ(1), Erkelens DW.

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Comment in

Ned Tijdschr Geneeskd. 1993 Sep 11;137(37):1898.

Familial mediterranean fever (or recurrent hereditary polyserositis) is a genetic disorder with an autosomal recessive pattern of inheritance which occurs mostly in patients with eastern Mediterranean origin. Two Dutch patients are described, a 25-year-old women and her 58-year-old father, who suffered from recurring abdominal complaints, fever, and increased erythrocyte sedimentation rate, without evidence of Middle Eastern ancestry or hyperimmunoglobulinemia D.

PMID: 8366955 [Indexed for MEDLINE]

5207. Am J Med Genet. 1993 Jul 1;46(6):689-93.

Regional mapping of the gene for familial Mediterranean fever on human chromosome 16p13.

Fischel-Ghodsian N(1), Bu X, Prezant TR, Oeztas S, Huang ZS, Bohlman MC, Rotter JI, Shohat M.

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(1)Ahmanson Department of Pediatrics, Cedars-Sinai Medical Center, Los Angeles, CA 90048.

Familial Mediterranean fever (FMF) is an autosomal recessively inherited inflammatory disorder characterized by recurrent short episodes of fever, peritonitis, arthritis, and pleuritis. Recently, linkage was demonstrated between FMF and the VNTR probes 3'HVR and 5'HVR of the alpha-globin complex at 16p13.3

(theta = 0.06-0.10, Lodmax = 9.76-14.47) and the insertion/deletion polymorphism detected by the probe CMM65 of D16S84 (theta = 0.04, Lodmax = 9.17). We have now mapped the FMF gene between the two flanking markers D16S283/D16S291 (theta = 0.038) and D16S80 (theta = 0.159). The proximity of the microsatellite markers in D16S283 and D16S291 to the FMF gene allows preclinical diagnosis in most pedigrees with affected individuals.

DOI: 10.1002/ajmg.1320460619

PMID: 8362911 [Indexed for MEDLINE]

5208. Hum Genet. 1993 Jul;91(6):527-34.

Evidence for linkage of the gene causing familial Mediterranean fever to chromosome 17q in non-Ashkenazi Jewish families: second locus or type I error?

Aksentijevich I(1), Gruberg L, Pras E, Balow JE Jr, Kovo M, Gazit E, Dean M, Pras M, Kastner DL.

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(1)Arthritis and Rheumatism Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD 20892.

Familial Mediterranean fever (FMF) is an autosomal recessive disorder of unknown pathogenesis, characterized by recurrent, self-limited attacks of fever with synovitis, peritonitis, or pleurisy. Using DNAs from affected Israeli families, we have recently mapped the gene causing FMF (designated MEF) to the short arm of chromosome 16, with two-point lod scores in excess of 20. In this report we consider the possibility of a second FMF susceptibility locus. Before discovering linkage to markers on chromosome 16, we had found suggestive evidence for linkage to chromosome 17q, with the following maximal two-point lod scores: D17S74 (pCMM86),  $Z = 2.47$ , (theta = 0.20); D17S40 (pLEW101),  $Z = 2.15$  (theta = 0.15); D17S35 (CRI-pP3-1),  $Z = 1.78$  (theta = 0.15); D17S46 (pLEW108),  $Z = 1.69$  (theta = 0.18), D17S254,  $Z = 2.30$  (theta = 0.20). Moreover, multipoint linkage analysis using D17S74 and D17S40 as fixed loci gave  $Z = 3.27$  approximately 10 centimorgans (cM) telomeric to D17S40. Data with the chromosome 17 markers alone in our families suggested locus heterogeneity. Nevertheless, our families were not separable into complementary subsets showing linkage either to chromosome 16 or

to chromosome 17. We also examined the possibility that the positive lod scores for chromosome 17 might reflect a secondary, modifying locus. By several measures of disease severity, families with positive lod scores for chromosome 17 loci had no worse disease than those with negative lod scores for these loci. We conclude that chromosome 17 does not encode a major FMF susceptibility gene for some of the families, nor does it encode a disease-modifying gene. Rather, it would appear that linkage to chromosome 17 is a "false positive" (type I) error. These results reemphasize the fact that a lod score of 3.0 corresponds to a posterior probability of linkage of 95%, with an attendant 1 in 20 chance of observing a false positive.

PMID: 8340105 [Indexed for MEDLINE]

5209. *Pediatr Med Chir.* 1993 Jul-Aug;15(4):361-5.

[Autonomic neural functioning in children with the periodic syndrome].

[Article in Italian]

Meossi C(1), Domenici R, Saponati G, Castelli S.

Author information:

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The pathogenesis of periodic syndrome (recurrent abdominal pain, cyclic vomiting, headache and other equivalents of childhood migraine) is often related in the literature to a "neuro-vegetative dysfunction", by which occasional stimuli (environmental, metabolic, emotional) should find a particular somatic expression. The homeostatic role of the autonomic nervous system could be deficient in these cases, but systematic research has never been done to explore this hypothesis. We have evaluated the autonomic nervous function in 38 children (12 M, 26 F) with periodic syndrome, by cardiovascular autonomic function tests. They consist of ortho- and parasympathetic parameters obtained by ECG registration and pressure monitoring during deep breathing, Valsalva manoeuvre, lying to standing postural change, sustained handgrip. In the absence of adequate pediatric references values, we have previously standardized these tests in a population of 198 healthy children (94 M, 104 F), aged 8.3-15.7 years. Results

have been compared with our standard reference values, matching them by t-test for independent data: in both sexes, significant differences have been found out in only one of 11 parameters ( $p < 0.05$ ) of the autonomic tests performed.

Children affected by periodic syndrome reveal a reduced heart rate variation in transition from the early orthosympathetic phase to the late parasympathetic one after lying to standing passage, showing a smaller fluctuation of autonomic feedback systems. The physiological meaning of this result is unclear. However, in children with periodic syndrome no prevalence of ortho- or parasympathetic systems is evident.

PMID: 8265455 [Indexed for MEDLINE]

5210. *Pediatr Neurol.* 1993 Jul-Aug;9(4):301-2.

Neurologic manifestations in familial Mediterranean fever.

Gedalia A(1), Zamir S.

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(1)Pediatric Rheumatology Unit, Soroka Medical Center, Ben Gurion University of the Negev Beer Sheva, Israel.

Neurologic involvement in children with familial Mediterranean fever is relatively uncommon and rarely described in the pediatric literature. Although headaches occur frequently, meningitis and convulsions are rare. Thirteen of 101 children with familial Mediterranean fever developed neurologic manifestations. Of these 13 patients, 10 had headaches during acute episodes of the fever. Two patients had convulsions with fever before the age of 5 years; the convulsions and acute episodes recurred at ages 9 and 10 years. Another patient had two episodes of aseptic meningitis followed by convulsive disorder before the diagnosis of familial Mediterranean fever was made; his convulsions were resistant to antiepileptic drugs alone and subsided only when colchicine was added. The possibility of neurologic involvement should be considered in patients with familial Mediterranean fever.

PMID: 8216544 [Indexed for MEDLINE]

5211. Curr Opin Genet Dev. 1993 Jun;3(3):425-31.

Integrating maps of chromosome 16.

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The recently published, detailed cytogenetic-based physical map of chromosome 16 has the highest resolution of any autosomal cytogenetic map thus far constructed. The genetic map has been integrated with the cytogenetic map to facilitate the regional localization of disease genes by linkage. Disease genes for tuberous sclerosis, familial Mediterranean fever, Rubinstein-Taybi syndrome and Morquio A syndrome have now been assigned to chromosome 16. The search for the adult polycystic kidney disease gene has recently been narrowed to the analysis of candidate loci on chromosome 16, and localization of the gene determining juvenile Batten disease has been further refined by disequilibrium mapping.

PMID: 8353417 [Indexed for MEDLINE]

5212. Clin Pediatr (Phila). 1993 Jun;32(6):357-9.

Thyroid involvement in children with familial Mediterranean fever.

Gedalia A(1), Leiberman E, Lifshitz M, HersHKovitz A, Kuperman O, Gorodischer R.

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(1)Department of Pediatrics, LSU Medical Center, New Orleans 70112-2822.

DOI: 10.1177/000992289303200607

PMID: 8344047 [Indexed for MEDLINE]

5213. J Clin Neuroophthalmol. 1993 Jun;13(2):141-3.

Optic neuritis associated with familial Mediterranean fever.

Lossos A(1), Eliashiv S, Ben-Chetrit E, Reches A.

Author information:

(1)Department of Neurology, Hadassah Hebrew University Hospital, Jerusalem, Israel.

Familial Mediterranean fever (FMF) is an inherited disorder characterized by recurrent attacks of fever and polyserositis of unknown origin.

Neuro-ophthalmologic involvement is rare. We describe a previously unreported association of FMF with optic neuritis in two patients.

PMID: 8340482 [Indexed for MEDLINE]

5214. Isr J Med Sci. 1993 Apr;29(4):212-4.

Ischemic colitis complicating AA amyloidosis and familial Mediterranean fever.

Kyzer S(1), Korzets A, Zevin D, Rath-Wolfson L, Chagnac A, Chaimoff C, Levi J.

Author information:

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PMID: 8491572 [Indexed for MEDLINE]

5215. Blood. 1993 Mar 15;81(6):1424-7.

Inactivation of interleukin-8 by the C5a-inactivating protease from serosal fluid.

Ayesh SK(1), Azar Y, Babior BM, Matzner Y.

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The complement fragment C5a and the cytokine interleukin-8 (IL-8) are proinflammatory peptides with potent chemotactic activity toward neutrophils. We have previously shown that C5a can be inactivated by a protease that is found in normal synovial and peritoneal fluids but is absent from serosal fluids obtained from patients with familial Mediterranean fever (FMF). We report here that serosal fluids can also eliminate the chemotactic activity of IL-8. The agent responsible for IL-8 elimination appears to be the C5a-inactivating protease, because the pure protease can inactivate IL-8, inactivation of IL-8 by normal peritoneal fluid is partly prevented by an antibody raised against the purified C5a-inactivating protease, and IL-8 is not inactivated by peritoneal fluids from patients with FMF. The ability of this protease to inactivate both, early (C5a) and late (IL-8) inflammatory mediators identifies it as a potentially significant regulator of inflammation.

PMID: 8453091 [Indexed for MEDLINE]

5216. Fetal Diagn Ther. 1993 Mar-Apr;8(2):129-34.

Successful full-term pregnancy in familial Mediterranean fever complicated with amyloidosis: case report and review of the literature.

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Author information:

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Pregnancy during familial Mediterranean fever complicated with amyloidosis and severe nephrotic syndrome is rare and may cause several maternal and fetal complications. Asymmetrical intrauterine growth retardation, superimposed preeclampsia, thromboembolic phenomena, resistant anemia and renal failure only partially represent the possible complications. A successful outcome of a full-term pregnancy is presented and the efficiency of colchicine, a high protein

diet, acetylsalicylic acid and dipyridamole is discussed.

DOI: 10.1159/000263761

PMID: 8338626 [Indexed for MEDLINE]

5217. Am J Med Genet. 1993 Feb 1;45(3):340-4.

Familial Mediterranean fever in the colchicine era: the fate of one family.

Zemer D(1), Livneh A, Pras M, Sohar E.

Author information:

(1)Heller Institute of Medical Research, Sheba Medical Center, Tel-Hashomer, Tel-Aviv University Medical School, Israel.

In order to demonstrate the effect of prophylactic colchicine treatment on the natural history of familial Mediterranean fever (FMF), a family is presented with 6 out of 9 siblings affected by FMF. Each patient represents a different stage of the amyloidotic kidney disease of FMF and the effect of continuous colchicine treatment on its course. Considered together, the members of this family present an almost complete clinical, genetic, and behavioral picture of the disease.

DOI: 10.1002/ajmg.1320450311

PMID: 8434621 [Indexed for MEDLINE]

5218. Ren Fail. 1993;15(3):379-84.

Familial Mediterranean fever-associated amyloidosis.

Méry JP(1), Kenouch S.

Author information:

(1)Department of Nephrology, Hôpital Bichat, Paris, France.

PMID: 8516494 [Indexed for MEDLINE]



5219. Harefuah. 1993 Jan 1;124(1):21-4.

[Familial Mediterranean fever: from the clinical syndrome through the localization of the gene to the exploration of the biochemical anomaly].

[Article in Hebrew]

Pras M, Zemer D, Langevitz.

PMID: 8436306 [Indexed for MEDLINE]

5220. Ann Rheum Dis. 1993 Jan;52(1):81.

Arthritis in hyperimmunoglobulinaemia D.

Loeliger AE, Kruize AA, Bijlsma JW, Loeliger AE, Derksen RH.

Comment in

Ann Rheum Dis. 1993 Oct;52(10):765-6.

PMCID: PMC1004963

PMID: 8427522 [Indexed for MEDLINE]

5221. Contrib Nephrol. 1993;102:187-97.

The kidney in familial Mediterranean fever.

Zemer D(1), Livneh A, Pras M, Sohar E.

Author information:

(1)Heller Institute of Medical Research, Chaim Sheba Medical Center,  
Tel-Hashomer, Israel.

PMID: 8416182 [Indexed for MEDLINE]

5222. Bull Hosp Jt Dis. 1993 Spring;53(1):25-8.

Total hip replacement in familial Mediterranean fever.

Salai M(1), Langevitz P, Blankstein A, Zemmer D, Chechick A, Pras M, Horoszowski H.

Author information:

(1)Department of Orthopaedic Surgery, Chaim Sheba Medical Center, Tel-Hashomer Hospital, Tel Aviv, Israel.

Familial Mediterranean fever (FMF) is a hereditary disorder affecting people of Mediterranean stock, mainly Sephardic Jews and Armenians. It is characterized by attacks of arthritis, either short, self-limited episodes typically lasting 72 hours or protracted attacks lasting from two weeks to one year. The latter form affects mainly the large joints of the lower limb. The hip joint is the most vulnerable and likely to be affected by the protracted attacks, which may result in destruction of the articular cartilage and, in some cases, aseptic necrosis of the femoral head. Eighteen FMF patients (19-52 years) underwent 22 total hip replacements between 1971 and 1985 at our hospital. Six of the 18 initial prostheses experienced aseptic loosening. This relatively high incidence led us to recommend implantation of cementless hip prostheses following meticulous synovectomy as the treatment of choice. The results of these surgeries and the uniqueness of total hip replacement in FMF patients are presented here and discussed.

PMID: 8374487 [Indexed for MEDLINE]

5223. Ann Med Interne (Paris). 1993;144(4):293-4.

[Pseudo-periodic disease with hyper IgD].

[Article in French]

Morand C, Bressollette L, Mottier D, Granier H, Roegel JC, Dien G.

PMID: 8368724 [Indexed for MEDLINE]

5224. *Pediatr Radiol*. 1993;23(7):565-6.

Ultrasound and MRI findings in a case of childhood amyloid goiter.

Mache CJ(1), Schwingshandl J, Riccabona M, Ranner G, Ring E, Fock C, Ratschek M, Malle E, Borkenstein MH.

Author information:

(1)Department of Pediatrics, University of Graz, Austria.

Goiter secondary to amyloidosis is rare in clinical practice and only a few descriptions of its radiologic features have been reported. We present the ultrasound and MRI findings of thyroid amyloidosis in a 7-year-old Turkish boy with familial Mediterranean fever.

PMID: 8309770 [Indexed for MEDLINE]

5225. *Ren Fail*. 1993;15(5):629-33.

Transplantation for renal amyloidosis.

Kiliçturgay S(1), Haberal M.

Author information:

(1)Turkish Transplantation and Burn Foundation Hospital, Ankara.

Renal transplantation therapy performed for amyloid nephropathy is controversial because of the fatal effects of the disease. Amyloidosis is a relatively frequent disease and is generally associated with familial Mediterranean fever (FMF) in Turkey. Renal transplantation in the treatment of amyloid nephropathy started in January 1985. Till now, 18 (3.2%) renal transplantations have been performed on

patients who had amyloid nephropathy. The mean follow-up period was 34.6 months. Fourteen renal grafts still function well (creatinine: 1-3.2 mg/dL). The overall 1-year patient and graft survival rates were 88.9% and 83.0%, respectively. These rates are not statistically different from renal transplantations done for other cases of renal failure. Therefore, patients with end-stage renal failure due to amyloidosis can be considered as appropriate candidates for renal transplantation.

PMID: 8290709 [Indexed for MEDLINE]

5226. Klin Khir. 1993;(4):37-9.

[The diagnosis and treatment procedure in periodic disease].

[Article in Ukrainian]

Fedorenko ST.

The main forms of periodic disease are presented, clinical cases with the different forms are described. A special attention is paid to the problems of diagnosis and treatment in the emergency surgery of the abdominal organs is abdominal form of the disease.

PMID: 8277683 [Indexed for MEDLINE]

5227. Akush Ginekol (Sofiia). 1993;32(2):41-2.

[A rare combination of pregnancy and periodic disease treated with colchicine].

[Article in Bulgarian]

Tanchev S, Popov I, Tomov S.

The authors describe familial Mediterranean fever cases in the country for the first time. More uncommon is the combination of colchicin treatment during the

pregnancy. The outcome for mother and child is favorable. Republic of Bulgaria is mentioned as a possible region of appearance of that illness.

PMID: 8010403 [Indexed for MEDLINE]

5228. Urol Nefrol (Mosk). 1993 Jan-Feb;(1):28-31.

[Blood lipids in renal amyloidosis].

[Article in Russian]

Srinivas KV, Neverov NI, Kolonduk NV, Tambovtseva EV, Kozlova RI.

Serum lipids were estimated in patients with renal amyloidosis (RA): 21 with familial Mediterranean fever (FMF) and 24 with secondary renal amyloidosis versus FMF patients without renal dysfunction or having chronic glomerular nephritis. All the RA patients had dyslipidemia of atherogenic nature the severity of which correlated with that of renal disorder. Our results showed the presence of dyslipidemia early during RA course. It is renal involvement that results in dyslipidemia observed in FMF patients.

PMID: 7941122 [Indexed for MEDLINE]

5229. Bull Soc Pathol Exot. 1993;86(5 Pt 2):410-3.

[Pathology of travelers in the Antilles. Role of imported metropolitan pathology].

[Article in French]

Strobel M(1), Gabriel JM, Cousin P, Daijardin JB, De Caunes F, Dorak B.

Author information:

(1)CHRU, Pointe-à-Pitre, Guadeloupe.

A preliminary and retrospective review--with a southern perspective--of some traveller's pathologies, mostly imported, and leading to hospital admission in Guadeloupe (FWI). End stage patients (cancer, AIDS...) frequently travel for a last, "compassional" trip. Ischemic heart disease is the leading pathology imported from the mother country (France). As well as in diabetes or psychiatric illness, destabilization frequently occurs as a consequence of travel (jet lag). Compulsive tennis plus dehydration cause the very common stone passage of nephrolithiasis. Concern is growing for heroin withdrawal syndrome or cocaine (crack)-abuse, and for supply for rare and expensive anticancer, antigraft rejection or antinfective (AIDS) agents. Much more familiar to us are photodermatitis, larva migrans, dengue, or ciguatera, locally acquired. On the other hand some pathologies are quite "exotic" to us: Kaposi sarcoma, Lyme, or Behçet disease, familial mediterranean fever, brucellosis.

PMID: 7819791 [Indexed for MEDLINE]

5230. J Intern Med. 1992 Dec;232(6):517-8.

Secondary amyloidosis (AA).

Gertz MA(1).

Author information:

(1)Division of Hematology and Internal Medicine, Mayo Clinic and Foundation, Rochester, MN.

PMID: 1474356 [Indexed for MEDLINE]

5231. Am J Hum Genet. 1992 Dec;51(6):1349-54.

The gene for familial Mediterranean fever in both Armenians and non-Ashkenazi Jews is linked to the alpha-globin complex on 16p: evidence for locus homogeneity.

Shohat M(1), Bu X, Shohat T, Fischel-Ghodsian N, Magal N, Nakamura Y, Schwabe AD,

Schlezing M, Danon Y, Rotter JI.

Author information:

(1)Department of Medical Genetics, Beilinson Medical Center, Petah Tikva, Israel.

Familial Mediterranean fever (FMF) is a recurrent inflammatory disorder characterized by short episodes of fever, peritonitis, pleuritis, and arthritis. While FMF has been shown to be inherited in an autosomal recessive fashion in both non-Ashkenazi Jews and Armenian families, clinical differences have raised the possibility of genetic heterogeneity. As its pathogenesis is unknown, mapping of the gene for FMF may provide the first objective method for early and accurate diagnosis of this disease. After excluding 45% of the entire human genome, we studied 14 Armenian and 9 non-Ashkenazi Jewish families with FMF and tested linkage with the alpha-globin locus on chromosome 16. Analysis of the PvuII length polymorphism of the 3' HVR (hypervariable region) probe showed significant linkage with the FMF gene (maximum lod score [lodmax] = 9.76 at maximum recombination fraction [theta] = .076). In the Armenians, the lodmax = 3.61 at theta = .10; and for the non-Ashkenazi Jews, lodmax = 6.28 at theta = .06. There was no evidence for genetic heterogeneity between the Armenians and the non-Ashkenazi Jews (chi 2 = 1.28; P = .26) or within either ethnic group (chi 2 = .00; P = .50). Thus, the gene for FMF is linked to the alpha-globin complex on chromosome 16p in both non-Ashkenazi Jews and Armenians.

PMCID: PMC1682901

PMID: 1463015 [Indexed for MEDLINE]

5232. Am J Dis Child. 1992 Dec;146(12):1419-20.

Acute scrotal involvement in children with familial Mediterranean fever.

Gedalia A, Mordehai J, Mares AJ.

PMID: 1456246 [Indexed for MEDLINE]

5233. Semin Arthritis Rheum. 1992 Dec;22(3):139-50.

The arthritis of familial Mediterranean fever.

Garcia-Gonzalez A(1), Weisman MH.

Author information:

(1)Department of Medicine, University of California, San Diego 92103.

Familial Mediterranean fever (FMF) is a disease of unknown etiology and pathogenesis. In addition to fever, arthritis is among its most frequent manifestations. The arthritis of FMF is typically an acute, episodic, self-limited process with no sequelae. The radiographic features of FMF arthritis are usually limited to transient, often severe osteoporosis. Synovial fluid analysis may mimic septic arthritis with very high white blood cell counts; cultures are uniformly negative. The course of FMF is almost always benign, with no residual articular incapacity. Some patients, limited to certain ethnic groups, develop renal amyloidosis. Colchicine therapy modifies the natural history of the disease by decreasing the attack frequency and preventing amyloid deposition. At present, a lipocortin deficiency appears to be the likely candidate for a pathogenic mechanism. An unusual case with dramatic periarticular features (periostitis) and a protracted course with an excellent response to synovectomies is reported here. There is no explanation for the exuberant periarticular bone formation noted in this case, but a variety of recently discovered growth factors may be implicated.

PMID: 1295087 [Indexed for MEDLINE]

5234. Presse Med. 1992 Nov 7;21(37):1768-73.

[Familial amyloidosis].

[Article in French]

Grateau G(1), Roux ME.

Author information:

(1)Département de Médecine interne, Hôpital Cochin, Paris.



Familial amyloidosis is characterized by its great clinical and genetic heterogeneity. The most frequent form is amyloidotic neuropathy which may be due to deposits of several amyloid proteins, such as transthyretin, apolipoprotein A1 and gelsolin. Other varieties include predominant lesions of another organ, such as kidney, heart, eye or skin. In most of these lesions, a punctual mutation affects the amyloid protein itself. In other varieties, the amyloid protein is not affected by mutation and, rarely, unknown. The advances achieved in our understanding of transthyretin deposition should improve our knowledge of amyloidosis in general.

PMID: 1488422 [Indexed for MEDLINE]

5235. Head Neck. 1992 Nov-Dec;14(6):492-5.

Temporomandibular arthritis in familial Mediterranean fever.

Tovi F(1), Gatot A, Fliss D.

Author information:

(1)Department of Otolaryngology, Head and Neck Surgery, Soroka Medical Center, Beer-Sheva, Israel.

Temporomandibular joint arthritis is a rare manifestation of familial Mediterranean fever and should be considered in patients of Mediterranean origin. Recently we treated four patients suffering from this condition, and intra-articular corticosteroid injection resulted in rapid resolution of the pain and disability in two. Computed tomography confirmed the usefulness of this therapeutic modality.

PMID: 1468924 [Indexed for MEDLINE]

5236. Am J Med. 1992 Nov;93(5):587.

Tumor necrosis factor in pathogenesis of familial Mediterranean fever.

Dilşen N, Gül A, Mege JL, Sanguedolce MV.

Comment on

Am J Med. 1991 Apr;90(4):434-8.

PMID: 1442867 [Indexed for MEDLINE]

5237. J Rheumatol Suppl. 1992 Oct;35:1-9.

Familial Mediterranean fever in children.

Gedalia A(1), Adar A, Gorodischer R.

Author information:

(1)Pediatric Rheumatology Unit, Soroka Medical Center, Ben Gurion University of Negev, Beer Sheva, Israel.

PMID: 1433029 [Indexed for MEDLINE]

5238. Transplant Proc. 1992 Oct;24(5):1788-9.

The results of transplantation of patients with amyloid nephropathy.

Kilicturgay S(1), Tokyay R, Arslan G, Bilgin N, Haberal M.

Author information:

(1)Turkish Transplantation and Burn Foundation Hospital, Ankara.

PMID: 1412844 [Indexed for MEDLINE]

5239. Transplant Proc. 1992 Oct;24(5):1783-4.

Renal transplantation in patients with amyloidosis due to familial Mediterranean fever.

Shmueli D(1), Lustig S, Nakache R, Yussim A, Bar-Nathan N, Shaharabani E, Shapira Z.

Author information:

(1)Organ Transplant Department Beilinson Medical Center, Petach Tiqva, Israel.

PMID: 1412842 [Indexed for MEDLINE]

5240. J Intern Med. 1992 Oct;232(4):365-9.

Autosomal dominant 'Mediterranean fever' in a Finnish family.

Karenko L(1), Pettersson T, Roberts P.

Author information:

(1)Fourth Department of Surgery, Helsinki University Central Hospital, Finland.

Erratum in

J Intern Med 1993 Jan;233(1):101.

A 23-year-old Finnish man was examined because of an 8-year history of recurrent bouts of fever and abdominal pain. His father had been repeatedly investigated because of similar episodes since he was 24 years old, and one of the father's sisters was reported to have had recurrent periods of fever. The clinical features closely resembled those of familial Mediterranean fever (FMF), a syndrome rarely described in families of European descent. Unlike typical FMF, which is inherited as an autosomal recessive trait, the mode of inheritance of the syndrome in our family may be regarded as dominant. During a recent attack, serum concentrations of interleukin-1-beta, interleukin-6 and acute phase reactants, including serum amyloid A protein, were high. No signs of amyloidosis were detected in our patients.

PMID: 1402641 [Indexed for MEDLINE]

5241. Am J Reprod Immunol. 1992 Oct-Dec;28(3-4):245-6.

Colchicine treatment in conception and pregnancy: two hundred thirty-one pregnancies in patients with familial Mediterranean fever.

Rabinovitch O(1), Zemer D, Kukia E, Sohar E, Mashiach S.

Author information:

(1)Department of Gynecology and Obstetrics, Sheba Medical Center, Tel-Aviv University Medical School, Israel.

The effect of maternal use of colchicine on fetuses is unknown. The children of 116 women with Familial Mediterranean Fever (225 completed pregnancies) were studied. There was no unusual frequency of fetal abnormality among women taking colchicine before or during pregnancy. Colchicine treatment does not apparently harm mother or child.

PMID: 1285892 [Indexed for MEDLINE]

5242. Am J Reprod Immunol. 1992 Oct-Dec;28(3-4):243-4.

The effect of pregnancy on renal function in amyloidosis of familial Mediterranean fever.

Cabili S(1), Livneh A, Zemer D, Rabinovitch O, Pras M.

Author information:

(1)Heller Institute of Medical Research, Sheba Medical Center, Tel-Hashomer, Israel.

The effect of pregnancy on kidney function was studied in 29 pregnancies of 17 patients with familial Mediterranean fever (FMF) and amyloidosis. Pregnancy associated deterioration of renal function occurred in seven patients who had advanced renal disease at conception, marked by serum creatinine  $\geq 1.5$  mg/dl or urine protein  $\geq 2$  g/24 h. This finding suggests that the severity of

renal disease at conception may predict the fate of kidney function during pregnancy and puerperium.

PMID: 1285891 [Indexed for MEDLINE]

5243. Am J Reprod Immunol. 1992 Oct-Dec;28(3-4):241-2.

Mapping of the familial Mediterranean fever gene to chromosome 16.

Gruberg L(1), Aksentijevich I, Pras E, Kastner DL, Pras M.

Author information:

(1)Department of Medicine F, Sheba Medical Center, Tel Hashomer, Israel.

Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent attacks of fever, synovitis, peritonitis, or pleurisy. Some patients eventually develop systemic amyloidosis. The biochemical cause of the disease is unknown. We have conducted a genome-wide search for the FMF locus using 125 different DNA markers and mapped the FMF gene to the short arm of chromosome 16. The study was performed on 35 Israeli families primarily of North African and Iraqi origin. For the five markers D16S82 (p41-1 SacI), D16S80 (24-1 TaqI), D16S84 (pCMM65 TaqI), D16S83 (pEKMDA2-1 RsaI), and HBA (5'HVR RsaI) we obtained maximum lod scores of 2.72 (theta = 0.08), 10.34 (theta = 0.04), 9.66 (theta = 0.050), 9.35 (theta = 0.03), and 14.31 (theta = 0.08), respectively. Multipoint analysis with HBA and D16S84 defined as a fixed loci gave a maximum lod score of 19.86 centromeric to D16S84. Crossovers defined by these markers place the FMF gene in an area of approximately 5 cM between D16S80 and D16S84. Other genes mapped to this area (16p13.3) include phosphodiesterase IB (PDE1B), hydroxyacyl-glutathione hydrolase (HAGH), phosphoglycolate phosphatase (PGP), and the gene that causes adult polycystic kidney disease (PKD1). None of these genes bear an obvious pathophysiological relationship to FMF. Using additional markers from this region we hope to localize more precisely the FMF gene and to offer the possibility of prenatal diagnosis in selected cases. Our ultimate goal is to isolate and characterize the FMF gene.

PMID: 1285890 [Indexed for MEDLINE]

5244. Minerva Chir. 1992 Sep 30;47(18):1505-7.

[Pseudo-acute abdomen in familial Mediterranean fever. A case report].

[Article in Italian]

Brigli G(1), Bennicelli F, Maresca P, Franco A, Camera L, Cremonté LG, Fiore G, Stabilini L.

Author information:

(1)Divisione di Chirurgia Generale, Ospedale S. Giacomo, Novi Ligure, Alessandria.

The Authors report a case of familial mediterranean fever with pseudo-acute abdomen recently observed and emphasize how a careful anamnesis can avoid unnecessary surgical intervention.

PMID: 1461527 [Indexed for MEDLINE]

5245. Am J Med Genet. 1992 Sep 15;44(2):183-8.

Familial Mediterranean fever: analysis of inheritance and current linkage data.

Shohat M(1), Danon YL, Rotter JL.

Author information:

(1)Department of Pediatrics, Children Hospital, Beilinson Medical Center, Petah Tikva, Israel.

Familial Mediterranean fever (FMF) is a genetic disorder characterized by recurrent attacks of fever and inflammation of serosal surfaces. Unlike many mendelian disorders, the mode of transmission has been subject to some controversy as segregation analysis studies have always demonstrated fewer "observed" than "expected" affected individuals. Despite efforts to map the gene causing FMF, no definite linkage has been yet identified. This review analyses

the epidemiologic and genetic characteristics in order to evaluate critically the inheritance of the disease and provide a perspective on the current biochemical and molecular genetic studies whose aim is to locate the gene for this disease.

DOI: 10.1002/ajmg.1320440213

PMID: 1456289 [Indexed for MEDLINE]

5246. Am J Med Genet. 1992 Sep 15;44(2):179-82.

Twin studies in familial Mediterranean fever.

Shohat M(1), Livneh A, Zemer D, Pras M, Sohar E.

Author information:

(1)Heller Institute of Medical Research, Sheba Medical Center, Tel Hashomer, Israel.

Familial Mediterranean fever (FMF) is a genetic disease characterized by recurrent short episodes of fever, accompanied by peritonitis, pleuritis, or arthritis. The disease is almost completely ethnically restricted to patients of Mediterranean descent--Sephardic Jews, Armenians, Anatolian Turks, and Arabs. Although many family studies have been performed, no twin study has been reported as yet. We studied 21 di- and monozygotic twin sets, identified among the 1,943 FMF patients in our registry. Full concordance was observed in all the 10 monozygotic twin sets. In the 11 dizygotic twins, concordance for FMF disease was found in only 3 pairs. Variability in the clinical manifestations and degree of severity have been noted within twins. These findings provide definitive evidence for the genetic cause of FMF. They also support the single gene autosomal recessive model, and provide support for the contention that the lower observed than expected incidence found in FMF is due to genetically affected but clinically undiagnosed patients.

DOI: 10.1002/ajmg.1320440212

PMID: 1456288 [Indexed for MEDLINE]

5247. Eur J Clin Invest. 1992 Sep;22(9):630-4.

Colchicine analogues: effect on amyloidogenesis in a murine model and, in vitro, on polymorphonuclear leukocytes.

Wolach B(1), Gotfried M, Jedeikin A, Lishner M, Brossi A, Ravid M.

Author information:

(1)Department of Pediatrics, Sackler Faculty of Medicine Tel-Aviv University, Israel.

Colchicine has been used in diverse clinical settings such as gout, familial Mediterranean fever, liver cirrhosis, Behcet's disease and pericarditis. It also has an antimitotic potential hitherto unexplored due to its narrow therapeutic toxic ratio. The aim of the present study was to compare the effectiveness and the toxicity of colchicine and three analogues: thiocolchicine, 2,3 dimethyl-colchicine and 3-dimethylthiocolchicine in the blockage of amyloid synthesis in a murine model. 3-demethylthiocolchicine was equipotent to colchicine in the blockage of casein induced amyloidogenesis. However, it was markedly less toxic (LD50 11.3 mg kg<sup>-1</sup> vs. 1.6 mg kg<sup>-1</sup>). Thiocolchicine was toxic (LD50 1.0 mg kg<sup>-1</sup>) and 2,3 didemethyl-colchicine was far less effective. The effect of 3-dimethylthiocolchicine on polymorphonuclear leukocytes was then compared to colchicine. The effect of this analogue on inhibition of chemotaxis was equivalent to that of colchicine whereas the latter was superior to the analogue in the suppression of phagocytosis (by a ratio of 2:1) and in the inhibition of bactericidal activity (by a ratio of 10:1). Since in therapeutic concentrations the only detectable effect of colchicine on PMNs is inhibition of chemotaxis, our data may point to 3-demethylthiocolchicine as an optional, perhaps superior alternative to colchicine for some of its therapeutic indications.

PMID: 1459179 [Indexed for MEDLINE]

5248. Dtsch Med Wochenschr. 1992 Aug 14;117(33):1237-40.

[Toxic myopathy with kidney failure as a colchicine side effect ifn familial Mediterranean fever].

[Article in German]



Stefanidis I(1), Böhm R, Hägel J, Maurin N.

Author information:

(1)Medizinische Klinik II, Technische Hochschule Aachen.

A 24-year-old woman with familial Mediterranean fever (FMF) had for one year been treated with colchicine, 1 mg daily, for repeated bouts of fever, abdominal pain and arthritis. She was also known to have renal amyloidosis. Lately she had developed gastrointestinal symptoms, muscle pain and obvious, predominantly proximal muscular weakness in both legs. The cause of the symptoms was rhabdomyolysis with an increased creatinine activity of 1000 U/l and marked myoglobinuria (1600 micrograms/l), as well as renal failure with normal uric acid and a creatinine clearance of 3 ml/min per 1.73 m<sup>2</sup>. Serum creatinine concentration was 970 µmol/l, urea 34 mmol/l. Muscle biopsy corresponded to a subacute necrotizing myopathy with vacuole formation, signs typical of toxic damage. Renal biopsy confirmed advanced amyloidosis. The colchicine dose was reduced to 0.5 mg/d. The renal failure responded to conservative treatment. The myopathy symptoms receded within 4 weeks, creatinine clearance rising to 25 ml/min per 1.73 m<sup>2</sup>. 12 months after reduction of the colchicine dose the patient was without any FMF-related symptoms.

DOI: 10.1055/s-2008-1062436

PMID: 1499522 [Indexed for MEDLINE]

5249. Curr Opin Rheumatol. 1992 Aug;4(4):479-83.

Whipple's disease, familial Mediterranean fever, adult-onset Still's disease, and enteropathic arthritis.

McMenemy A(1).

Author information:

(1)University of Texas Medical School, Houston.

Whipple's disease is a rare multisystem disorder of infectious etiology. Efforts to culture the responsible organism have been unsuccessful. Nucleotide sequencing and amplification of bacterial 16S ribosomal DNA revealed the organism to be most

similar to bacteria of the *Rhodococcus*, *Streptomyces*, and *Arthrobacter* genera. Several clinical studies of the long-term use of colchicine for the treatment of familial Mediterranean fever demonstrate its utility for symptom control and prevention of complications by amyloidosis in both adults and children. Normal growth, development, and subsequent fertility were seen in children treated with colchicine. Adult-onset Still's disease has previously been thought to have a generally good outcome, although some patients develop chronic arthritis and disability. No markers have been available for prognosis. A study of 62 patients revealed the presence of polyarthritis, root joint involvement, and rash at initial presentation to be associated with a poorer outcome. Enteropathic arthritis may be seen as a complication of both Crohn's disease and ulcerative colitis. The onset of peripheral arthritis coincides with or follows the onset of bowel symptoms in most cases, whereas spondylitis may precede the onset of inflammatory bowel disease by years. HLA-B27 is present in 50% to 75% of cases of spondylitis. No HLA association with inflammatory bowel disease or peripheral arthritis has been consistently found.

PMID: 1380277 [Indexed for MEDLINE]

5250. Am J Med Sci. 1992 Jul;304(1):29-31.

Case report: severe pyoderma associated with familial Mediterranean fever--favorable response to colchicine in three patients.

Lugassy G(1), Ronnen M.

Author information:

(1)Institute of Hematology, Barzilai Medical Center, Ashkelon, Israel.

Familial Mediterranean fever (FMF) is an autosomal recessive disorder that occurs most frequently among Sephardic Jews and Armenians. It is characterized by recurrent episodes of fever, peritonitis, pleuritis, and arthritis. Skin lesions are seen in some patients. Diagnosis of FMF usually is made on clinical grounds only, typically when recurrent attacks of abdominal pain, fever, and arthritis are observed in a patient with an appropriate ethnic background and family history. To date, there are no specific diagnostic laboratory tests for FMF. Three patients with severe recurrent Pyoderma are covered in this report. In all

three cases, the cutaneous lesions were associated with clinical manifestations of FMF and responded to colchicine therapy favorably. The importance of such an association and its therapeutic consequences are emphasized.

PMID: 1642250 [Indexed for MEDLINE]

5251. Clin Immunol Immunopathol. 1992 Jul;64(1):36-45.

A canine febrile disorder associated with elevated interleukin-6.

Rivas AL(1), Tintle L, Kimball ES, Scarlett J, Quimby FW.

Author information:

(1)Department of Pathology, New York State College of Veterinary Medicine, Cornell University, Ithaca 14853.

Familial Mediterranean Fever (FMF) is a human disorder characterized by recurrent fever of unknown origin (RFUO), renal amyloidosis, and evidence of peritonitis, pleuritis, and/or synovitis. This report suggests that Chinese Shar-pei (CSP) dogs suffer from a similar syndrome. CSP dogs with RFUO (n = 15) showed greater levels of IL-6 in serum than normal controls, hypergammaglobulinemia, and normal or supranormal in vitro lymphocyte blastogenesis in response to mitogen stimulation, when compared to healthy afebrile dogs. In patients 2 years old or older, RFUO was associated with renal failure, renal amyloidosis, and swollen joints. An epidemiological survey of privately owned dogs indicated a RFUO prevalence of 23% in CSP dogs (n = 132) and 1% in dogs of all breeds (n = 98). Increased levels of circulating cytokines, such as IL-6, have been shown to influence such processes as the febrile response, antibody production, and the synthesis of amyloid precursors. We propose that CSP dogs with RFUO, renal amyloidosis, and joint inflammation may serve as an animal model of FMF and that the clinical syndrome is associated with elevated levels of circulating IL-6.

PMID: 1606750 [Indexed for MEDLINE]

5252. Isr J Med Sci. 1992 Jul;28(7):427-9.

Plasma dopamine beta-hydroxylase activity in familial Mediterranean fever.

Courillon-Mallet A(1), Cauet N, Dervichian M, Launay JM, Cattan D.

Author information:

(1)Service de Gastroentérologie, Faculté de Médecine de Créteil, Centre Hospitalier Villeneuve Saint Georges, France.

PMID: 1506166 [Indexed for MEDLINE]

5253. Intern Med. 1992 Jul;31(7):893-8.

Periodic fever compatible with familial Mediterranean fever.

Takahashi M(1), Ebe T, Kohara T, Inagaki M, Isonuma H, Hibiya I, Mori T, Watanabe K, Ikemoto H.

Author information:

(1)Department of Internal Medicine, Juntendo University School of Medicine, Tokyo, Japan.

A 55-year-old male presented with a recurrent fever of over 38 degrees C, occurring at irregular intervals 1-6 times a month with chest, back or abdominal pain. After admission to our hospital, we found the following characteristics: 1) the febrile attacks were accompanied by obvious inflammatory findings and pleuritis or peritonitis; 2) the patient's elder sister had a similar periodic fever; and 3) there were no apparent causative factors responsible for his symptoms. Therefore, we diagnosed this as a case compatible with familial Mediterranean fever. The febrile attacks have been completely suppressed by daily colchicine. This is the seventh case of familial Mediterranean fever reported in Japan.

PMID: 1450498 [Indexed for MEDLINE]

5254. N Engl J Med. 1992 Jun 4;326(23):1509-13.

Mapping of a gene causing familial Mediterranean fever to the short arm of chromosome 16.

Pras E(1), Aksentijevich I, Gruberg L, Balow JE Jr, Prosen L, Dean M, Steinberg AD, Pras M, Kastner DL.

Author information:

(1)Arthritis and Rheumatism Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD 20892.

**BACKGROUND:** Familial Mediterranean fever is an autosomal-recessive disease characterized by acute attacks of fever with sterile peritonitis, pleurisy, or synovitis. The biochemical basis of the disease is unknown, but determining the chromosomal location of the gene for the disorder should be a first step toward defining the biochemical events.

**METHODS AND RESULTS:** As part of a systematic genome-wide search, we sought evidence of linkage between familial Mediterranean fever and chromosome 16 DNA markers in 27 affected non-Ashkenazi Jewish families from Israel. Two loci from the subtelomeric region of the short arm of chromosome 16 (16p) had lod scores sufficient to establish linkage (a score greater than or equal to 3). One DNA marker (D16S84) gave a maximal lod score of 9.17 (odds of 10(9.17) to 1 in favor of linkage) at a recombination frequency (theta) of 0.04. A probe associated with the hemoglobin alpha complex (5'HVR) gave a maximal lod score of 14.47 at a theta of 0.06. Multipoint linkage analysis indicated that the following was the most likely gene order: the centromere, the gene for familial Mediterranean fever, D16S84, hemoglobin alpha, and the telomere. The maximal multipoint lod score was 19.86. There was a striking degree of homozygosity at chromosome 16p loci in the affected offspring of eight consanguineous couples.

**CONCLUSIONS:** The gene that causes familial Mediterranean fever in non-Ashkenazi Jews maps to the short arm of chromosome 16.

DOI: 10.1056/NEJM199206043262301

PMID: 1579134 [Indexed for MEDLINE]

5255. Dtsch Med Wochenschr. 1992 Jun 12;117(24):961.

["Etiocholanolone fever"?].

[Article in German]

Winckelmann G(1).

Author information:

(1)Deutsche Klinik für Diagnostik, Wiesbaden.

PMID: 1600874 [Indexed for MEDLINE]

5256. Curr Opin Rheumatol. 1992 Jun;4(3):295-300.

Treatment of gout and crystal arthropathies and uses and mechanisms of action of nonsteroidal anti-inflammatory drugs.

Abramson SB(1).

Author information:

(1)New York University Medical Center, New York.

Nonsteroidal anti-inflammatory agents have anti-inflammatory, analgesic, and antipyretic actions. Nonsteroidal anti-inflammatory drugs are the preferred class of agents for the treatment of gout and other crystal-induced arthropathies. The use of colchicine for other than the prophylaxis of acute attacks is discouraged owing to side effects, which include death. The inhibition of the enzyme prostaglandin H synthase by most nonsteroidal anti-inflammatory drugs explains many of their effects and toxicities. However, it is likely that additional biologic actions are important. These include the inhibition of the transcription of the gene for prostaglandin H synthase, a direct central effect on peripheral inflammation, and the modulation of the functions of a variety of cells (eg, neutrophils, lymphocytes, and chondrocytes). This review focuses on the current controversy in the treatment of gout and discusses the recent literature on the actions of nonsteroidal anti-inflammatory drugs.

PMID: 1599806 [Indexed for MEDLINE]

5257. Med Clin (Barc). 1992 May 9;98(18):718.

[Interleukin-6 and multiple myeloma].

[Article in Spanish]

García Vela JA.

PMID: 1602889 [Indexed for MEDLINE]

5258. Minerva Med. 1992 May;83(5):307-10.

[Familial Mediterranean fever and electroencephalographic changes. A clinical case].

[Article in Italian]

Gentiloni N(1), Gabbrielli N, Caradonna P, Schiavino D, Anti M, David M, Segni G, Gambassi G.

Author information:

(1)Istituto di Clinica Medica, Università Cattolica del Sacro Cuore, Roma.

The Authors describe the case of a non-Hebrew Italian girl suffering from short-lasting fever episodes, associated with abdominal colic, since the age of 3. The occurrence of acute arthrosynovitis during the last episode, at 12 years of age, clinically confirms the diagnosis of familial mediterranean fever, as previously supposed. The increase in urinary coproporphyrins, with normal values of delta-aminolevulinic acid and porphobilinogen poses the problem of the differential diagnosis between hereditary coproporphyria and secondary coproporphinuria. The importance of this case lies in the presence of electroencephalographic alteration since the first years of life, suggesting a temporal epilepsy for which the patient was at length submitted to anti-epileptic treatment. Electroencephalographic alterations, of different type and uneasy

interpretation, are described in the literature with a frequency which does not seem accidental. Renal biopsy does not show amyloid, nor the RMN reveals cerebral abnormalities. The anti-epileptic therapy being withdrawn, the patient was treated with daily administrations of colchicine (1 mg/die); 18 months after, she is disease free.

PMID: 1589138 [Indexed for MEDLINE]

5259. Am J Med. 1992 May;92(5):579-80.

Tumor necrosis factor in familial Mediterranean fever.

Ozyilkan E, Simsek H, Telatar H.

Comment on

Am J Med. 1991 Apr;90(4):434-8.

PMID: 1580310 [Indexed for MEDLINE]

5260. Med Klin (Munich). 1992 Apr 15;87(4):185-7.

[Recurrent abdominal pain and fever: familial Mediterranean fever].

[Article in German]

von Schönfeld J(1), Boekstegers A, Breuer N.

Author information:

(1)Abteilung Gastroenterologie, Medizinischen Universitätsklinik Essen.

PMID: 1579097 [Indexed for MEDLINE]

5261. Rev Clin Esp. 1992 Apr;190(7):381.



[Familial mediterranean fever or the need for an early diagnosis].

[Article in Spanish]

Bonilla F, Enríquez R, Lacueva J, González C.

PMID: 1620935 [Indexed for MEDLINE]

5262. Ann Ital Med Int. 1992 Apr-Jun;7(2):114-7.

[Familial Mediterranean fever: a report of 2 cases of Italian origin].

[Article in Italian]

Marinone C(1), Bisbocci D, Pellacani A, Chiandussi L.

Author information:

(1)Dipartimento di Medicina e Oncologia Sperimentale, Università degli Studi di Torino.

Familial Mediterranean fever is an inherited disease, occurring almost exclusively in Arabs, Jews and Turks. Cases are very rarely described in the USA, USSR, France, and patients are all natives to the Mediterranean area. This paper describes two cases of familial Mediterranean fever in brothers native to Campania, Italy. Both had complained of repeated episodes of fever, with acute abdomen, thoracalgia and arthralgia since the age of about 20. One of them had had pleuritis when he was 6 years old. In the period preceding our first observation, both underwent laparotomy to evaluate abdominal symptoms, with negative results. After ruling out other diseases with similar signs and symptoms, we raised the hypothesis of familial Mediterranean fever, despite the fact that the literature has described very few Italian natives affected by this disease. The diagnostic hypothesis was confirmed by the positivity of the metaraminol provocation test. At the same time we evaluated the presence of amyloidosis by rectal biopsy, with negative results. Treatment with colchicine 1 mg/day per os was established. Dramatic improvement of the symptoms was observed in both patients. The present paper stresses the importance of familial

Mediterranean fever, its correct diagnosis in Italy and the fundamental role played by the metaraminol provocation test as a determinant diagnostic tool. It allows establishment of appropriate treatment as soon as possible, so that renal amyloidosis, the most severe complication and major prognostic determinant of familial Mediterranean fever, can be prevented. Inappropriate, useless and potentially harmful surgical diagnostic procedures are also avoided.

PMID: 1467126 [Indexed for MEDLINE]

5263. Ann Intern Med. 1992 Mar 1;116(5):426.

Reversal of the nephrotic syndrome by colchicine in amyloidosis of familial Mediterranean fever.

Zemer D, Livneh A, Langevitz P.

Comment in

Ann Intern Med. 1992 Nov 1;117(9):795-6.

PMID: 1736782 [Indexed for MEDLINE]

5264. J Rheumatol. 1992 Mar;19(3):494-6.

Acute colchicine intoxication--possible role of erythromycin administration.

Caraco Y(1), Putterman C, Rahamimov R, Ben-Chetrit E.

Author information:

(1)Division of Medicine, Hadassah University Hospital, Ein Kerem, Jerusalem, Israel.

A 29-year-old patient with familial Mediterranean fever and amyloidosis involving the kidney, liver, and gastrointestinal tract received longterm colchicine, 1 mg daily. In the last year she developed diarrhea and abdominal pain, that coincided with toxic colchicine blood levels. After 2 weeks of oral erythromycin therapy

she was hospitalized for acute, life threatening colchicine toxicity, with fever, diarrhea, abdominal pain, myalgia and lower extremity parasthesias and later convulsions and alopecia. Pancytopenia evolved into rebound leukocytosis, disturbed liver function and hypoglycemia. After a long stormy course she improved. Colchicine toxicity with combined liver and renal impairment and the role of erythromycin in her colchicine toxicity are discussed.

PMID: 1578471 [Indexed for MEDLINE]

5265. J Rheumatol. 1992 Mar;19(3):416-8.

Decreased interleukin 1 activity released from circulating monocytes of patients with familial Mediterranean fever during in vitro stimulation by lipopolysaccharide.

Rozenbaum M(1), Katz R, Rozner I, Pollack S.

Author information:

(1)Department of Rheumatology, Bnai Zion Medical Center, Haifa, Israel.

Familial Mediterranean fever (FMF) is an inherited disorder of unknown etiology characterized by recurrent episodes of serous membrane inflammation. Interleukin 1 (IL-1) is a mediator of inflammatory processes. We hypothesized that IL-1 may play a role in acute attacks of FMF. Thus we tested IL-1 production by monocytes derived from patients with FMF. Nine patients were tested during acute attacks and 9 were asymptomatic when tested. Monocytes derived from peripheral blood of patients and controls were stimulated with lipopolysaccharide (LPS) and IL-1 activity in the supernatant was tested using a T helper cell line (D10-4G.1). IL-1 secretion during acute attacks was decreased whereas IL-1 production in asymptomatic patients was comparable to healthy controls. Followup of symptomatic patients during the recovery period revealed normalization of IL-1 secretion. Addition of indomethacin (prostaglandin E2 inhibitor) to LPS stimulated monocytes did not change IL-1 activity in patients or healthy controls. We conclude that in vitro IL-1 activity in patients with FMF is associated with the intensity of the inflammatory process.

PMID: 1578456 [Indexed for MEDLINE]

5266. Z Gastroenterol. 1992 Mar;30 Suppl 1:35-9.

Pharmacokinetics of colchicine: a review of experimental and clinical data.

Sabouraud A(1), Rochdi M, Urtizberea M, Christen MO, Achtert G, Scherrmann JM.

Author information:

(1)INSERM U26, Hôpital Fernand Widal, Paris, France.

Thanks to the development of a sensitive and specific radioimmunoassay for colchicine, the pharmacokinetics of colchicine is now well-established after single oral doses. Absorption is characterized by a zero-order rate constant while disposition appears biexponential with a rapid distribution phase ( $t_{1/2} = 1.8$  h) and a long elimination phase ( $t_{1/2} = 20$  h). All studies confirm the large total body clearance (35 l/h) predominantly by the extrarenal route and the large distribution volume (700 l). Further studies need to be performed to investigate colchicine absorption and to describe the metabolic pathway of the drug. To date, relationships between colchicine plasma levels and pharmacological effects have not been defined. Monitoring of plasma levels in patients with familial Mediterranean fever should improve treatment with colchicine. However, the therapeutic range has not been precisely determined. The use of colchicine in the treatment of liver cirrhosis and primary biliary cirrhosis is a recent development; so, assuming that a large part of total body clearance depends on hepatic function, the influence of hepatic diseases on colchicine disposition needs to be investigated in order to define the most appropriate therapeutic dosing.

PMID: 1449014 [Indexed for MEDLINE]

5267. Arch Intern Med. 1992 Feb;152(2):421.

A proposed mechanism of the inflammatory attacks in familial Mediterranean fever.

Schattner A, Hahn T.

PMID: 1739380 [Indexed for MEDLINE]

5268. Kidney Int. 1992 Feb;41(2):414-9.

Spectrum of renal involvement in familial Mediterranean fever.

Said R(1), Hamzeh Y, Said S, Tarawneh M, al-Khateeb M.

Author information:

(1)Department of Medicine, Jordan University, Amman.

Kidney biopsies were performed on fifteen patients with a long-standing history of familial Mediterranean fever (FMF) and evidence of renal involvement. On light microscopy, seven patients were found to have amyloidosis, six mesangial proliferative glomerulonephritis (MsPGN) and two patients rapid progressive glomerulonephritis (RPGN). Immunofluorescent studies of the six biopsies with MsPGN were positive for mesangial IgA deposits (IgA nephropathy) in three patients and IgM mesangial deposits in three (IgM nephropathy). We conclude that in patients with FMF and renal involvement, non-amyloid renal lesions (IgA nephropathy, IgM nephropathy and RPGN) should be considered in the differential diagnosis in addition to amyloidosis.

PMID: 1552714 [Indexed for MEDLINE]

5269. Med Clin (Barc). 1992 Jan 18;98(2):61-3.

[Familial Mediterranean fever and myeloma: an undescribed association].

[Article in Spanish]

Esquinas Blanco G(1), Jiménez Rojas C, Macías Montero MC, Rodríguez Heredia JM, Gallegos Cid A, García-Arroba J.

Author information:

(1)Hospital Universitario, Getafe, Madrid.

An atypical case of familial mediterranean fever is presented in a 55 year old male with neither family antecedents nor ethnic determinants. The patient presented isolated articular involvement and positive response in the metaraminol provocation and colchicine suppression test. It was associated with monoclonal type IgG kappa gammopathy which evolved over one year until obtaining criteria, although asymptomatic, for myeloma. The increase of the monoclonal component and the infiltration of the bone medulla by plasmatic cells were considered as signs of progression inducing the initiation of treatment despite the lack of symptoms. Both entities are discussed and a mechanism justifying their association is proposed: interleukin-6 produced by macrophages in the inflammatory articular foci due to the deficiency of the C5a inhibitor existing in familial mediterranean fever, may act on a plasmatic cell clone in which receptors for IL-6 exist as a paracrine growth factor.

PMID: 1545623 [Indexed for MEDLINE]

5270. Nephron. 1992;60(4):418-22.

Colchicine prevents kidney transplant amyloidosis in familial Mediterranean fever.

Livneh A(1), Zemer D, Siegal B, Laor A, Sohar E, Pras M.

Author information:

(1)Heller Institute of Medical Research, Sheba Medical Center, Tel-Hashomer, Israel.

Twenty-one familial Mediterranean fever (FMF) patients who received a kidney transplant for terminal renal failure due to amyloidosis were studied retrospectively to evaluate the prophylactic effect of colchicine on graft amyloidosis. Proteinuria, highly suggestive of kidney transplant amyloidosis, developed in 11 patients within a median of 3 years after transplantation (range 0.5-10 years). In 10 patients, repeated urinalyses for protein were negative during a median of 5 years after transplantation (range 1-13). Patients who developed proteinuria or transplant amyloidosis received smaller colchicine doses

than patients without proteinuria--mean 0.69 (range 0-1) versus 1.53 (range 1-2) milligrams per day ( $p = 0.0002$ ), suggesting that colchicine prevents or delays development of transplant amyloidosis. This prophylactic effect of colchicine was complete at a dose of 1.5 mg/day or more and absent at a daily dose of 0.5 mg or less. In patients who received 1 mg/day, individual variability in the response to colchicine was observed. We conclude that the development of amyloidosis of the kidney transplant in FMF is inevitable at a colchicine dose lower than 1 mg/day, unpredictable at 1 mg/day and usually preventable with 1.5 mg/day or more.

DOI: 10.1159/000186801

PMID: 1584316 [Indexed for MEDLINE]

5271. Acta Neuropathol. 1992;83(4):440-4.

Colchicine myopathy in a case of familial Mediterranean fever: immunohistochemical and ultrastructural study of accumulated tubulin-immunoreactive material.

Himmelmann F(1), Schröder JM.

Author information:

(1)Institut für Neuropathologie, Klinikum der Rheinisch-Westfälischen Technischen Hochschule, Aachen, Federal Republic of Germany.

Severe colchicine myopathy occurred in a 24-year-old patient treated with colchicine because of familial mediterranean fever complicated by renal amyloidosis. In addition to prominent autophagic vacuoles containing heterogeneous osmiophilic material and pleomorphous bodies, cytoplasmic deposits of finely granular material were detected that have not been noted in previous cases of colchicine myopathy. This granular material was immunoreactive for antibodies to tubulin, alpha-tubulin, and beta-tubulin. These observations substantiate the suggestion that alterations of the microtubular network represent the initial step in the pathogenesis of colchicine myopathy.

PMID: 1575022 [Indexed for MEDLINE]

5272. Turk J Pediatr. 1992 Jan-Mar;34(1):5-14.

Immunofluorescence study of childhood renal amyloidosis.

Tinaztepe K(1), Güçer KS.

Author information:

(1)Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.

In this paper, the findings of immunofluorescence (IF) studies of 57 patients with childhood biopsy-proven renal amyloidosis are presented. All specimens were investigated by the direct IF technique and the simultaneous use of antisera to human IgG, IgM, IgA, fibrinogen and C3. Antisera to C1q, C4, HbsAg, IgE (in each of ten cases), kappa and lambda light chains of immunoglobulins (Igs) and albumin (in each of five cases) were also used. AA type amyloidosis was determined in all patients by Wright's potassium permanganate reaction. In thirty-four of these patients (60%), Familial Mediterranean Fever (FMF) was found to be the underlying disease for renal amyloidosis. In 39 cases (68.5%), renal biopsy showed positive fluorescence staining while in 18 cases (31.5%), fluorescence staining was negative. The immunofluorescence pattern of glomerular deposits was neither granular nor linear but large isolated or confluent masses which were located in the mesangium and in the capillary walls, and were similar in all cases whatever the antisera used. The areas showing immunofluorescence staining almost corresponded to the locations of amyloid deposits. Immunoreactants showed various combinations of deposition with the exception of IgE, HbsAg and albumin antisera which yielded continuously negative reactions. C3 was the immunoreactant most commonly encountered. Kappa and lambda light chains of Igs were demonstrated in one of five biopsy specimens tested. Although it was not diagnostic, this IF pattern was found to be rather characteristic. Demonstration of immunoglobulins and other components of the humoral immune system is not a rare occurrence in renal amyloidosis, and passive absorption of plasma proteins does not simply explain these immunohistologic findings.

PMID: 1509531 [Indexed for MEDLINE]

5273. Turk J Pediatr. 1992 Jan-Mar;34(1):15-20.



Evaluation of the hypercoagulable state by measuring protein C and antithrombin III levels in nephrotic syndrome and in familial Mediterranean fever-related amyloidosis.

Topaloğlu R(1), Saatçi U, Bakkaloğlu A, Beşbaş N, Başsoy Y.

Author information:

(1)Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.

The levels of protein C (PC) and antithrombin III (AT III) antigens (ag) were measured in the plasma of 39 patients with various histologic types of primary nephrotic syndrome (NS) and in 12 patients with amyloidosis secondary to familial Mediterranean fever (FMF). The controls comprised 15 healthy children. Normal or elevated PC levels were observed in primary NS patients (mean 64%, range 36-98%) and in amyloidosis patients (mean 58%, range 48-70%). There was no difference found between PC ag levels in primary NS and in amyloidosis patients. In addition, no correlation existed between protein selectivity and the PC ag levels in the primary NS patients. Normal and decreased levels of AT III were observed (mean 29 mg/dl, range 11.1-39 mg/dl) in the patients with primary NS and amyloidosis (mean 31 mg/dl range, 21-39 mg/dl). The AT III ag levels of these two groups did not differ and no correlation was found between protein selectivity and AT III levels in primary NS patients. These results suggest that in patients with primary NS, or amyloidosis secondary to FMF, hypercoagulability is not related to a deficiency in PC ag levels due to a dynamic balance between urinary losses, increased rate of hepatic synthesis, catabolism and the distribution of PC in the body compartments. Patients with low AT III levels may be more susceptible to thromboembolic complications than patients with normal levels.

PMID: 1509525 [Indexed for MEDLINE]

5274. Ter Arkh. 1992;64(9):81-6.

[Heart involvement in patients with periodic disease and amyloidosis].

[Article in Russian]

Vinogradova OM, Kochubei LN, Golyzhnikov VA, Tomas Nlu, Eventov AZ, Pisareva NA.

PMID: 1481162 [Indexed for MEDLINE]

5275. Ren Fail. 1992;14(4):555-62.

Normal renin-aldosterone-insulin and potassium interrelationship in FMF patients and amyloid nephropathy.

Shemer J(1), Royburt M, Cabili S, Iaina A, Pras M, Eliahou H.

Author information:

(1)Department of Internal Medicine, Sheba Medical Center, Tel-Hashomer, Israel.

The renin-aldosterone system and plasma insulin were studied in 19 patients with familial Mediterranean fever (FMF). Their relationships to serum potassium level at rest and before and after oral glucose loading are described. An interesting finding is the occurrence of hyperkalemia in the absence of oliguria, in the advanced stages of renal failure. No differences were found in the activity of the renin-angiotensin-aldosterone system to explain these variations in serum potassium found in some of the patients. The response of the renin-aldosterone system to glucose loading showed no abnormality, and the regular relationship between serum potassium, plasma renin activity (PRA), aldosterone, insulin, and plasma pH is maintained. Levels of insulin, potassium, and bicarbonate in serum or plasma pH were found similar in FMF patients with normal renal function with and without proteinuria. Further decrease in renal function due to the progression of the underlying disease is manifested by an increase in FENa<sup>+</sup> and FEK<sup>+</sup> and a hyperchloremic metabolic acidosis, as is the case in other patients with chronic renal failure.

PMID: 1462007 [Indexed for MEDLINE]

5276. Padiatr Padol. 1992;27(4):105-7.

[Familial Mediterranean fever--a case report].

[Article in German]

Unsinn KM(1), Fischer H.

Author information:

(1)Universitäts-Kinderklinik Innsbruck, Österreich.

A case of a ten years old boy with recurrent fever and abdominal pain starting at the age of five years is reported. Later the attacks were accompanied by chest pain. There were only indifferent changes in laboratory examination. Neither a wide range of antibiotics, nor appendectomy and tonsillectomy prevented the boys symptoms. The diagnose was established after five years by a positive Metaraminol test, that precipitated a disease-like attack. The therapeutic use of colchicine-salicylate reduced the severity and frequency of attacks in out patient. In agreement with other authors it should be emphasized, that in general the benefit of colchicine outweighs possible side effects of a long term therapy also in children.

PMID: 1408288 [Indexed for MEDLINE]

5277. Wien Klin Wochenschr. 1992;104(7):208-10.

[Familial Mediterranean fever. Case of a 48-year-old patient with recurrent abdominal pain].

[Article in German]

Hofer JF(1), Franz B, Holzinger G.

Author information:

(1)Medizinische Abteilung des Landeskrankenhauses Freistadt.

A 48 year-old male patient from Turkey underwent laparotomy 13 years before admission to one unit because of persistent pain in the upper abdomen and fever. Subsequently, he was repeatedly admitted to surgical departments with recurrent upper abdominal pain and fever. The patient was admitted for medical

investigation to our department with fever and left pleuritic pain. During this observation period he repeatedly had attacks of fever lasting for one day with leucocytosis. The diagnosis of familial Mediterranean fever was made. Therapy with colchicine (1.5 mg/day) led to complete remission, maintained over the follow-up period of 2 years to date.

PMID: 1381854 [Indexed for MEDLINE]

5278. Scand J Rheumatol. 1992;21(6):312-3.

Familial Mediterranean fever and polyarteritis nodosa.

Ozen S(1), Saatci U, Balkanci F, Besbas N, Bakkaloglu A, Tacal T.

Author information:

(1)Department of Pediatric Nephrology and Radiology Hacettepe University, Faculty of Medicine, Ankara, Turkey.

PMID: 1362008 [Indexed for MEDLINE]

5279. Pediatrie. 1992;47(11):751-6.

[Periodic disease of the child].

[Article in French]

Koné-Paut I(1), Bernard JL.

Author information:

(1)Unité de recherche en épidémiologie et immuno-oncologie pédiatriques, faculté de médecine Nord, Marseille, France.

Familial mediterranean fever is a childhood disease which usually starts around the age of 4 years. Its onset is insidious with common and misleading symptoms such as fever and abdominal pain. Accordingly, this disease is often recognized

belatedly from evocative data from previous history such as the recurrence of attacks, familial descent from certain ethnic groups and the lack of other obvious etiology. The clinical picture within this age group is similar to that observed in adults and does not present any clinical or biological originality. Colchicine remains the only efficient treatment to prevent both acute manifestations and amyloidosis. The former is geared toward its current use among children (growth retardation and gonadic disturbances) and is not really relevant, at least in this particular disease.

PMID: 1342415 [Indexed for MEDLINE]

5280. Clin Neurol Neurosurg. 1992;94(3):261-3.

Pseudotumor cerebri with familial Mediterranean fever.

Gökalp HZ(1), Başkaya MK, Aydın V.

Author information:

(1)Department of Neurosurgery, University of Ankara, School of Medicine, Turkey.

Pseudotumor cerebri (PC) is a condition that occurs predominantly in obese women, and long lists of putative causes and associations have been reported. We describe here the case of a woman in whom PC coexisted with familial Mediterranean fever (FMF). A review of the literature revealed no report of an association of these two conditions.

PMID: 1327619 [Indexed for MEDLINE]

5281. Nephrol Dial Transplant. 1992;7(3):273-4.

Renal transplantation and pregnancy in a patient with familial Mediterranean fever amyloidosis taking triple-drug immunosuppression and colchicine.

Vergoulas G, Papagiannis A, Takoudas D, Papanikolaou V, Gakis D, Antoniadis A.

PMID: 1315009 [Indexed for MEDLINE]

5282. Dtsch Med Wochenschr. 1991 Nov 22;116(47):1783-7.

[Sacroiliitis in familial Mediterranean fever].

[Article in German]

Connemann BJ(1), Steinhoff J, Benstein R, Sack K.

Author information:

(1)Klinik für Innere Medizin, Medizinische Universität Lübeck.

A 15-year-old girl of Turkish descent had for one year complained of severe recurrent fever-associated deep back pains. Since she was three years of age she had suffered from repeated attacks of fever and severe abdominal pain which ceased spontaneously in 1-3 days. On physical examination the sacrum and iliosacral joints were very painful to percussion, and she limped. Radiography revealed symmetric destructive sacroiliitis. Despite the unusual location of the arthritis, the triad of fever, abdominal pain and arthritis, as well as her belonging to an ethnic "at risk" group, pointed to the diagnosis of familial mediterranean fever (FML) or recurrent hereditary polyserositis. This diagnosis was confirmed by a positive metaraminol provocation test in that infusion of metaraminol reproduced the typical pains. Collagen diseases, rheumatic disease, acute porphyria and chronic infectious processes were excluded. The sacroiliitis quickly responded to long-term administration of colchicine, 0.5 mg twice daily. The patient also has Hageman factor deficiency whose significance remains unclear.

DOI: 10.1055/s-2008-1063817

PMID: 1935671 [Indexed for MEDLINE]

5283. Klin Padiatr. 1991 Nov-Dec;203(6):458-61.

[Familial Mediterranean fever].

[Article in German]

Rupieper C(1), Heller K.

Author information:

(1)Kinderklinik Marienhospitals Witten.

Familial Mediterranean Fever is a genetically determined disease occurring predominantly in Arabs, Armenians, Jews and very rarely in Turks. It is characterized by moderately elevated body temperature and by abdominal, pulmonary or arthritic complaints. These symptoms are recurrent appearing at short intervals and persisting for not more than two days. Renal amyloidosis may be a complication. Thus, treatment should be continued for life. The pathomechanism of the disease is not clear. Colchicine has been shown to give good symptomatic relief. Surprisingly, the prolonged use of this mitotic poison is virtually devoid of untoward side effects, even in pregnancy and childhood.

DOI: 10.1055/s-2007-1025474

PMID: 1758151 [Indexed for MEDLINE]

5284. Schweiz Rundsch Med Prax. 1991 Oct 22;80(43):1165-6.

[What is your diagnosis? Destructive arthropathy in familial mediterranean fever].

[Article in German]

Wehrli R(1), Kissling RO.

Author information:

(1)Leitender Arzt Orthopädische Universitätsklinik Balgrist, Zürich.

PMID: 1947549 [Indexed for MEDLINE]

5285. J Clin Gastroenterol. 1991 Oct;13(5):587-8.

Primary gastric lymphoma occurring in familial Mediterranean fever.

Paraf F, Paraf A, Brousse N.

PMID: 1744402 [Indexed for MEDLINE]

5286. Ann Saudi Med. 1991 Sep;11(5):576-84.

Recurrent hereditary polyserositis or familial Mediterranean fever: An overview.

Cook GC(1).

Author information:

(1)Department of Clinical Sciences, Hospital for Tropical Diseases, London.

The etiology and pathogenesis of recurrent hereditary polyserositis (RHP) remain undetermined. There is a good evidence for a genetic basis (transmission being by a recessive Mendelian mode of inheritance), but not all cases have a family history and an infective (or other environmental) components has not been excluded. The marked variation in presentation and complications (in particular the prevalence of amyloid deposition) in different series suggests that this might not be a homogeneous entity. Vascular involvement is a basic prerequisite for the periodic attacks, and evidence for transient immunological abnormalities is incontrovertible. There are no reliable diagnostic techniques. Colchicine is of value in treatment, but its mode of action is unclear. More macro- and microepidemiological studies are required and will be of paramount importance. Clinical observations and molecular genetic studies should address the possibility that two or more immunological or metabolic defects might be interwoven; why for example do only some affected groups develop AA amyloidosis? Simple, non-invasive diagnostic tests are required for the uncomplicated disease and also for the presence of amyloid deposition. Preventive strategies might eventually involve genetic engineering techniques, but in the immediate future, education of doctors and other health care workers - to raise the "index of awareness" of RHP, in order that colchicine treatment can be commenced early in the disease - forms an important strategy. Colchicine therapy is not without complications and an alternative chemotherapeutic agent should be sought.



PMID: 17590796

5287. Mayo Clin Proc. 1991 Sep;66(9):919-25.

Pulmonary hypertension and familial Mediterranean fever: a previously unrecognized association.

Johnson WJ(1), Lie JT.

Author information:

(1)Division of Nephrology and Internal Medicine, Mayo Clinic, Rochester, MN 55905.

Familial Mediterranean fever is an autosomal recessive inherited disorder characterized by recurrent episodes of fever accompanied by inflammation of the peritoneum, pleura, synovial membranes, and skin. The disorder predominantly affects persons of Mediterranean origin. The most serious complication of the disease is amyloidosis, which is the cause of death in a substantial proportion of adult patients with the disorder. Only one previous report has described pulmonary hypertension in a patient with systemic amyloidosis associated with multiple myeloma. Herein we describe the first known occurrence of pulmonary hypertension due to pulmonary amyloidosis in a 48-year-old woman with familial Mediterranean fever. Postmortem examination showed extensive deposits of amyloid in the pulmonary vessels, alveolar capillary walls, and myocardium, which explained the hypoxia, hypotension, and terminal cardiac arrhythmias that were the immediate cause of death in this patient.

PMID: 1921502 [Indexed for MEDLINE]

5288. Klin Med (Mosk). 1991 Sep;69(9):67-9.

[Clinico-endoscopic data and the status of local immunity in intestinal lesions in patients with periodic disease].

[Article in Russian]

Arutiunian VM, Eganian GA, Aramian MKh.

Clinicoendoscopic and immunological evaluation of periodic disease patients shows that the disease-related inflammation of the colon is pathogenetically coupled with secretory IgA hypoproduction and abnormal intestinal eubiotic microflora. These facts should be allowed for when making differential diagnosis between periodic disease and gastrointestinal inflammations.

PMID: 1839411 [Indexed for MEDLINE]

5289. Schweiz Med Wochenschr. 1991 Aug 17;121(33):1166-8.

[Periodic disease and periarteritis nodosa in the same patient: coincidence?].

[Article in French]

Pechère M(1), Helfer C, Laurencet FL.

Author information:

(1)Clinique médicale thérapeutique, Hôpital cantonal universitaire, Genève.

Familial Mediterranean fever (FMF) chiefly affects patients of Arabic, Jewish, Armenian or Turkish origin and takes the form of recurrent episodes of peritonitis, arthritis or pleurisy. Periarteritis nodosa (PAN) is a vasculitis affecting elderly people and manifested by a general deterioration, unexplained fever and peripheral neuropathy or muscular weakness. We describe a patient presenting both diseases. Ours is the seventh reported case associating these two affections. This association was suspected by SACHS and co-workers who discovered an increased frequency of PAN in patients with FMF compared to the expected rate for the whole population (7). These observations warrant a search for PAN in young patients affected by FMF and showing signs of vasculitis.

PMID: 1681586 [Indexed for MEDLINE]

5290. Hum Genet. 1991 Aug;87(4):506-8.

Exclusion of linkage between familial Mediterranean fever and the human serum amyloid A (SAA) gene cluster.

Sack GH Jr(1), Talbot CC Jr, McCarthy BG, Harris EL, Kastner D, Gruberg L, Pras M.

Author information:

(1)Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland.

We studied the relationship between the autosomal recessive trait familial Mediterranean fever (FMF) and the serum amyloid A (SAA) genes by comparing alleles of a highly polymorphic dinucleotide repeat and a conventional restriction fragment length polymorphism (RFLP) in the SAA gene cluster in Israeli FMF kindreds. By haplotype analysis, our data indicate a minimum crossover frequency of 22% between the SAA gene marker and FMF. By conventional linkage analysis this eliminates a minimum of 10.4 cM including and surrounding the SAA gene cluster as the site of the FMF mutation although SAA proteins are prominent physiologic markers of the acute attacks.

PMID: 1679035 [Indexed for MEDLINE]

5291. Arthritis Rheum. 1991 Aug;34(8):973-7.

Long-term colchicine treatment in children with familial Mediterranean fever.

Zemer D(1), Livneh A, Danon YL, Pras M, Sohar E.

Author information:

(1)Department of Medicine, Heller Institute of Medical Research, Sheba Medical Center, Tel-Hashomer, Israel.

Three hundred fifty children (younger than age 16) who had familial Mediterranean fever (FMF) were given continuous prophylactic treatment with colchicine (1-2 mg/day) for 6-13 years. Complete remission of febrile attacks was achieved in 64%

of the patients, and partial remission in 31%. Protracted attacks of arthritis virtually disappeared. None of the children developed amyloidosis while on the colchicine regimen. Side effects of colchicine were insignificant, and did not prompt permanent discontinuation of treatment in any of the children. Their growth, development, and subsequent fertility were normal. The efficacy of long-term colchicine treatment of children with FMF makes early diagnosis life saving.

PMID: 1859491 [Indexed for MEDLINE]

5292. Curr Opin Rheumatol. 1991 Aug;3(4):597-600.

Whipple's disease, familial Mediterranean fever, and adult-onset Still's disease.

McMenemy A(1).

Author information:

(1)University of Texas Medical School, Houston.

Whipple's disease is a multisystem disorder thought to be caused by infection by rod-shaped bacilli. Early diagnosis remains difficult, because initial clinical features are nonspecific. Ultrasonography and computed tomographic scanning were used to demonstrate distinctive lymphadenopathy in Whipple's disease. Magnetic resonance imaging showed central nervous system lesions that were reversible with antibiotic therapy. Familial Mediterranean fever, or recurrent polyserositis, is an autosomal recessive disorder common among patients of Mediterranean heritage. Erysipelas-like skin lesions are commonly described. Other skin lesions, including Schönlein-Henoch purpura, nonspecific purpura, diffuse erythema, and angioneurotic edema are now reported. Renal complications, thought previously to be due primarily to amyloid, are also caused by immunoglobulin deposition resulting in mesangial proliferative glomerulonephritis. Adult-onset Still's disease is a systemic illness characterized by quotidian fever and a fleeting, salmon-colored rash. The long-term evolutions of juvenile-onset and adult-onset Still's disease were compared and found to be similar, except for the occurrence of amyloidosis in the latter group of patients. Prognosis of patients with articular features was worse than that of patients with extra-articular features. A multicenter survey of Japanese patients found few significant differences

between Japanese and non-Japanese cases. Less well-recognized features of adult-onset Still's disease, including neurologic complications, uveitis, and peritonitis, are reported.

PMID: 1716941 [Indexed for MEDLINE]

5293. Medicine (Baltimore). 1991 Jul;70(4):246-56.

Secondary systemic amyloidosis: response and survival in 64 patients.

Gertz MA(1), Kyle RA.

Author information:

(1)Dysproteinemia Clinic, Mayo Clinic, Rochester, Minnesota 55905.

From 1956 through 1989, 38 men and 26 women were seen at the Mayo Clinic with biopsy-proven AA. The underlying disorder was rheumatic disease in 42, infectious disease in 11, inflammatory bowel disease in 6, and other causes in 5. All patients were symptomatic at the time of diagnosis. Fifty-eight of the 64 patients had proteinuria or renal insufficiency. Fourteen also had significant symptoms of gastrointestinal amyloid, and 6 had amyloid goiter. None of the patients had symptomatic cardiac involvement, and only 3 had palpable hepatomegaly. Renal, gastric, rectal, fat, and marrow biopsies were positive for amyloid in 100%, 94%, 82%, 58%, and 46% of tested patients, respectively. The median survival of the entire group was 24.5 months. Thirty-five of the 47 deceased patients died as a direct result of their amyloidosis, primarily from complications of renal failure. Nine were successfully treated and had regression of the disease. Two with bronchiectasis responded to long-term cyclic antibiotic therapy, as did 1 patient with osteomyelitis. One patient with inflammatory bowel disease responded to surgical resection, and 1 with familial Mediterranean fever responded to colchicine. Four patients with rheumatic disease were treated with cyclophosphamide (in 2) and methotrexate (in 2), with complete resolution of their renal disease. All 9 successfully treated patients are alive, with a median follow-up of 58 months. Statistical analysis revealed that creatinine values greater than or equal to 2.0 mg/dl (P less than 0.003) and a serum albumin value less than 2.5 g/dl (P less than 0.02) were associated with a poorer survival. The single strongest variable associated with poor survival was a serum creatinine

level greater than 2 mg/dl at presentation, with a median survival of 11.2 months compared to patients with a creatinine level less than 2.0 mg/dl, with a median survival of 56.9 months.

PMID: 2067409 [Indexed for MEDLINE]

5294. J Pediatr. 1991 Jul;119(1 Pt 1):164.

Breast-feeding during colchicine therapy for familial Mediterranean fever.

Milunsky JM.

Comment on

J Pediatr. 1990 Jun;116(6):997-9.

PMID: 2066854 [Indexed for MEDLINE]

5295. Pediatr Med Chir. 1991 Jul-Aug;13(4):417-22.

[A diagnostic controversy: the significance of 14-6/sec positive spikes in clinical electroencephalography].

[Article in Italian]

Domenici R(1), Meossi C, Stefani G, Castelli S.

Author information:

(1)U.O. Pediatria, Ospedale di Lucca, Italia.

There has been a great deal of discussion as to the clinical significance of E.E.G. 14-6 per second positive spikes (14-6 PS), a short burst lasting one second or less which occurs during light sleep in monopolar recordings, mainly in the posterior temporal regions and usually involving the parietal and occipital regions as well, for the most part in unsymmetrical fashion. Early interpretations stress the epileptic nature of vegetative attacks in patients

with an inter-critical E.E.G. reading characterized by 14-6 P.S. Subsequently, however, this hypothesis has been refuted, mainly because E.E.G. intra-critical recordings have never shown evidence of any sort of paroxysmal activity. At present time experts think that the presence of 14-6 PS may be merely an indication of an electrical alteration associated with disorders in the neurovegetative area. In order to evaluate the possibility of using them as a diagnostic marker of migraine equivalents and periodic syndromes, we reviewed wake and sleep E.E.G. recordings, carried out consecutively and hence not selectively, in 617 children aged 5-16 years. 14-6 PS were present in 109 children (17.6%), 63 of whom showed evident symptoms of periodic syndrome (headache, recurrent abdominal pain, cyclic vomiting, kinesis, etc.); hence 46 E.E.G. recordings were false positive. 510 children were lacking in 14-6 PS, 91 of these presented symptoms of periodic syndromes (false negative). 14-6 PS are hence a marker 40.9% sensitive, 90.1% specific, with a predictable value of 57.7%. The search for 14-6 PS in children with periodic syndrome is not particularly sensitive as a test, but it is fairly specific: it may well constitute an useful element in diagnosis.

PMID: 1754477 [Indexed for MEDLINE]

5296. Scand J Immunol. 1991 Jun;33(6):783-6.

Characterization of high molecular weight amyloid A proteins.

Prelli F(1), Pras M, Shtrasburg S, Frangione B.

Author information:

(1)Department of Pathology, New York University Medical Center, New York 10016.

Human amyloid A protein (AA) is usually composed of the NH<sub>2</sub>-terminal 76 amino acid residue of serum amyloid A protein (SAA), although lower and higher molecular weight fragments have been reported. We studied the primary structure of six AA proteins with molecular weights of 11 kDA-15kDA, as determined by SDS-PAGE. Automated Edman degradation of the intact purified proteins and sequence analysis of enzymatic peptides revealed that the AA proteins were composed of only 74 to 87 residues. Moreover, fragments of apolipoprotein E or histones 2a, 3 and 4 were associated with these AA molecules. Thus, AA

heterogeneity may reflect diverse processing of the SAA precursor and a very close association with other proteins.

PMID: 2047766 [Indexed for MEDLINE]

5297. Am J Med Sci. 1991 Jun;301(6):375-8.

Urinary albumin excretion in patients with familial Mediterranean fever: a pilot study.

Oren S(1), Viskoper JR, Ilan S, Schlesinger M.

Author information:

(1)Department of Internal Medicine B, Barzilai Medical Center, Ashkelon, Israel.

Amyloidosis of the kidney is the most threatening complication in familial Mediterranean fever (FMF), and colchicine has been shown to reduce its occurrence. In the preclinical stage of kidney amyloidosis, no proteinuria is observed by the standard Albustix method. However, whether these patients have normal or increased urinary albumin excretion is not known. The purpose of this study was to evaluate albumin excretion in FMF patients treated with colchicine and to compare these values to those of a normal control group. Twenty-two subjects with FMF were compared with 16 normal subjects matched with regard to age and body surface area. The two groups did not differ with regard to female/male ratio and arterial pressure. Urine samples were collected overnight while patients were recumbent and in the daytime while they were ambulant. After measuring albumin concentration (Ua) by radio-immunoassay and creatinine concentration through the standard method, the urinary albumin excretion rate (UaV) and urinary albumin creatinine ratio (Ua/c) were calculated. In the FMF group, three patients had microalbuminuria--defined as an albumin excretion rate higher than 20 micrograms/min. Two of them had this condition only in the early morning collection. These three patients were characterized by a longer duration of symptoms (18 vs. 9 years). No patient in the control group had microalbuminuria. The mean UaV in the FMF group did not differ significantly from that of the control group.(ABSTRACT TRUNCATED AT 250 WORDS)



PMID: 2039023 [Indexed for MEDLINE]

5298. Klin Med (Mosk). 1991 Jun;69(6):47-50.

[Condition of the heart in periodic disease].

[Article in Russian]

Ter-Kasparova MR.

PMID: 1774910 [Indexed for MEDLINE]

5299. Postgrad Med J. 1991 May;67(787):490-1.

Hyperimmunoglobulinaemia D and periodic fever mimicking familial Mediterranean fever in the Mediterranean.

Topaloğlu R, Saatçi U.

PMCID: PMC2398873

PMID: 1852679 [Indexed for MEDLINE]

5300. Ann Clin Lab Sci. 1991 May-Jun;21(3):205-15.

Familial Mediterranean fever in a fraternal twin: a laboratory evaluation.

Topouzian NB(1), Bowie LJ.

Author information:

(1)Department of Pathology and Laboratory Medicine, Evanston Hospital, IL 60201.

Familial Mediterranean fever (FMF) is an autosomal recessive disease of unknown etiology and has no known diagnostic markers. Periodic attacks of pain and fever can be precipitated by dietary fat or dairy products and by the same factors that

are known to elevate serum free fatty acids (FFA). Several tests related to lipid metabolism were made on the serum and urine of a fraternal twin with FMF during attacks and remission. The results were compared with those of the unaffected, asymptomatic twin and healthy adults. Low density lipoprotein-cholesterol was elevated in both twins. Gas chromatography revealed many urinary FFA during attacks and fewer during remission. Urinary organic acids determined by gas chromatography/mass spectrometry (GC/MS) revealed slight elevations of glycollic, oxalic, and methylmalonic acids during an attack. Serum gamma-glutamyl transferase (GGT) levels were at or below the low limits of normal for both twins. Hematological studies revealed low values for erythrocyte parameters for the affected twin. Both twins had low serum iron and an increased iron binding capacity. These findings may represent a defect in fatty acid metabolism which is being compensated by alternate pathways which may generate oxidants. Both FFA and oxidants are injurious to cell membranes and may be the cause of the polyserositis which occurs during an attack.

PMID: 1676578 [Indexed for MEDLINE]

5301. Dtsch Med Wochenschr. 1991 Apr 5;116(14):548-52.

[Familial Mediterranean fever].

[Article in German]

Better OS(1), Zemer D.

Author information:

(1)Rambam Hospital Haifa.

DOI: 10.1055/s-2008-1063647

PMID: 2013257 [Indexed for MEDLINE]

5302. Nihon Rinsho. 1991 Apr;49(4):806-13.

[Familial Mediterranean fever and familial amyloidotic polyneuropathy].

[Article in Japanese]

Araki S(1), Ando Y.

Author information:

(1)First Department of Internal Medicine, Kumamoto University Medical School.

PMID: 2072535 [Indexed for MEDLINE]

5303. J Rheumatol. 1991 Apr;18(4):606-8.

Determination of autoantibodies in patients with familial Mediterranean fever and their first degree relatives.

Swissa M(1), Schul V, Korish S, Livneh A, Pras M, Shoenfeld Y.

Author information:

(1)Research Unit of Autoimmune Diseases, Heller Institute, Israel.

Sera samples of 168 patients with familial Mediterranean fever (FMF) and their 184 first degree relatives were analyzed for the presence of autoantibodies to ssDNA, dsDNA, poly (I), poly (G), cardiolipin, histones, RNP and Ro(SSA), using an enzyme linked immunosorbent assay (ELISA). A similar analysis was employed on culture fluids of Epstein-Barr virus (EBV) transformed B lymphocytes derived from patients with FMF and healthy controls. No increased incidence of these antibodies was observed among patients with FMF and their relatives compared to healthy controls. It is possible that autoimmune features observed in FMF are the result of nonspecific changes occurring in inflammation and not due to autoimmune mechanisms.

PMID: 2066952 [Indexed for MEDLINE]

5304. Am J Med. 1991 Apr;90(4):434-8.

Tumor necrosis factor in familial Mediterranean fever.

Schattner A(1), Lachmi M, Livneh A, Pras M, Hahn T.

Author information:

(1)Department of Medicine A, Kaplan Hospital, Rehovot, Israel.

Comment in

Am J Med. 1992 Nov;93(5):587.

Am J Med. 1992 May;92(5):579-80.

**PURPOSE:** The pleiotropic inflammatory effects of tumor necrosis factor (TNF) prompted a study of this cytokine in familial Mediterranean fever (FMF), a recurrent polyserositis of unknown etiology.

**PATIENTS AND METHODS:** Thirty-six asymptomatic and 24 patients with acute FMF were studied and compared with 20 matched healthy subjects. TNF levels were measured by bioassay in the plasma and in supernatants of peripheral blood mononuclear cells (PBMC) incubated alone or with an inducer (lipopolysaccharide, phytohemagglutinin [PHA], or Sendai virus). Cytotoxicity could be abolished in all cases by preincubation with monoclonal anti-TNF-alpha antibodies.

**RESULTS:** No TNF was found in plasma and non-induced PBMC supernatants. Induced TNF production was markedly decreased in patients with acute FMF and increased in asymptomatic FMF patients to levels over those of control subjects (p less than 0.05). Thus, PHA-induced TNF levels were 4 U/mL in patients with acute FMF, 25 U/mL in asymptomatic patients, and 14 U/mL in healthy control subjects (median values), and the other inducers gave similar results. Retesting of patients first studied during an acute episode when their disease was quiescent also revealed a fivefold increase in TNF production. These results were independent of the use of colchicine, which also had no effect on TNF levels when taken by volunteers (1 mg/day) or when added to the PBMC cultures ( $10^{-7}$  M).

**CONCLUSIONS:** Since TNF has a very short half-life in plasma, the capacity of PBMC to respond to TNF inducers may more accurately reflect its synthesis. A marked decrease in this response in acute FMF suggests "exhaustion" of cells that are already highly activated to produce TNF and the possible participation of TNF in the pathogenesis of FMF.

PMID: 2012083 [Indexed for MEDLINE]

5305. Postgrad Med J. 1991 Mar;67(785):223-6.

Colchicine--expanding horizons.

Schattner A(1).

Author information:

(1)The Weizmann Institute of Science, Rehovot, Israel.

PMCID: PMC2399002

PMID: 2062768 [Indexed for MEDLINE]

5306. Rev Clin Esp. 1991 Mar;188(4):214-5.

[Metaraminol provocation test in a case of familial Mediterranean fever].

[Article in Spanish]

Buades J, Orfila J.

Comment on

Rev Clin Esp. 1990 Jan;186(1):47-8.

PMID: 1784750 [Indexed for MEDLINE]

5307. Acta Gastroenterol Belg. 1991 Mar-Apr;54(2):209-13.

[Recurrent peritonitis caused by familial Mediterranean fever].

[Article in Dutch]

Dhondt A(1), De Potter W, Mast A, Van Maele V.

Author information:

(1)Dienst Gastro-enterologie, Algemene Kliniek Heilige Familie, Gent.

The authors report a case of Familial Mediterranean Fever (FMF) in a Turkish patient. FMF is characterised by paroxysmal attacks of fever, peritonitis and/or pleuritis or arthritis. FMF is almost exclusively confined to populations of Mediterranean origin and it is often familial. The diagnosis is mainly clinical. Recently an enhanced dopamine beta-hydroxylase (DBH) activity was described as a diagnostic test. We confirmed this in our patient. FMF was successfully treated by chronic colchicine therapy: 1-2 mg daily, which reduced DBH activity to normal levels.

PMID: 1755276 [Indexed for MEDLINE]

5308. BMJ. 1991 Feb 9;302(6772):349-50.

Recurrent hereditary polyserositis.

Broadbent PG, Raynes JG, McAdam KP, Anis MH.

Comment on  
BMJ. 1990 Nov 17;301(6761):1110-1.

PMCID: PMC1668985  
PMID: 2001518 [Indexed for MEDLINE]

5309. Semin Arthritis Rheum. 1991 Feb;20(4):241-6.

Colchicine prophylaxis in familial Mediterranean fever: reappraisal after 15 years.

Ben-Chetrit E(1), Levy M.

Author information:

(1)Department of Medicine A, Hadassah University Hospital, Jerusalem, Israel.

As determined in this study of 45 patients, the prolonged use of colchicine

therapy in familial Mediterranean fever (FMF) is safe and effective in preventing flares of FMF and amyloidosis. It has acceptable adverse effect profile and can be used in children and pregnant women. Its discontinuation predisposes patients to acute FMF attacks and the development of amyloidosis. Articular involvement is less responsive to colchicine and may require therapy with nonsteroidal antiinflammatory drugs.

PMID: 2042056 [Indexed for MEDLINE]

5310. J Gynecol Obstet Biol Reprod (Paris). 1991;20(4):554-61.

[Periodic disease and pregnancy].

[Article in French]

Cousin C(1), Palaric JC, Jacquemard F, Lucas J, Giraud JR.

Author information:

(1)Clinique Gynécologique et Obstétricale, Centre Hospitalier Universitaire (Hôtel-Dieu), Rennes.

The authors report a case of familial Mediterranean fever in a pregnant woman treated with Colchicine. She delivered normally at term. A review of the literature shows that colchicine does not have a teratogenic effect which it was long thought to have. All the same it is best to carry out fetal karyotype examination using early amniocentesis. Furthermore, colchicine improves fertility which is disturbed in these patients and pregnancy has a good effect on the disease.

PMID: 1885892 [Indexed for MEDLINE]

5311. Pharmacotherapy. 1991;11(3):196-211.

Colchicine: a state-of-the-art review.

Levy M(1), Spino M, Read SE.

Author information:

(1)Division of General Pediatrics, Hospital for Sick Children, Toronto, Ontario, Canada.

Colchicine is an ancient drug that is attracting renewed interest because of its actions at a subcellular level. Specifically, it interferes with microtubule growth and therefore affects mitosis and other microtubule-dependent functions. Various mechanisms have been proposed to account for the action of colchicine in acute gouty arthritis, its interaction with cellular membrane and cyclic 3',5'-adenosine monophosphate, and its action in amyloidosis. Pharmacokinetic studies have been relatively limited and their results somewhat contradictory, with mean terminal elimination half-lives of 19 minutes to 9 hours being reported. Some of these differences may be attributed to assay difficulties. Colchicine can cause gastrointestinal side effects and should be used with care to protect patients from toxic doses. Colchicine-induced myopathy and neuropathy may be more frequent than previously recognized, and therefore patients receiving long-term therapy should be monitored carefully. Bone marrow depression has been reported, primarily in cases of acute colchicine intoxication, and intravenous administration of the drug has been associated with severe pancytopenia and death. Colchicine intoxication causes multiple organ failure. Because of its cytogenic effects and reported association with Down's syndrome, the agent should not be used by pregnant women.

PMID: 1862011 [Indexed for MEDLINE]

5312. Rev Neurol (Paris). 1991;147(5):403-5.

[Recurrent aseptic meningitis in periodic disease or Mollaret's meningitis?].

[Article in French]

Collard M(1), Sellal F, Hirsch E, Mutschler V, Marescaux C.

Author information:

(1)Clinique Neurologique, Strasbourg.



A 33 year-old Sephardic Jewish man with familial mediterranean fever (FMF), presented during a 7 year period, 6 episodes of aseptic meningitis, improving within less than 24 h after spinal tap. Cerebrospinal fluid analysis showed a mixed leucocytic pleocytosis ranging from 100 to 1,000 cell/mm<sup>3</sup>. Spinal fluid cultures for bacteria, viruses and viral antibodies were always negative. Our case supports other reports showing that recurrent aseptic meningitis, although rare, may occur in FMF. It usually responds to treatment with colchicine, like other manifestations of the disease. FMF meningitis has been compared to Mollaret's meningitis whose cause is undetermined. However, Mollaret's meningitis, unlike FMF, is sporadic and ubiquitous, is not transmitted genetically and affects men and women equally. Moreover, in Mollaret's meningitis transient neurological abnormalities, such as signs of encephalitis have often been reported: polyserositis or associated amylosis are absent, there is no biological inflammatory syndrome, and in 65% of the patients the CSF contains specific large mononuclear-derived cells called endothelial cells. Such abnormalities have not been described in FMF.

PMID: 1853039 [Indexed for MEDLINE]

5313. Adv Hum Genet. 1991;20:69-123, 309-11.

Genetic aspects of amyloidosis.

Jacobson DR(1), Buxbaum JN.

Author information:

(1)Medical Service, New York Veterans Affairs Medical Center, New York.

PMID: 1839349 [Indexed for MEDLINE]

5314. Ter Arkh. 1991;63(8):117-20.

[Selective involvement of the gastrointestinal tract in amyloidosis in a female patient with periodic disease and intact kidneys].

[Article in Russian]

Arutiunian VM, Eganian GA, Khachatrian VA.

The authors describe a rare case of amyloidosis in a female patient suffering from periodic disease (PD) for 18 years without any clinico-laboratory signs of renal impairment but with marked clinical, (malabsorption, cachexia), endoscopic, x-ray and other manifestations of gastrointestinal amyloidosis. This case is of interest since patients suffering from amyloidosis due to PB develop malabsorption very rarely, namely in 2-3% of cases. As a rule, it develops in patients with pronounced chronic renal failure on hemodialysis or with a history of kidney transplantation. In this particular case, the patient demonstrated selective marked damage to the gastrointestinal tract, with the kidneys remaining practically intact. A possibility of the indicated variety of amyloidosis should be considered in specification of the genesis of persistent diarrhea in PB patients.

PMID: 1792600 [Indexed for MEDLINE]

5315. Ann Ital Med Int. 1991 Jan-Mar;6(1 Pt 2):107-16.

Amyloidosis: clinical picture, immunological and biomolecular features, treatment prospects.

Dammacco F(1).

Author information:

(1)Istituto di Patologia Speciale Medica, Università degli Studi di Bari, Italy.

Amyloidosis is the name given to a group of clinically protean diseases whose common feature is the tissue accumulation of amyloid fibrils which have specific optical and staining properties, and are both insoluble in physiological solvents and resistant to proteolytic enzymes. Fibril deposition and progressive extracellular infiltration eventually result in atrophy due to compression. The structure of these fibrils embraces a wide range: immunoglobulin light chain or their fragments, acute phase proteins, hormones, protease inhibitors, beta

2-microglobulin, natriuretic peptides, and proteins whose function is still unknown. Despite this heterogeneity, however, they share a common crystallographic beta-pleated sheet structure. The clinical spectrum includes apparently primary forms, amyloidosis of myeloma, forms secondary to familial Mediterranean fever, Alzheimer's disease, forms associated with type 2 diabetes or medullary carcinoma of the thyroid, inherited-familial amyloidosis, and other less common conditions. Two pathogenetic phases are involved: enhanced production of precursor proteins and their abnormal enzyme cleavage, resulting in the formation of intermediate products corresponding to the amyloid fibrils. The results of treatment are still disappointing: alkylating agents and/or cortico-steroids are used in primary forms and for amyloidosis of myeloma; colchicine in familial Mediterranean fever; DMSO in renal amyloidosis; plasmapheresis in inherited-familial forms, together with the supportive management obviously dictated by clinical manifestations.

PMID: 1742146 [Indexed for MEDLINE]

5316. Am J Ophthalmol. 1990 Dec 15;110(6):702-3.

Recurrent bilateral panuveitis and rhegmatogenous retinal detachment in a patient with familial Mediterranean fever.

Hirsh A, Huna R, Ashkenazi I, Bartov E, Blumenthal M.

PMID: 2248339 [Indexed for MEDLINE]

5317. Br J Rheumatol. 1990 Dec;29(6):459-61.

Autoantibodies in familial Mediterranean fever (recurrent polyserositis).

Ben-Chetrit E(1), Levy M.

Author information:

(1)Hadassah University Hospital, Department of Medicine, Jerusalem, Israel.

The presence of autoantibodies in our familial Mediterranean fever (FMF) patients was investigated using various immunological techniques. Immunofluorescence screening of 50 FMF sera revealed only one positive for antinuclear antibodies. ELISA assay and nitrocellulose filter assay revealed no difference between FMF sera and healthy controls with regard to the presence of anti-dsDNA antibodies. In Western blotting using HeLa cell extract, FMF patients' sera neither detected anti-Sm, RNP, SSA/Ro, SSB/La antibodies nor any new common band. These findings suggest that it is unlikely that FMF belongs to the family of the autoimmune 'collagen' diseases.

PMID: 2257455 [Indexed for MEDLINE]

5318. Arch Dermatol. 1990 Dec;126(12):1621-4.

IgD immune complex vasculitis in a patient with hyperimmunoglobulinemia D and periodic fever.

Boom BW(1), Daha MR, Vermeer BJ, van der Meer JW.

Author information:

(1)Department of Dermatology, University Hospital, Leiden, The Netherlands.

We describe a 27-year-old Dutch woman with the hyperimmunoglobulinemia D and periodic fever syndrome. During febrile attacks she occasionally presented with skin lesions on the distal parts of her upper and lower extremities, with the histologic picture of a leukocytoclastic vasculitis. Clear perivascular deposits of IgD and C3 were presented in early lesional skin on immunofluorescence investigation. Circulating IgD immune complexes were demonstrated on several occasions, both during and in between clinical attacks. These findings are consistent with an IgD immune complex-mediated pathogenesis for the skin lesions. In 10 patients with other forms of immune complex vasculitis of the skin, minimal perivascular deposits of IgD were found in four cases. In these cases, however, IgD was never found as the solitary immunoglobulin class.

PMID: 2147822 [Indexed for MEDLINE]

5319. BMJ. 1990 Nov 17;301(6761):1110-1.

Recurrent hereditary polyserositis.

Cook GC.

Comment in

BMJ. 1991 Feb 9;302(6772):349-50.

PMCID: PMC1664282

PMID: 2252918 [Indexed for MEDLINE]

5320. Clin Genet. 1990 Nov;38(5):332-9.

Genetic marker family studies in familial Mediterranean fever (FMF) in Armenians.

Shohat T(1), Shohat M, Petersen GM, Sparkes RS, Langfield D, Bickal J, Korenberg JR, Schwabe AD, Rotter JL.

Author information:

(1)Department of Medicine, Cedars-Sinai Medical Center, UCLA School of Medicine.

Familial Mediterranean fever is an autosomal recessive disease manifested by recurrent short episodes of fever associated with polyserositis. It is common in a variety of Mediterranean and near Eastern populations. The biochemical defect is unknown, and there have been few studies of genetic marker associations or linkage with the disease. We have screened blood samples from members of 14 nuclear Armenian families, the population with the highest known gene frequency, for 19 different polymorphic phenotypic genetic markers. These 14 families included 31 affected and 43 unaffected family members. No association was found with any of the markers studied. Linkage could be excluded at the distance of 0-15% recombination with 14 markers. Linkage could not be excluded with 5 other markers. These results exclude the FMF gene from those portions of the human gene map that are at least 0.5% recombination distance from these 14 genetic markers, and represent the first comprehensive step in the eventual localization and isolation of the FMF gene.

PMID: 2282713 [Indexed for MEDLINE]

5321. Int J Gynaecol Obstet. 1990 Oct;33(2):165-9.

Pregnancy and complicated familial Mediterranean fever.

Shimoni Y(1), Shalev E.

Author information:

(1)Department of Obstetrics and Gynecology, Central Emek Hospital, Afula, Israel.

Familial Mediterranean Fever (FMF) is an inherited disease, closely following the pattern of autosomal recessive inheritance. Amyloidosis is the most severe complication of the disease. The prevalence of pregnancy loss in women with FMF is considered to be high. There is no information to support the possibility of increase risk of late pregnancy complications or change in the natural course of the disease. Two cases are presented with complicated FMF. One case with proved amyloidosis and the second patient with ascites. Pregnancy and neonatal outcome were uneventful in both. No further deterioration in the systemic disease occurred.

PMID: 1976551 [Indexed for MEDLINE]

5322. Tissue Antigens. 1990 Sep;36(3):103-7.

Familial Mediterranean fever--linkage studies with genetic markers on chromosome 6.

Shohat T(1), Shohat M, Tyan DB, Wang SJ, Sparkes RS, Schwabe AD, Rotter JL.

Author information:

(1)Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA.

Familial Mediterranean Fever (FMF) is an autosomal recessive disease manifested

by recurrent short episodes of fever associated with polyserositis. Although the biochemical defect is unknown, there are several immunologic abnormalities which have been described in this disease. To examine critically whether there is linkage between FMF and the immunogenetic region (major histocompatibility complex-MHC) on chromosome 6, including the HLA, BF, and GLO1 loci, blood samples from members of 13 nuclear Armenian families were tested for these genetic markers. These 13 families included 28 affected and 42 unaffected family members. Linkage could be excluded at 7.5% recombination with the HLA ABC and D loci. Linkage could be excluded at 2.5% recombination for GLO1. Linkage could not be excluded with BF individually, but can be rejected based on the haplotype data. No association was found with either BF, GLO1, and HLA DQ alleles. HLA DR4 was found more often in affected cases than in controls; however, after adjusting for the number of antigens tested this was not significant. Our results would appear to exclude the immunogenetic region on chromosome 6 from linkage with FMF in the Armenian population.

PMID: 2278043 [Indexed for MEDLINE]

5323. Biull Eksp Biol Med. 1990 Sep;110(9):296-7.

[Level of leukotrienes B4 and C4 in the blood of patients with periodic disease].

[Article in Russian]

Gabrielian ES, Grigorian SV, Davtian DG, Mkhitarian GS, Panosian AG.

The level of LTB4 and LTC4 in blood plasma of patients with familial mediterranean fever is significantly higher than in healthy donors:  $53 \pm 10$  pg/ml for LTB4 (normal -  $25 \pm 5$  pg/ml) and  $175 \pm 22$  pg/ml for LTC4 (normal  $67 \pm 19$  pg/ml). The more increase of the LTB4 and LTC4 content in plasma is observed during attacks of fever -  $107 \pm 21$  pg/ml (LTB4) and  $249 \pm 34$  pg/ml (LTC4). Hyperbaric oxygenation of patients, used to relieve pain and fever, reduces the level of leukotrienes.

PMID: 2176555 [Indexed for MEDLINE]

5324. Aten Primaria. 1990 Sep;7(8):595.

[Report of a case of familial Mediterranean fever].

[Article in Spanish]

Esteban MA, Botaya MA, Godoy F, Sánchez S.

PMID: 2104166 [Indexed for MEDLINE]

5325. Genomics. 1990 Sep;8(1):83-9.

Serum amyloid A and P protein genes in familial Mediterranean fever.

Shohat M(1), Shohat T, Rotter JI, Schlesinger M, Petersen GM, Pribyl T, Sack G, Schwabe AD, Korenberg JR.

Author information:

(1)Department of Pediatrics, Cedars-Sinai Medical Center, Los Angeles, CA 90048.

Two recent studies have suggested the involvement of serum amyloid A (SAA) and P (APCS) genes in familial Mediterranean fever (MEF). To test the role of SAA and APCS in MEF and MEF-amyloidosis, we studied 17 informative families (15 Armenians, 2 non-Ashkenazi Jews) and 8 MEF patients with amyloidosis using a candidate gene approach. No evidence for any MEF-associated polymorphism was found in any of the 41 Armenian and Jewish MEF patients tested. Our family studies allowed us to rule out tight linkage between SAA and MEF (lod score = -2.16, theta less than or equal to 0.06). For APCS we found that the allele frequency in the MEF-amyloidosis patients was similar to that in 18 unrelated MEF patients without amyloidosis and their 33 healthy parents. Finally, we excluded close genetic linkage between APCS and MEF at 8.5 cM or less (lod score = -2.2).

PMID: 1981994 [Indexed for MEDLINE]



5326. Isr J Med Sci. 1990 Aug;26(8):459-60.

Decreased incidence of asthma in patients with familial Mediterranean fever.

Danon YL(1), Laor A, Shlezinger M, Zemer D.

Author information:

(1)Medical Corps, Israel Defense Forces, Beilinson Medical Center, Petah Tikva, Israel.

PMID: 2401614 [Indexed for MEDLINE]

5327. Curr Opin Rheumatol. 1990 Aug;2(4):600-4.

Whipple's disease, familial Mediterranean fever, and adult-onset Still's disease.

McMenemy A(1).

Author information:

(1)University of Texas Medical School, Houston.

PMID: 1698427 [Indexed for MEDLINE]

5328. Rev Invest Clin. 1990 Jul;42 Suppl:97-100.

[Colchicine: rationale for its use in liver disease].

[Article in Spanish]

Kershenobich D(1), Borovoy J, Guevara RL.

Author information:

(1)Departamento de Gastroenterología, Instituto Nacional de la Nutrición "Salvador Zubirán", Tlalphan, 14000 México, DF.

Colchicine is a substance derived from the Colchicum Autumnale plant, its pharmacological uses have been demonstrated over the years. Initially used for the treatment of acute gout, it has been utilized for a wide variety of diseases, including mediterranean familial fever, alcoholic, posthepatitic and primary biliary liver cirrhosis. We have demonstrated in different studies that colchicine reduces markedly mortality rates in cirrhotics and the levels of interleukin-1 in patients with primary biliary cirrhosis.

PMID: 19256145 [Indexed for MEDLINE]

5329. Arch Intern Med. 1990 Jun;150(6):1347.

Persistent fever as the only symptom of familial Mediterranean fever.

Halabe-Cherem J(1), Islas-Andrade S, Lifshitz A, Nellen H.

Author information:

(1)Hospital de Especialidades Centro Médico Nacional y Subjefatura de Investigación, Instituto Mexicano del Seguro Social, Medellin.

We describe a 54-year-old man who suffered from familial Mediterranean fever, but the fever has been the only symptom during a 10-year period. During this period, results of laboratory tests and roentgenographic studies were negative. On the basis of these findings we propose that familial Mediterranean fever can be included in the causes of persistent fever in patients with long periods of fever.

PMID: 2353868 [Indexed for MEDLINE]

5330. Arch Intern Med. 1990 Jun;150(6):1289-91.

Proposed mechanism of the inflammatory attacks in familial Mediterranean fever.

Matzner Y(1), Ayesh SK, Hochner-Celniker D, Ackerman Z, Ferne M.

Author information:

(1)Hematology Unit, Hadassah University Hospital Mount Scopus, Jerusalem, Israel.

Peritoneal and synovial fluids of patients with familial Mediterranean fever lack a protein that inhibits neutrophil chemotaxis by antagonizing the complement-derived inflammatory mediator C5a. The C5a inhibitor activity was studied with the use of a C5a binding assay where peritoneal fluids were tested for their ability to inhibit recombinant C5a binding to dibutyryl cyclic adenosine monophosphate-induced U937 cells. In contrast to normal peritoneal fluids, those from patients with familial Mediterranean fever contained less than 1% C5a inhibitor activity. Gel filtration and ion exchange chromatography of peritoneal fluids from those patients did not yield any fraction that inhibited C5a binding. We suggest that the serosal tissue of patients with familial Mediterranean fever is devoid of C5a inhibitor activity and that this deficiency may explain in part the local inflammatory episodes characteristic of this disease.

PMID: 2353861 [Indexed for MEDLINE]

5331. Rev Clin Esp. 1990 Jun;187(2):94-5.

[Familial Mediterranean fever. The metaraminol test as a cause of severe cephalalgia].

[Article in Spanish]

Martínez Vázquez C, Rodríguez García M, González Yebra-Pimentel I, Moreiras M, Estévez F.

PMID: 2244064 [Indexed for MEDLINE]

5332. Q J Med. 1990 Jun;75(278):607-16.

The cutaneous manifestations in children with familial Mediterranean fever (recurrent hereditary polyserositis). A six-year study.

Majeed HA(1), Quabazard Z, Hijazi Z, Farwana S, Harshani F.

Author information:

(1)Department of Pediatrics, Faculty of Medicine, University of Kuwait.

In a six-year study of 46 children with familial Mediterranean fever (recurrent hereditary polyserositis), 20 children (43 per cent) developed cutaneous manifestations. Ten children had 18 episodes of erysipelas-like erythema which proved to be specific for the disease. Twelve children (26 per cent) had 31 episodes of non-specific purpuric rash and six children (13 per cent) had nine episodes of Henoch-Schönlein purpura. Other manifestations included diffuse erythema of the face, and/or trunk, angioneurotic oedema, diffuse erythema of the palms and soles followed by mild desquamation of the skin, Raynaud's phenomenon and a subcutaneous nodule. The mean frequency of the cutaneous lesions was 1.6/patient/year before colchicine therapy and 0.4/patient/year after colchicine therapy ( $p = 0.0005$ ). The high incidence of cutaneous manifestations and their response to colchicine strongly suggest that skin involvement is an integral part of familial Mediterranean fever.

PMID: 2217666 [Indexed for MEDLINE]

5333. J Pediatr. 1990 Jun;116(6):997-9.

Long-term colchicine prophylaxis in children with familial Mediterranean fever (recurrent hereditary polyserositis).

Majeed HA(1), Carroll JE, Khuffash FA, Hijazi Z.

Author information:

(1)Department of Pediatrics, Faculty of Medicine, University of Kuwait, Safat.

Comment in

J Pediatr. 1991 Jul;119(1 Pt 1):164.

PMID: 2112191 [Indexed for MEDLINE]

5334. Clin Nephrol. 1990 May;33(5):227-31.

IgM nephropathy associated with familial Mediterranean fever.

Said R(1), Hamzeh Y.

Author information:

(1)Department of Medicine, Medical School, Jordan University, Amman.

Three patients with a long-standing history of familial Mediterranean fever (FMF) were found to have both microscopic hematuria and proteinuria during the acute attacks. Kidney biopsies from all patients revealed diffuse mesangial proliferative glomerulonephritis with intense IgM and C3 deposits; all were negative for amyloidosis. To our knowledge this is the first time the development of IgM nephropathy in patients with FMF is described.

PMID: 2354558 [Indexed for MEDLINE]

5335. Ann Rheum Dis. 1990 May;49(5):338.

Cricothyroid arthritis in a child with familial Mediterranean fever.

Khuffash FA, Majeed HA.

PMCID: PMC1004086

PMID: 2344219 [Indexed for MEDLINE]

5336. J Immunol. 1990 Apr 15;144(8):3066-70.

Partial characterization of a C5a-inhibitor in peritoneal fluid.

Ayesh SK(1), Ferne M, Flechner I, Babior BM, Matzner Y.

Author information:

(1)Hematology Unit, Hadassah University Hospital Mount Scopus, Jerusalem, Israel.

We have recently described a 40-kDa protein in peritoneal fluid that neutralized the chemotactic activity of the C fraction C5a. It was deficient in peritoneal fluids of patients suffering from familial Mediterranean fever. Further characterization of the inhibitor with the use of <sup>125</sup>I-rC5a binding to dibutyryl cAMP-induced U937 cells revealed dependence on the peritoneal fluid concentration, on the time of incubation and on temperature and pH. Fractionation of <sup>125</sup>I-C5a on Sephadex G-50 column, before and after incubation with peritoneal fluid, revealed similar fractionation patterns despite loss of biologic activity of the treated C5a (but not its binding to polyclonal anti-C5a antibody). Analysis of rC5a by SDS-PAGE before and after treatment with partially purified C5a inhibitor, revealed slight modification of the inhibitor-treated C5a. Using various protease inhibitors (i.e., PMSF) suggested that the C5a inhibitor is a serine protease. It neutralized C5a by means of limited proteolysis which did not change C5a immunologic properties and changed only slightly its m.w. but abolished its receptor binding and chemotactic functions. It is suggested that the C5a inhibitor plays a role in the regulation of inflammation in serosal tissues and that its deficiency in familial Mediterranean fever may explain the attacks of sterile inflammation characteristic of this disease.

PMID: 2324495 [Indexed for MEDLINE]

5337. Gac Med Mex. 1990 Mar-Apr;126(2):130.

[Comments on the article "Abdomen agudo o saturnismo. Un dilema diagnóstico?"].

[Article in Spanish]

Halabe-Cherem J, Romero-Romero E, Lifshitz-Guinberg A.

PMID: 2387488 [Indexed for MEDLINE]

5338. Eur J Pediatr. 1990 Mar;149(6):448.

Steroid treatment in myalgia due to familial Mediterranean fever.

Broide E, Klinovsky E, Aladjem M.

PMID: 2332020 [Indexed for MEDLINE]

5339. Rev Infirm. 1990 Mar;40(5):44-8.

[Periodic disease].

[Article in French]

Vinceneux P, Pouchot J.

PMID: 2089588 [Indexed for MEDLINE]

5340. Rev Clin Esp. 1990 Feb;186(2):82-3.

[Mixed cryoglobulinemia secondary to Mediterranean boutonneuse fever].

[Article in Spanish]

Pérez Calvo JI(1), Martín Lorenzo B, Nerín Delapuerta I, Socías Crespí L, Echave Salcedo B, Díez Manglano J, Bueno Gómez J.

Author information:

(1)Servicio de Medicina Interna B, Hospital Clínico Universitario, Zaragoza.

Comment in

Rev Clin Esp. 1991 Mar;188(4):215.

A clinical case of Mediterranean Boutonneuse Fever (MBF) with circulating cryoglobulins during the acute phase, with no clinical symptoms is described and considered an epiphenomenon of the infection. The possible relationship between

the infection and the cryoglobulinemia are discussed. The patient is also added to the increasing list of patients reported of Boutonneuse Fever in the Mediterranean area during the observation period.

PMID: 2330441 [Indexed for MEDLINE]

5341. Lancet. 1990 Jan 20;335(8682):176.

Dopamine-beta-hydroxylase activity in familial Mediterranean fever.

Ben-Chetrit E, Gutman A, Levy M.

PMID: 1967473 [Indexed for MEDLINE]

5342. Lancet. 1990 Jan 13;335(8681):75-7.

Visual evoked responses in children with migraine: a diagnostic test.

Mortimer MJ(1), Good PA, Marsters JB, Addy DP.

Author information:

(1)Birmingham and Midland Eye Hospital, UK.

Comment in

Lancet. 1990 Feb 24;335(8687):480.

The visual evoked responses (VERs) to both flash and pattern stimulation were recorded in 44 children with migraine, with or without aura, and 8 with periodic syndrome. The controls were 50 age and sex matched children. VERs of 50 sex matched adults with migraine were also recorded. The fast wave amplitude in children with migraine was higher than that in controls. The amplitude was higher in younger children with migraine (under 13 years) than that in older children or adults with migraine. Children with periodic syndrome had VERs similar to those of children with migraine. The VER, especially in children, may prove to be a useful test in the diagnosis of migraine.



PMID: 1967420 [Indexed for MEDLINE]

5343. *Pediatrics*. 1990;(5):42-6.

[Clinico-immunological parallels in children with periodic disease].

[Article in Russian]

Astvatsatryan VA, Eridzhanian AKh, Tevosian VK.

Children aged 3 to 15 years afflicted with periodic disease were subjected to clinical and immunological examinations. The role played by derangements of certain components of the immune system in the development and course of periodic disease was outlined. Assay of T lymphocytes and immunoglobulins of the main classes in the blood serum and saliva of children with periodic disease was found to be of the diagnostic and prognostic value. To assess the gravity of periodic disease and to predict it, it is necessary to carry out a comprehensive estimation of the clinical findings and of the data pertaining to humoral, cellular and local immunity.

PMID: 2399066 [Indexed for MEDLINE]

5344. *Rev Clin Esp*. 1990 Jan;186(1):47-8.

[Provocation test using metaraminol in a case of familial Mediterranean fever].

[Article in Spanish]

Mateo L, Rodríguez J, Nolla JM, Ruiz JM.

Comment in

*Rev Clin Esp*. 1991 Mar;188(4):214-5.

PMID: 2320774 [Indexed for MEDLINE]

5345. Ter Arkh. 1990;62(5):79-85.

[Gastroenteropathies in patients with periodic disease and amyloidosis].

[Article in Russian]

Eganian GA, Arutiunian VM.

The reported and the authors' data are provided on the pathogenesis, morphofunctional characteristics and clinical manifestations of acute and chronic gastroenteropathies in patients suffering from periodic disease with and without amyloidosis. Under discussion is the significance of changes in the gastrointestinal tract for the diagnosis of periodic disease, its association with other diseases and early recognition of amyloidosis.

PMID: 2204142 [Indexed for MEDLINE]

5346. Ann Trop Paediatr. 1990;10(3):255-9.

Epidemiology of juvenile chronic arthritis and other connective tissue diseases among children in Kuwait.

Khuffash FA(1), Majeed HA, Lubani MM, Najdi KN, Gunawardana SS, Bushnaq R.

Author information:

(1)Department of Paediatrics, Faculty of Medicine, Kuwait University, Safat.

An 8-year hospital-based retrospective study on the epidemiology of juvenile chronic arthritis (JCA), systemic lupus erythematosus (SLE) and other connective tissue diseases among children in Kuwait is described. There were 108 children with JCA, 20 children with SLE, 23 children with other connective tissue diseases and 24 children with arthritis of familial Mediterranean fever (FMF). The average annual incidence of JCA was 2.84 cases/10(5) children under the age of 12 years and the 1988 prevalence was 18.7/10(5). The polyarticular, systemic and

oligoarticular onset types were observed in 42, 29 and 29%, respectively. The incidence and prevalence of SLE were 0.53 and 3.37/10(5), respectively. The findings are compared with those from other countries.

PMID: 1703741 [Indexed for MEDLINE]

5347. Clin Rheumatol. 1989 Dec;8(4):507-11.

Palindromic rheumatism in Israel--a disease entity? A survey of 34 patients.

Eliakim A(1), Neumann L, Horowitz J, Buskila D, Kleiner-Baumgarten A, Sukenik S.

Author information:

(1)Rheumatology Unit, Soroka Medical Center, Beer-Sheva, Israel.

Over a period of 10 years 34 patients were diagnosed as suffering from palindromic rheumatism. Eighty-one percent of the patients were of North African origin. This is significantly higher ( $p = 0.01$ ) than the age-adjusted origin of the general population in the region. Attacks were usually monoarthritic or oligoarthritic in nature. The joint most often involved was the knee.

Prophylactic therapy with colchicine was ineffective. Gold salts brought about partial remission in three of six patients. Despite a relatively long average follow-up period of 9.3 years and the finding of a positive rheumatoid factor in 12% of the patients, not one of the patients developed rheumatoid arthritis. In 50% of the patients we detected an unexplained elevation in serum globulins and immunoglobulins. The possible association between this syndrome and Familial Mediterranean Fever is discussed.

PMID: 2612120 [Indexed for MEDLINE]

5348. Am J Clin Pathol. 1989 Dec;92(6):821-5.

Amyloid goiter and arthritides after kidney transplantation in a patient with systemic amyloidosis and Muckle-Wells syndrome.

Schwarz RE(1), Dralle H, Linke RP, Nathrath WB, Neumann KH.

Author information:

(1)Department für Addominal und Transplantationschirurgie, Medizinische Hochschule Hannover, F.R. Germany.

A case of hereditary AA amyloidosis with Muckle-Wells syndrome is described. After a successful kidney transplantation for chronic renal failure due to renal amyloid deposits at age 21, the patient, a white female now 26 years of age, developed a large amyloid goiter as a manifestation of the systemic amyloidosis and recurrent monarthritides. Both observations are novel for this disease. Subtotal thyroidectomy and oral colchicine administration, known to be effective in preventing complications of familial Mediterranean fever, another hereditary type of AA amyloidosis, proved highly effective in the management of this unusual case.

PMID: 2589249 [Indexed for MEDLINE]

5349. Am J Kidney Dis. 1989 Nov;14(5):412-6.

Rapid progressive glomerulonephritis in patients with familial Mediterranean fever.

Said R(1), Hamzeh Y, Tarawneh M, el-Khateeb M, Abdeen M, Shaheen A.

Author information:

(1)Department of Medicine, School of Medicine, Jordan University, Amman.

Two patients with a long-standing history of familial Mediterranean fever (FMF) presented with gross hematuria, oliguria, and acute renal failure; both required dialysis support. Kidney biopsies from both patients revealed crescentic rapid progressive glomerulonephritis (RPGN) without amyloidosis. One patient recovered renal function with methylprednisolone pulse therapy and cyclophosphamide. The second patient did not improve and required regular hemodialysis. He is asymptomatic on colchicine therapy. To our knowledge, these are the first cases documenting the presence of RPGN in patients with FMF.

PMID: 2816934 [Indexed for MEDLINE]

5350. Lancet. 1989 Oct 28;2(8670):1050.

Tumour necrosis factor in familial Mediterranean fever.

Schattner A, Lachmi M, Hahn T, Edlan K, Zemer D, Livney A, Pras M.

PMID: 2572790 [Indexed for MEDLINE]

5351. Med J Aust. 1989 Oct 2;151(7):422.

Familial Mediterranean fever in Australian children.

Douglas W.

Comment on

Med J Aust. 1989 Jul 17;151(2):108-10.

PMID: 2796823 [Indexed for MEDLINE]

5352. Am J Med Genet. 1989 Oct;34(2):168-72.

Familial Mediterranean fever in Armenians: autosomal recessive inheritance with high gene frequency.

Rogers DB(1), Shohat M, Petersen GM, Bickal J, Congleton J, Schwabe AD, Rotter JL.

Author information:

(1)Department of Pediatrics, Harbor-UCLA Medical Center, Torrance.

Familial Mediterranean fever (FMF) is a recurrent episodic inflammatory disorder

of unknown pathogenesis that occurs with high frequency in non-Ashkenazi Jews and Armenians. However, there are some differences in the clinical manifestations of FMF in these ethnic groups. FMF has been reported to be an autosomal recessive disease in non-Ashkenazi Jews, with a male/female ratio of 1.7, indicating reduced penetrance in females. However, the inheritance is less clear for Armenians. To resolve this problem, we studied prospectively families of 64 Armenian index cases randomly ascertained at the UCLA FMF clinic. Fifty-three families containing 176 sibs in addition to the probands were analyzed by genetic segregation analysis (exclusions included: six single-child families, four families in which one of the parents was also affected, and a family with incomplete information). Upper and lower bounds of the segregation ratio were estimated, and ranged from .10 +/- .03 to .18 +/- .05 when only definitely affected sibs were classified as affected; .17 +/- .04 to .27 +/- .05 when considering "possibly affected" sibs as affected; and .19 +/- .04 to .30 +/- .05 when incomplete penetrance in females was corrected. A value of .25 is the expected segregation ratio for autosomal recessive inheritance, and our data are consistent with this mode of inheritance. We can reject autosomal dominant inheritance, where the expected segregation ratio is .5. Using extended pedigree data, we calculated an FMF gene frequency of 0.073 and a carrier rate of 1/7, which is about four times the frequency in non-Ashkenazi Jews.(ABSTRACT TRUNCATED AT 250 WORDS)

DOI: 10.1002/ajmg.1320340206

PMID: 2816993 [Indexed for MEDLINE]

5353. Isr J Med Sci. 1989 Oct;25(10):553-6.

Determination by ELISA of anti-DNA antibodies in patients with familial Mediterranean fever.

Flatau E(1), Shneyour A, Hadad N, Shimoni Z.

Author information:

(1)Department of Internal Medicine B, Central Emek Hospital, Afula, Israel.

Positive titers of antibodies against double-stranded (ds) and single-stranded (ss) DNA were found in the sera of 4 and 6 patients, respectively, of 18 who had familial Mediterranean fever (FMF). While anti-dsDNA antibodies were found only

in patients with active disease, there was no correlation between the presence of anti-ssDNA antibodies and disease activity. The antibody titers were lower than those found in patients with active systemic lupus erythematosus. This may be due in part to the fact that all the FMF patients were treated with colchicine.

PMID: 2807853 [Indexed for MEDLINE]

5354. Isr J Med Sci. 1989 Oct;25(10):547-9.

Familial Mediterranean fever--an autoimmune disorder or a genetic defect in a regulatory mechanism of inflammation.

Matzner Y(1).

Author information:

(1)Hematology Unit, Hadassah University Hospital, Mt. Scopus, Jerusalem, Israel.

PMID: 2807850 [Indexed for MEDLINE]

5355. Postgrad Med J. 1989 Oct;65(768):776-8.

Retroperitoneal lymphadenopathy in familial Mediterranean fever.

Rimon D(1), Meir Y, Cohen L.

Author information:

(1)Department of Internal Medicine B, Faculty of Medicine, Technion-Israel Institute of Technology, Lady Davis Carmel Hospital, Haifa, Israel.

Peripheral lymphadenopathy is rarely observed, whereas mesenteric lymphadenopathy is found occasionally on laparotomies in patients with familial Mediterranean fever (FMF). Retroperitoneal lymphadenopathy was reported only once in an autopsy of a patient with FMF. Our case is the second one, and the first one to be diagnosed during life, by means of abdominal ultrasonography and computerized tomography. In patients with FMF, where lymph node biopsy was done, the

pathological finding was non-specific lymphoid hyperplasia.

PMCID: PMC2429824

PMID: 2694140 [Indexed for MEDLINE]

5356. Arch Fr Pediatr. 1989 Oct;46(8):627-8.

[Colchicine in the first trimester of pregnancy and vertebral malformations].

[Article in French]

Dudin A, Rambaud-Cousson A, Shehatto M, Thalji A.

PMID: 2604518 [Indexed for MEDLINE]

5357. Rev Rhum Mal Osteoartic. 1989 Oct;56(10):703-4.

[Periodic disease and ankylosing spondylarthritis. Familial association].

[Article in French]

Hamza M(1), Ayed K, Bardi R, Sellami S.

Author information:

(1)Département de Médecine, Hôpital La Rabta, Tunis, Tunisie.

PMID: 2595232 [Indexed for MEDLINE]

5358. Am J Med Genet. 1989 Oct;34(2):163-7.

Hypothesis: familial Mediterranean fever--a genetic disorder of the lipocortin family?



Shohat M(1), Korenberg JR, Schwabe AD, Rotter JL.

Author information:

(1)Medical Genetics Birth Defects Center, Ahmanson Pediatric Center, Los Angeles, CA.

Familial Mediterranean fever is an autosomal recessively inherited disorder of unknown cause characterized by recurrent attacks of inflammation, involving mainly the peritoneum, pleura, synovia, and skin. Based on a phenotype analysis, we propose that its manifestations may be related to a genetic defect in one of the family of lipocortin proteins. Evidence is presented supporting an abnormality in the first step of prostaglandin/leukotriene synthesis.

DOI: 10.1002/ajmg.1320340205

PMID: 2530899 [Indexed for MEDLINE]

5359. Turk J Pediatr. 1989 Oct-Dec;31(4):281-7.

Amyloidosis in children with familial Mediterranean fever.

Koçak H(1), Beşbaş N, Saatçi U, Bakkaloğlu A.

Author information:

(1)Department of Pediatrics, Ondokuz Mayıs University Faculty of Medicine, Samsun.

In this survey 113 children with secondary amyloidosis due to familial Mediterranean fever are reviewed in regard to their respective histories, and physical and laboratory findings. The beneficial effects of colchicine in the treatment of this condition are evaluated. The number of children presented with amyloidosis secondary to familial Mediterranean fever was considerable. The male-female ratio was 4/3. It was observed that the number of patients with amyloidosis increased through the adolescent period, and that most of the cases demonstrated phenotype I (74.33%). Another important finding was the increase of partial thromboplastin time in 96 out of 113 cases (84.95%). All the symptoms of the periodic attacks were relieved by colchicine. A significant difference was found between the serum total protein and albumin values before and after colchicine therapy.

PMID: 2486428 [Indexed for MEDLINE]

5360. Clin Rheumatol. 1989 Sep;8(3):408-12.

Ankylosing spondylitis. An unusual manifestation of familial Mediterranean fever. Report of a case complicated by amyloidosis and polyneuropathy.

Knockaert DC(1), Malysse IG, Peetermans WE.

Author information:

(1)Department of Internal Medicine, University Hospital Gasthuisberg, Leuven, Belgium.

We report a case of familial Mediterranean fever (FMF) with typical clinical and roentgenological findings of ankylosing spondylitis. The spinal involvement in FMF is discussed. A second unusual feature of this case is the occurrence of polyneuropathy which could possibly be ascribed to the slowly evolving amyloidosis during continuous colchicine treatment.

PMID: 2805617 [Indexed for MEDLINE]

5361. Am J Med. 1989 Sep;87(3):363-5.

Fatal colchicine toxicity.

[No authors listed]

Comment on

Am J Med. 1989 Mar;86(3):356-7.

PMID: 2773978 [Indexed for MEDLINE]

5362. Postgrad Med J. 1989 Sep;65(767):681-3.

Perirenal and renal subcapsular haematoma as presenting symptoms of polyarteritis nodosa.

Schlesinger M(1), Oren S, Fano M, Viskoper JR.

Author information:

(1)Department of Immunology, Barzilai Medical Center, Ashkelon, Israel.

Two young men, were hospitalized due to acute massive blood loss with left abdominal flank pain. In both cases renal angiography showed signs of a haemorrhagic event in the left kidney, perirenal in one and subcapsular in the other. Microaneurysms indicated a diagnosis of polyarteritis nodosa, supported by renal biopsy in one case. Renal haemorrhage is an infrequent presentation of polyarteritis nodosa. Furthermore, one patient suffered also from familial Mediterranean fever, and is the fifth reported case with this combination of diseases.

PMCID: PMC2429190

PMID: 2575253 [Indexed for MEDLINE]

5363. Harefuah. 1989 Sep;117(5-6):126-8.

[The liver in juvenile rheumatoid arthritis].

[Article in Hebrew]

Brik R(1), Shapira D, Lorber M, Nahir M.

Author information:

(1)Pediatrics Dept., Rambam Medical Center, Haifa.

Hepatic involvement in juvenile rheumatoid arthritis of the systemic type (JRA) is a diagnostic challenge because of the varied clinical picture it presents. We describe a 21-year-old woman in whom JRA had started at the age of 4 years as an illness resembling familial Mediterranean fever. This long-standing illness was

complicated by liver damage and needle biopsy showed massive hepatic deposition of amyloid. It is possible that this patient may have developed JRA as a complication of familial Mediterranean fever.

PMID: 2485752 [Indexed for MEDLINE]

5364. Ann Intern Med. 1989 Aug 1;111(3):259-60.

The metaraminol test and adverse cardiac effects.

Buades J, Bassa A, Altés J, Vicens JM, Cabrer B.

PMID: 2751185 [Indexed for MEDLINE]

5365. Med J Aust. 1989 Jul 17;151(2):108-10.

Familial Mediterranean fever in six Australian children.

Moore PJ(1), Mansour A, McDonald JD, Kemp A, Kamath KR, Dorney SF.

Author information:

(1)Endocrinology Unit, Children's Hospital, Winnipeg, Manitoba, Canada.

Comment in

Med J Aust. 1989 Oct 2;151(7):422.

Six Australian children fulfilled the diagnostic criteria for familial Mediterranean fever. None had a family history of the disease, but five children came from ethnic groups that typically were associated with the disease. The symptoms commenced before five years of age in all the children, and three children underwent unnecessary operations because of the symptoms of recurrent fever and abdominal pain. All six children benefited from colchicine prophylaxis by mouth. More cases can be expected to be recognized in Australia because of the large number of Australian children with a Mediterranean heritage.

PMID: 2661976 [Indexed for MEDLINE]

5366. Arch Intern Med. 1989 Jul;149(7):1698.

Recurrent pulmonary atelectasis as a manifestation of familial Mediterranean fever.

Colebatch HJ.

Comment on

Arch Intern Med. 1987 Feb;147(2):378-9.

PMID: 2742448 [Indexed for MEDLINE]

5367. Revmatologiya (Mosk). 1989 Jul-Sep;(3):24-6.

[Pericarditis as one of the manifestations of periodic disease].

[Article in Russian]

Vinogradova OM, Tomas Nlu, Golyzhnikova VA.

The authors studied 34 patients with periodic disease. In its thoracic course the development of pericarditis was proved in 1/3 of the patients.

PMID: 2609056 [Indexed for MEDLINE]

5368. Dtsch Med Wochenschr. 1989 Jun 16;114(24):951-4.

[Fever of unknown origin and colchicine-sensitive amyloidosis: familial Mediterranean fever?].

[Article in German]

Schneider W(1), Wehmeier A.

Author information:

(1)Medizinische Klinik und Poliklinik der Universität Düsseldorf.

A 39-year-old man who had for 20 years suffered from recurrent fever, abdominal pain and joint pains was diagnosed to have generalized amyloidosis type AA. Suspected of having familial mediterranean fever (FMF) he was treated with colchicine, 2 mg daily. Within four years the fever bouts became milder and the amyloidosis no longer progressed. Since the patient was a foundling it was impossible to prove FMF, despite the typical signs and the successful treatment.

DOI: 10.1055/s-2008-1066699

PMID: 2731480 [Indexed for MEDLINE]

5369. Eur J Pediatr. 1989 Jun;148(7):636-41.

Familial Mediterranean fever (recurrent hereditary polyserositis) in children: analysis of 88 cases.

Majeed HA(1), Barakat M.

Author information:

(1)Department of Paediatrics, Kuwait University, Safat.

The clinical profile, course and complications of familial Mediterranean fever (recurrent hereditary polyserositis) seen in 88 children over a period of 11 years are presented. Forty eight children (55%) started their illness below the age of 5 years, and the mean age of onset was 4.9 years. Peritonitis occurred in 85% of children, arthritis in 50%, pleuritis in 33% and erysipelas-like lesions in 16%. Two children developed renal amyloidosis, and one third of the children were subjected to unnecessary operative surgery, reflecting the diagnostic difficulties. The arthritis was mono-articular in 80% and polyarticular in 20% of children with arthritis, and was seronegative (rheumatoid factor and antinuclear antibodies). Human leucocyte antigen (HLA) typing for the B-27 antigen carried out in ten children with arthritis was negative. The synovial attack showed a wide variation in the clinical presentation, course and duration of arthritis,

causing diagnostic difficulties. The difficulties in the differentiation of recurrent hereditary polyserositis (familial Mediterranean fever) arthritis from the common causes of acute and chronic juvenile arthritis and the seronegative spondyloarthropathies are discussed. Of 45 children treated with colchicine, 42 children (93%) achieved a therapeutic response.

PMID: 2663516 [Indexed for MEDLINE]

5370. Med Clin (Barc). 1989 May 20;92(19):757.

[Regression of nephrotic syndrome in amyloidosis secondary to familial Mediterranean fever during maintenance therapy using colchicine].

[Article in Spanish]

Sirera G, Tural C, Bonal J, Caralps A.

PMID: 2755254 [Indexed for MEDLINE]

5371. Z Rheumatol. 1989 May-Jun;48(3):143-6.

[Familial Mediterranean fever--an important differential diagnosis in systemic juvenile chronic arthritis].

[Article in German]

Michels H(1), Häfner R, Vogel P.

Author information:

(1)Rheuma-Kinderklinik Garmisch-Partenkirchen.

Familial Mediterranean Fever (FMF), characterized by recurring episodes of fever, serositis, arthritis, skin changes and complicated by amyloidosis in 30%-60% of cases frequently begins in childhood. Systemic juvenile rheumatoid arthritis (systemic JRA, Still's disease) is the most important differential diagnosis. In

our series of 10 patients the mean age of onset was 4.9 +/- 2.2 years (range 2-9 years). The mean time period elapsed before the diagnosis was established was 4.1 +/- 2.7 years (range 1.5-10 years). Three of our 10 patients already had developed renal amyloidosis at the time of diagnosis. Essential criteria for differential diagnosis against systemic JRA were positive family history for FMF (4/10), ethnic background (9/10 of Turkish decent), typical erysipeloid skin rashes (4/10), attacks of abdominal pain accompanied by fever (10/10) and the characteristic pattern of recurrent episodes lasting only a few days each (a patient's diary monitoring the attacks may be helpful). In problematic cases the metaraminol provocative test can be helpful. If an elevated plasma dopamine beta-hydroxylase activity appears to be a specific finding in FMF patients, this may well open up new avenues in the early diagnosis of the disease. Since amyloidosis can be prevented by prophylactic long lasting treatment with colchicine, a timely diagnosis of FMF is the physician's challenge.

PMID: 2781875 [Indexed for MEDLINE]

5372. Dtsch Med Wochenschr. 1989 Apr 28;114(17):665-8.

[Familial Mediterranean fever in a German family].

[Article in German]

Hawle H(1), Winckelmann G, Kortsik CS.

Author information:

(1)Deutsche Klinik für Diagnostik, Wiesbaden.

A 14-year-old German boy had the characteristic signs and symptoms of familial mediterranean fever with recurrent attacks of fever which ran a uniform course and were self-limiting. Laparoscopy revealed sterile peritonitis and marked humoral inflammatory signs. Each acute phase was confined to three days, alternating with symptom-free intervals which lasted for as long as several months. The boy's father and three other members of the paternal family have had similar disease symptoms. Even in patients who are not members of a predisposed ethnic group familial mediterranean fever should be included in the differential diagnosis as a rare cause of recurrent episodes of fever of unknown aetiology.



DOI: 10.1055/s-2008-1066652

PMID: 2707135 [Indexed for MEDLINE]

5373. Ned Tijdschr Geneeskd. 1989 Apr 1;133(13):679-81.

[A patient with familial Mediterranean fever].

[Article in Dutch]

Tel W, ten Napel CH.

Familial Mediterranean fever, a genetic disorder with an autosomal recessive pattern of inheritance, occurs in patients originating from the eastern Mediterranean. Characteristic features are attacks of fever, peritonitis, pleuritis, synovitis and skin rash. The disease may be complicated by amyloidosis. Treatment with colchicine is generally successful.

PMID: 2716889 [Indexed for MEDLINE]

5374. Ned Tijdschr Geneeskd. 1989 Apr 1;133(13):676-9.

[Immigrants with abdominal pain: familial Mediterranean fever?].

[Article in Dutch]

Kingma PJ, Vismans FJ.

Three patients of Turkish origin with recurrent abdominal complaints and fever are presented. All had consanguineous parents and two were brothers. Biochemistry and haematology were normal except for a high sedimentation rate. With reference to these patients, some aspects of the diagnosis and the therapeutic approach of familial Mediterranean fever are discussed. In patients of Turkish origin who complain of abdominal pain, familial Mediterranean fever should probably be considered more often.

PMID: 2716888 [Indexed for MEDLINE]

5375. Ned Tijdschr Geneesk. 1989 Apr 1;133(13):651-2.

[Familial Mediterranean fever].

[Article in Dutch]

van der Meer JW.

PMID: 2654656 [Indexed for MEDLINE]

5376. J Rheumatol. 1989 Apr;16(4):536-9.

Polyarteritis nodosa and familial Mediterranean fever: a report of 2 cases and review of the literature.

Glikson M(1), Galun E, Schlesinger M, Cohen D, Haskell L, Rubinow A, Eliakim M.

Author information:

(1)Department of Medicine A, Hadassah University Hospital, Jerusalem, Israel.

Two cases of polyarteritis nodosa (PAN) in patients with familial Mediterranean fever (FMF) are reported. These and another 11 cases found in the literature suggest that PAN occurs more commonly in patients with FMF than would be expected in the general population. Perirenal hematoma, which is surprisingly high in patients with FMF, is a life threatening complication of PAN. The diagnosis of PAN in patients with FMF may be delayed due to the similarity of the clinical manifestations of both diseases.

PMID: 2568489 [Indexed for MEDLINE]

5377. Am J Med. 1989 Mar;86(3):356-7.

Fatal colchicine toxicity.

Simons RJ(1), Kingma DW.

Author information:

(1)Milton S. Hershey Medical Center, Pennsylvania State University, College of Medicine, Hershey 17033.

Comment in

Am J Med. 1989 Sep;87(3):363-5.

PMID: 2919622 [Indexed for MEDLINE]

5378. Ann Rheum Dis. 1989 Feb;48(2):163-5.

Chronic synovitis of the shoulder in familial Mediterranean fever: a disease of symptoms not signs.

Hughes RA(1), Scott JT.

Author information:

(1)Department of Rheumatology, Charing Cross Hospital, London.

Severe shoulder pain in a 41 year old Arab woman persisted for three months despite non-steroidal anti-inflammatory drug treatment. Isotope bone scanning and computed tomography showed inflammation of the glenohumeral joint and a large effusion, which needle aspiration had initially failed to reveal. A diagnosis of familial Mediterranean fever was made on the basis of a strongly suggestive past personal and family history, sterility of the joint effusion, and a good response to colchicine.

PMCID: PMC1003706

PMID: 2930268 [Indexed for MEDLINE]

5379. Br J Rheumatol. 1989 Feb;28(1):81-2.

Systemic lupus erythematosus and periodic peritonitis (FMF)

Bakir F, Saaed B.

PMID: 2917239 [Indexed for MEDLINE]

5380. Med Klin (Munich). 1989 Jan 15;84(1):23-31, 64.

[Differential diagnosis and therapy of cycle-dependent severe attacks of familial Mediterranean fever].

[Article in German]

Mergelsberg M, Martini M, Brecht T, Krönung G.

PMID: 2918851 [Indexed for MEDLINE]

5381. Ann Radiol (Paris). 1989;32(4):302-4.

[Encapsulating peritonitis in periodic disease. Apropos of a case studied by x-ray computed tomography].

[Article in French]

Bellin MF, Deutsch JP, Bletry O, Langlois P, Bousquet JC, Cortez A, Godeau P, Grellet J.

A case of encapsulating peritonitis complicating the course of familial Mediterranean fever is reported. This encapsulating peritonitis was responsible for abdominal pain and had a "pseudocystic" appearance on ultrasonography and computed tomography. Ultrasound guided aspiration produced a yellowish fluid rich in proteins and poor in cells. Surgical operation revealed a congested appearance of the peritoneum associated with a richly fibrinous appearance of the external

wall of the mass. The differential diagnosis is discussed.

PMID: 2817728 [Indexed for MEDLINE]

5382. Int Urol Nephrol. 1989;21(3):339-47.

Renal transplantation in amyloid nephropathy.

Heering P(1), Kutkuhn B, Frenzel H, Linke RP, Grabensee B.

Author information:

(1)Department of Nephrology, University of Medicine, Düsseldorf, FRG.

Renal transplantation was performed in 2 patients with end-stage renal disease due to AA-type amyloidosis. One patient with amyloidosis of rheumatoid arthritis (RA) origin died twelve months after renal transplantation in cardiogenic shock. AA-amyloid deposits were demonstrated in the graft even though there were excellent function and no proteinuria. The second patient with amyloid nephropathy due to familial Mediterranean fever (FMF) showed no impairment of graft function 24 months after transplantation. These 2 cases are compared to an additional 31 cases of renal transplantation for amyloid nephropathy described in the literature. Proteinuria was reported in 32.3% and amyloid was detected in the functioning graft in 41.4%. The function was excellent even when small amyloid deposits were present in the graft. Renal transplantation is indicated in cases of amyloid nephropathy of the AA-type, provided life threatening amyloid involvement of other organs is not present.

PMID: 2807785 [Indexed for MEDLINE]

5383. Ter Arkh. 1989;61(6):38-45.

[Efficacy of colchicine therapy in patients with periodic disease and amyloidosis according to repeated biopsies of the rectal mucosa].

[Article in Russian]

Serov VV, Vinogradova OM, Kochubei LN, Kovtun TI, Ivanov AA.

The authors provide the clinico-morphologic evidence for amyloid resorption in patients with periodic disease and amyloidosis under the effect of colchicine.

PMID: 2799713 [Indexed for MEDLINE]

5384. *Pediatrics*. 1989;(4):93-5.

[Classification of periodic disease in children].

[Article in Russian]

Astvatsatryan VA, Torosian EK, Tevosian VK.

PMID: 2734071 [Indexed for MEDLINE]

5385. *Acta Clin Belg*. 1989;44(1):37-51.

Amyloid proteins and amyloidoses: complexity updated.

Goffin YA.

Amyloid is a beta-pleated fibrillar protein principally constituted of light chains of immunoglobulins (kappa or lambda) in primary or myeloma-associated amyloidosis, of AA proteins in secondary amyloidosis and familial Mediterranean fever, and of variants of prealbumin - now called transthyretin - in senile amyloidosis and in familial polyneuropathies. Other identified amyloidogenic proteins involve APUD protein derivatives (calcitonin), beta 2 microglobulin in chronic hemodialysis-related amyloidosis and beta protein in Alzheimer disease. After a short review of experimental findings and theories concerning the pathogenesis of amyloid deposition, the clinical aspects of amyloidosis are discussed stressing their great diversity. The diagnostic approach is also examined, with particular emphasis on rectal and kidney biopsy and subcutaneous

adipose tissue aspirates. Finally, some comments on the treatment of amyloidosis (role of colchicine and DMSO) are made.

PMID: 2669433 [Indexed for MEDLINE]

5386. Ric Clin Lab. 1989 Jan-Mar;19(1):27-38.

The biochemical genetics of amyloid fibril proteins.

Carbonara AO(1), Bottaro A.

Author information:

(1)Dipartimento di Genetica, Università degli Studi di Torino.

Amyloidoses are a very heterogeneous set of diseases, characterized by extracellular deposition of fibrillar proteins in different tissues. It is still a matter of debate whether the different forms of amyloidosis can share some common etiological mechanisms, or they are completely unrelated. The biochemical characterization of the protein component of the deposits provides a powerful system of classification for the different amyloidotic disorders and shades light on the molecular mechanisms of selective precipitation from soluble precursors and of tissue-specific deposition. Furthermore, identification and analysis of the genes coding for the precursors, and clarification of the kind of inheritance in some familial forms of amyloidosis, make prevention through genetic counselling and predictive diagnosis possible.

PMID: 2669110 [Indexed for MEDLINE]

5387. Biomed Pharmacother. 1989;43(10):763-9.

Catecholamine metabolism in recurrent hereditary polyserositis. Pathogenesis of acute inflammation: the retention-leakage hypothesis.

Barakat MH(1), Malhas LN, Gumaa KK.

Author information:

(1)Department of Internal Medicine, Kuwait University.

Recurrent hereditary polyserositis (RHP), also known as familial Mediterranean fever, is a genetically-determined disease characterized by paroxysmal attacks of peritonitis, pleuritis, arthritis or inflammation of other serous membranes. We have previously suggested that the pathogenesis of this disease seems to be related to abnormal catecholamine metabolism. This study compares the plasma and urine catecholamine profile in patients with RHP during different clinical states to that in controls. In RHP there were lower plasma and higher urine dopamine levels in the asymptomatic state and during attacks, while norepinephrine levels remain unchanged. However, plasma epinephrine was significantly lower in the asymptomatic state but markedly higher during attacks. The urine epinephrine values in both situations were similar but significantly lower than in controls, suggesting abnormal renal excretion of epinephrine. The urine metanephrine was markedly elevated in the asymptomatic state compared to controls, but remained unchanged during the attacks, again suggesting defective renal clearance of metanephrine. Metaraminol infusion, which induces attacks in RHP patients, was associated with an increase in plasma dopamine and epinephrine (but not norepinephrine); yet the urinary levels of dopamine, epinephrine and metanephrine remained the same, confirming the dissociation between the plasma and urinary levels of these catecholamines, probably due to abnormalities in the renal clearance mechanism. We postulate that this dissociation leads to retention of these amines in the plasma which may subsequently leak through the serous membranes (the target organs) and incite an acute inflammatory process. Colchicine, the only known drug that protects against disease attacks, reduces the plasma levels of these amines, and thus may act by preventing retention that leads to leakage and subsequent inflammation.

PMID: 2640912 [Indexed for MEDLINE]

5388. Turk J Pediatr. 1989 Jan-Mar;31(1):1-18.

The association of nephrotic syndrome and renal vein thrombosis: a clinicopathological analysis of eight pediatric patients.

Tinaztepe K, Buyan N, Tinaztepe B, Akkök N.



Cases with a pathological diagnosis of renal venous thrombosis (RVT) associated with nephrotic syndrome (NS) were studied retrospectively for clinicopathological evaluation. The material consisted of 21 RVT cases which were diagnosed in 2000 consecutive pediatric necropsies, with an overall incidence of about one percent. Eight of the 21 RVT cases were associated with nephrotic syndrome (34%), and this group formed 0.4 percent of the total necropsies in our pediatric center. The glomerulopathies of these nephrotic patients consisted of three cases of Finnish-type congenital NS (FCNS), three cases of renal amyloidosis secondary to familial Mediterranean fever, and two cases of membranoproliferative glomerulonephritis (MPGN). The presence of sepsis associated with disseminated intravascular coagulation, and the morphological age of the thrombi suggested that the RVT was secondary to sepsis in the FCNS cases. In the MPGN and secondary renal amyloidosis cases, the long duration of both the nephrotic state and the administration of diuretics along with glucocorticoid treatment and also the newly formed thrombi without infarction are strong evidences, although not definite, that the RVT developed as a complication of the glomerulopathy. Even though there were no definite clinical criteria for the diagnosis of most of the RVT cases, we would like to emphasize the importance of flank pain, the rapid deterioration of renal functions in a stable nephrotic patient, as well as the hypercoagulable state in the consideration of the development of RVT which indicate the need for appropriate radiological studies for confirmation of this condition during life.

PMID: 2609431 [Indexed for MEDLINE]

5389. Nephrol Dial Transplant. 1989;4(3):201-4.

Cyclosporin: poorly tolerated in familial Mediterranean fever.

Cohen SL(1), Boner G, Shmueli D, Yusim A, Rosenfeld J, Shapira Z.

Author information:

(1)Renal Transplantation Unit, Beilinson Hospital, Petach Tiqvah, Israel.

Cyclosporin is poorly tolerated in patients with amyloidosis due to familial mediterranean fever who are receiving colchicine. There is a high incidence of

gastrointestinal side-effects and muscle weakness, both of which are reversible on stopping cyclosporin. Thus in patients with amyloidosis secondary to familial mediterranean fever treated with colchicine, the use of cyclosporin as an immunosuppressive agent may be restricted.

PMID: 2498778 [Indexed for MEDLINE]

5390. Lancet. 1988 Dec 3;2(8623):1280-3.

Plasma dopamine beta-hydroxylase: rapid diagnostic test for recurrent hereditary polyserositis.

Barakat MH(1), Gumaa KA, Malhas LN, el-Sobki NI, Moussa MA, Fenech FF.

Author information:

(1)Department of Internal Medicine, Faculty of Medicine, Kuwait University.

The diagnosis of recurrent hereditary polyserositis (RHP; also known as familial Mediterranean fever) remains one of exclusion since there has been no specific diagnostic laboratory test. A previous study suggested that the disorder is related to abnormal catecholamine metabolism. Plasma dopamine beta-hydroxylase (DBH) activity was assayed spectrophotometrically in 91 RHP patients and 162 controls. The activity was significantly higher in untreated symptom-free patients and in patients with acute attacks, than in controls (mean [SEM] 155.8 [14.1] vs 43.3 [1.9] mumol/min/1 p less than 0.0001). Colchicine treatment reduced DBH activity to control levels. The test showed a high diagnostic accuracy and specificity for RHP, whether the patient was symptom-free or having an acute attack. Moreover, it is easy to carry out.

PMID: 2904007 [Indexed for MEDLINE]

5391. Nihon Naika Gakkai Zasshi. 1988 Dec;77(12):1859-62.

[A case of familial Mediterranean fever with paroxysmal pseudo-obstruction of bowel].

[Article in Japanese]

Sugimoto H, Nagasaka K, Sakurai S, Sakai H, Sonobe K, Sato N, Kimura T, Yamaji T, Yamada S, Kobayashi S.

PMID: 3250990 [Indexed for MEDLINE]

5392. Am J Obstet Gynecol. 1988 Nov;159(5):1161-2.

Induction of ovulation causing recurrent bloody ascites in a woman with endometriosis.

Feigin RD(1), Glikson M, Gur H, Galun E, Younis JF, Beyth Y.

Author information:

(1)Department of Medicine, Hadassah University Hospital, Jerusalem, Israel.

Massive ascites associated with endometriosis is uncommon. Recurrent episodes of bloody ascites as a result of endometriosis occurred in a woman with familial Mediterranean fever, who underwent therapy for induction of ovulation. Ovulatory agents may provoke accumulation of ascites in patients with endometriosis.

PMID: 3189451 [Indexed for MEDLINE]

5393. Am J Med. 1988 Nov;85(5):715-7.

Meningitis in familial Mediterranean fever.

Schwabe AD(1), Monroe JB.

Author information:

(1)Department of Medicine, UCLA School of Medicine 90024-1736.

PMID: 3055980 [Indexed for MEDLINE]

5394. Rev Esp Enferm Apar Dig. 1988 Oct;74(4 Pt 1):401-2.

[Metaraminol provocation test for familial Mediterranean fever].

[Article in Spanish]

Lorente JA, García-Hoz F, Fernández CM, Ledo L, Bárcena R.

PMID: 3231877 [Indexed for MEDLINE]

5395. Clin Exp Rheumatol. 1988 Oct-Dec;6(4):395-7.

Abdominal fat tissue aspirate in amyloidosis of familial Mediterranean fever.

Tishler M(1), Pras M, Yaron M.

Author information:

(1)Department of Rheumatology, Ichilov Hospital, Tel Aviv Medical Center, Israel.

Abdominal fat tissue aspirates from 20 patients with biopsy-proved amyloidosis were investigated by polarized microscopy after staining with Congo-red. Positive results were obtained in 4 of 5 patients with primary amyloidosis (AL) and in none of 15 with amyloidosis (AA) of Familial Mediterranean Fever (FMF). We suggest that although this technique is simple, safe and effective in other forms of amyloidosis, it cannot be used as a diagnostic tool in FMF patients suffering from amyloidosis.

PMID: 2465860 [Indexed for MEDLINE]

5396. Clin Rheumatol. 1988 Sep;7(3):398-401.

Hyper-IGD syndrome: a new case treated with colchicine.

Ostuni PA(1), Lazzarin P, Ongaro G, Gusi R, Todesco S, Gambari PF.

Author information:

(1)Division of Rheumatology, University of Padova, Italy.

We report a new case of hyper-IgD syndrome, a recently described disease characterized by recurrent episodes of fever with headache, bilateral cervical lymphadenopathy and, more rarely, abdominal pain and diarrhoea. Polyclonal increase of serum IgD is the most important laboratory finding. Etiopathogenesis and differences with familial Mediterranean fever are discussed. Moreover, good results obtained with colchicine treatment are also reported.

PMID: 3229086 [Indexed for MEDLINE]

5397. Arch Neurol. 1988 Aug;45(8):926-7.

Mollaret's meningitis. A variant of recurrent hereditary polyserositis, both provoked by metaraminol.

Barakat MH(1), Mustafa HT, Shakir RA.

Author information:

(1)Department of Medicine, Faculty of Medicine, Kuwait University.

Mollaret's meningitis is a rare condition with a characteristic clinical and cerebrospinal fluid picture. In many ways it resembles recurrent hereditary polyserositis (familial Mediterranean fever) in its natural history, pattern of attacks, and response to colchicine. Association of the two conditions has been reported, so far, in two patients only. In our patient the symptoms of both conditions were induced by a metaraminol provocative infusion. We have previously introduced this as a specific diagnostic and confirmatory test for recurrent hereditary polyserositis. The possibility that the two conditions represent different manifestations of a single disease is therefore strengthened.

PMID: 3395269 [Indexed for MEDLINE]

5398. *Pediatr Pol.* 1988 Aug;63(8):490-3.

[Familial Mediterranean fever in the light of our observations].

[Article in Polish]

Siemieńska-Rywik S, Rostropowicz-Denisiewicz K, Gutowska B.

PMID: 3244495 [Indexed for MEDLINE]

5399. *Semin Arthritis Rheum.* 1988 Aug;18(1):14-28.

The clinical and biochemical spectrum of hereditary amyloidosis.

Varga J(1), Wohlgethan JR.

Author information:

(1)Division of Rheumatology, Thomas Jefferson University, Philadelphia, PA 19107.

Familial amyloidosis, once described as a puzzling and highly unusual form of polyneuropathy, is now recognized to be a collection of familial diseases with usually autosomal-dominant inheritance and widespread ethnic distribution. Familial amyloidosis occurs throughout the world and encompasses an extremely broad spectrum of clinical manifestations. In some families, progressive peripheral neuropathy dominates the illness, while in others, renal failure, ocular amyloid deposits, cardiac decompensation, or intracranial hemorrhage is the most significant clinical feature. The Portuguese (type I) and the Iowa (type III) neuropathies characteristically begin with lower limb involvement, while in the Indiana (type II) form, upper limb neuropathy is seen first; in the Japanese families with familial amyloid polyneuropathy, symptoms first become evident around age 40, whereas in the Texas family, onset is in the seventh decade. The prognosis for the different families is highly variable. Current classification of the familial amyloid polyneuropathy syndromes is based on their characteristic clinical presentations, but ongoing biochemical identification of the protein composition of amyloid substance in each form will make a more rational nosology

feasible in the near future. To date, no therapy has been shown to arrest or reverse the progressive accumulation of amyloid deposits in most forms of familial amyloidosis. Familial Mediterranean fever is a major exception, and the incidence of amyloidosis associated with this disease has been dramatically reduced by the widespread prophylactic use of colchicine. Technology currently available permits the reliable identification of asymptomatic relatives at risk for developing amyloid neuropathy as well as the prenatal identification of carriers of the mutant transthyretin gene. These strategies can be used in genetic counseling aimed at reducing the continued propagation of the mutant gene.

PMID: 2847318 [Indexed for MEDLINE]

5400. Ann Intern Med. 1988 Jul 15;109(2):164-5.

Acute orchitis in familial Mediterranean fever.

Eshel G(1), Zemer D, Bar-Yochai A.

Author information:

(1)Assaf-Harofeh Medical Center, Zrifin, Israel.

PMID: 3382109 [Indexed for MEDLINE]

5401. Isr J Med Sci. 1988 Jul;24(7):373-5.

Autoinflammatory response to self-antigens of lymphoblasts.

Klein I(1), Naor D.

Author information:

(1)Lautenberg Center for General and Tumor Immunology, Hebrew University-Hadassah Medical School, Jerusalem, Israel.

PMID: 3403236 [Indexed for MEDLINE]

5402. Clin Exp Rheumatol. 1988 Jul-Sep;6(3):305-17.

Colchicine in therapy. State of the art and new perspectives for an old drug.

Famaey JP(1).

Author information:

(1)Department of Rheumatology, Hôpital Universitaire Saint-Pierre, University of Brussels, Belgium.

Colchicine is the most specific treatment in acute gouty attacks. In several European countries, oral colchicine is still used for routine treatment of acute gout. Its selectivity is used as a diagnostic tool. It is also active in the treatment of acute crises of chondrocalcinosis and more occasionally of other arthritic crises (e.g. sarcoidosis). Colchicine appears to be the necessary adjuvant prophylactic drug when starting a hypouricemic treatment with uricosuric or uricolytic drugs for avoiding acute gouty crisis due to sudden mobilisation of the uric acid pool. Besides gout, colchicine is the drug of choice for treating familial mediterranean fever. It appears to be helpful in the treatment of Behçet's disease. It seems also useful for treating fibrosing conditions such as liver cirrhosis and scleroderma. As an adjuvant therapy, it helps treating dermatological disorders which are associated with leucocyte migration as an essential pathogenic factor (e.g. psoriasis, dermatitis herpetiformis, necrotising vasculitis ...). It has been advocated as an adjuvant therapy in malignant diseases as a support in radiotherapy and as an useful drug in various other diseases where it has been tried occasionally (e.g. Paget's disease of the bone, idiopathic thrombocytopenic purpura, disc syndrome). This very old drug remains a modern therapeutic agent.

PMID: 3052972 [Indexed for MEDLINE]

5403. J Clin Lab Immunol. 1988 Jul;26(3):125-8.

The immune regulation in familial Mediterranean fever (FMF).



Melamed A(1), Cabili S, Zakuth V, Spirer Z.

Author information:

(1)Pediatric Department, Rokach Hospital, Tel Aviv Medical Center, Israel.

In order to investigate a possible immune regulation imbalance in familial Mediterranean fever (FMF), the T-cell subsets and interleukin (IL)-1 and -2 production were examined in 39 patients (32 consecutive; 7 previous) and 14 controls. Results in the FMF group indicated no change in total T-cells and B-cells. The number of suppressor T-cells and helper cells were significantly decreased, as compared to the controls ( $14 \pm 5.2$ ,  $19 \pm 4.6$  vs.  $31 \pm 4.6$ ,  $41 \pm 5.3$ , respectively), and the NK cells were significantly increased ( $16 \pm 4.8$ ,  $36 \pm 2.1$ ). Peripheral blood monocytes from the patients with FMF produced higher amounts of IL-1 and lower amounts of IL-2 than those from the control subjects. The latter results were enhanced when the FMF group was subdivided on the basis of pretreatment with colchicine and presence of amyloidosis. This study, although preliminary, indicates an immune regulation imbalance in FMF patients. Further research is necessary to understand the interrelation of amyloidosis and colchicine treatment.

PMID: 2976426 [Indexed for MEDLINE]

5404. Postgrad Med J. 1988 Jun;64(752):453-4.

Pericardial involvement in familial Mediterranean fever.

Erol C(1), Sonel A, Candan I, Omürlü K, Akyol T.

Author information:

(1)Cardiac Research Center, Faculty of Medicine, University of Ankara, Cebeci-Ankara, Turkey.

Two patients with familial Mediterranean fever showed the classic features of pericardial involvement and one of them (Case 2) had pericardial effusion detected by echocardiography. These and previously published cases show that familial Mediterranean fever should be considered as a cause of pericarditis

and/or pericardial effusion.

PMCID: PMC2428878

PMID: 3211825 [Indexed for MEDLINE]

5405. J Assoc Physicians India. 1988 Jun;36(6):377-9.

Periodic peritonitis (recurrent polyserositis-or-familial Mediterranean fever)  
eight decades later.

Bakir F.

PMID: 3053636 [Indexed for MEDLINE]

5406. Monatsschr Kinderheilkd. 1988 May;136(5):243-5.

[The metaraminol provocation test in the diagnosis of familial Mediterranean  
fever].

[Article in German]

Huppertz H(1), Michels H.

Author information:

(1)Universitäts-Kinderklinik, Würzburg.

Familial Mediterranean Fever (FMF) is a cyclic inflammatory disease of unknown pathogenesis and autosomal recessive inheritance. Diagnosis is notoriously difficult by the lack of specific signs or laboratory tests although early diagnosis is mandatory to avoid developmental delay or possibly fatal amyloidosis by treatment with colchicine. In adults, Metaraminol Provocative Test (MPT) has been described as specific and highly sensitive in the diagnoses of FMF. We tested 18 children, 9 of whom suffered from FMF. They were ill for 5 years and had been treated as in-patients for 3 months without improvement (median values). 5 of the children with FMF had a positive test results. 4 children with FMF were

negative. All 9 children with other disorders were negative, too. During the course of diagnosis, they had been suspected of suffering from FMF. So, in childhood, MPT is specific for FMF but does not identify all children with FMF. However, a positive MPT may be a great help in diagnosing FMF.

PMID: 3405225 [Indexed for MEDLINE]

5407. Mol Biol Med. 1988 Apr;5(2):61-7.

Serum amyloid A (SAA) gene variations in familial Mediterranean fever.

Sack GH Jr(1).

Author information:

(1)Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD.

Novel structural changes in members of the serum amyloid A (SAA) gene family have been found in four patients of varied ethnic backgrounds with familial Mediterranean fever. Since the genes for these small acute phase proteins are generally well conserved, these observations suggest that alterations of serum amyloid A genes, their protein products and/or their regulation may be responsible for familial Mediterranean fever.

PMID: 2899833 [Indexed for MEDLINE]

5408. Rev Rhum Mal Osteoartic. 1988 Mar 15;55(4):261-3.

[Muscular manifestations in periodic disease].

[Article in French]

Bitar E(1), Salibra G, Khoury K, Nasr W, Akatchерian C, Majdalani E, Vassoyan J, Aoun JP, Ayoun SS, Tabet M, et al.

Author information:

(1)Service de Gastro-entérologie, Hôtel-Dieu de France, Beyrouth.

Between 1976 and 1983, the authors studied 50 new patients affected with periodic disease. 16 of them-mean age: 29-presented muscular manifestations. They may be grouped into two clinical aspects: muscular pain and contractures. The authors consider that these symptoms, first described in 1945, are an inherent part of the clinical picture of the disease. They discuss their relationship with periarteritis nodosa and remind the fact that their pathogenesis remains unknown.

PMID: 3287589 [Indexed for MEDLINE]

5409. Klin Med (Mosk). 1988 Mar;66(3):89-92.

[Conjunctival microcirculation in patients with periodic disease and amyloidosis].

[Article in Russian]

Arutiunian VM, Eganian GA, Kostina EL.

PMID: 3392931 [Indexed for MEDLINE]

5410. J Clin Immunol. 1988 Mar;8(2):148-56.

Enhanced neutrophil chemiluminescence in familial Mediterranean fever.

Anton PA(1), Targan SR, Vigna SR, Durham M, Schwabe AD, Shanahan F.

Author information:

(1)Department of Medicine, UCLA 90024.

Familial Mediterranean Fever is a disorder of unknown cause characterized by recurrent, self-limited paroxysms of serosal inflammation. Although the neutrophil is the predominant cell involved, no cellular abnormalities are known.

Chemiluminescence was studied in neutrophils from 20 asymptomatic patients with this disease and 21 healthy controls to evaluate the oxidative response to formyl-methionyl-leucyl-phenylalanine (f-met-leu-phe). In a subset of patients with familial Mediterranean fever, neutrophils but not monocytes were shown to have significantly enhanced chemiluminescence compared to controls. The enhanced responsiveness of neutrophils to f-met-leu-phe in this disease was found to occur at a postreceptor level. Receptor binding assays demonstrated no differences in binding affinity and receptor number between patients and controls. In addition, a similar enhancement in chemiluminescence was observed with an alternative stimulus (zymosan). In contrast to chemiluminescence, chemotaxis induced by f-met-leu-phe was not enhanced in patients with familial Mediterranean fever. The enhanced neutrophil chemiluminescence may identify a subclinical inflammatory state in attack-free patients with familial Mediterranean fever, as enhanced chemiluminescence is also observed in chronic inflammatory diseases with active inflammation.

PMID: 3372691 [Indexed for MEDLINE]

5411. Int J Artif Organs. 1988 Mar;11(2):63-4.

Renal amyloidosis--is it preventable?

Sakhuja V(1), Chugh KS.

Author information:

(1)Dept. of Nephrology, Postgraduate Medical Institute, Chandigarh, India.

PMID: 3372052 [Indexed for MEDLINE]

5412. Ann Rheum Dis. 1988 Jan;47(1):80-3.

Severe myalgia in familial Mediterranean fever: clinical and ultrastructural aspects.

Schapira D(1), Ludatscher R, Nahir M, Lorber M, Scharf Y.

Author information:

(1)Department of Rheumatology, Rambam Medical Center, Haifa, Israel.

Severe myalgia is an uncommon feature of familial Mediterranean fever (FMF). A patient is presented in whom acute myalgia and high fever were the sole clinical findings during an FMF attack. The ultrastructural picture of the muscle tissue during the acute stage was characterised by a large deposition of collagen fibrils. The myalgia subsided during colchicine treatment. The clinical and ultrastructural features of myalgia in FMF are discussed in the light of the relevant literature.

PMCID: PMC1003450

PMID: 3345109 [Indexed for MEDLINE]

5413. J Am Acad Dermatol. 1988 Jan;18(1 Pt 1):1-16.

Amyloid and amyloidosis.

Breathnach SM(1).

Author information:

(1)Department of Medicine (Dermatology), Charing Cross and Westminster Medical School, London, U.K.

Cutaneous lesions are present in up to 40% of patients with primary and myeloma-associated systemic amyloidosis and occur as a result of tissue deposition of immunoglobulin light chain material derived from a circulating paraprotein. The occurrence of waxy, purpuric mucocutaneous lesions provides a crucial early pointer to underlying occult plasma cell dyscrasia; the combination of the symptoms of the carpal tunnel syndrome, macroglossia, and specific mucocutaneous lesions is highly characteristic. Although secondary systemic (reactive) amyloidosis rarely gives rise to clinically evident cutaneous lesions, it may be etiologically related to a number of chronic dermatoses. Lesions of nodular primary localized cutaneous amyloidosis are indistinguishable from those of primary and myeloma-associated systemic amyloidosis, and they result from local plasma cell infiltration. Macular and papular (lichen amyloidosis) variants

of primary localized cutaneous amyloidosis may have a familial or racial basis and are characterized by a tendency for keratinocytes to undergo filamentous degeneration and apoptosis. The prognosis of patients with plasma cell dyscrasia-related systemic amyloidosis remains poor, since there is little response to therapy with cytotoxic agents, colchicine, or dimethylsulfoxide. Colchicine is the drug of choice in the prevention and treatment of the renal amyloidosis associated with familial Mediterranean fever, and dimethylsulfoxide may be useful in the management of patients with secondary systemic amyloidosis. Macular amyloid and lichen amyloidosis generally follow a chronic course with intractable pruritus; there have been isolated reports of the beneficial effect of dermabrasion, topical dimethylsulfoxide, and therapy with the aromatic retinoid, etretinate.

PMID: 3279077 [Indexed for MEDLINE]

5414. Acta Paediatr Hung. 1988-1989;29(1-2):191-5.

Increased neutrophil chemotaxis. A secondary phenomenon useful in the diagnosis and follow up of diseases with inflammatory component.

Matzner Y(1), Leibovici V.

Author information:

(1)Hematology Unit, Hadassah University Hospitals, Jerusalem, Israel.

PMID: 3255402 [Indexed for MEDLINE]

5415. Am J Nephrol. 1988;8(5):417-20.

IgA nephropathy in patients with familial Mediterranean fever.

Said R(1), Nasrallah N, Hamzah Y, Tarawneh M, al-Khatib M.

Author information:

(1)Department of Medicine, School of Medicine, Jordan University, Amman.

Two patients with a long-standing history of familial Mediterranean fever were found to have both microscopic hematuria and proteinuria during the acute attacks. Kidney biopsies from both patients revealed diffuse mesangial proliferative glomerulonephritis with intense mesangial IgA and C3 deposits and no evidence of amyloidosis. To our knowledge these are the first 2 cases documenting the presence of mesangial IgA nephropathy in patients with familial Mediterranean fever.

DOI: 10.1159/000167628

PMID: 3239600 [Indexed for MEDLINE]

5416. Ter Arkh. 1988;60(6):95-8.

[Acetylation phenotype in patients with periodic disease].

[Article in Russian]

Podymov VK, Vinogradova OM, Kovaleva VL, Kochubei LN, Galstian SM.

Acetylation phenotype distribution (activity of N-acetyltransferase enzyme) was studied in 29 patients with periodical disease (PD), 73 healthy persons (Armenians), and 20 patients (also Armenians) suffering from epithelial coccygeal cysts. The results obtained indicated the prevalence of slow acetylation phenotype (67%) in the entire Armenian population. PD was characterized by slow acetylation type (28 of 29 patients had slow acetylation with a high frequency of very slow inactivators). The other hereditary pathology, also specific for Armenians (epithelial coccygeal cysts), was characterized by another type of acetylation--a rapid one. The role of slow acetylation as a genetic marker of PD was discussed.

PMID: 3206381 [Indexed for MEDLINE]

5417. Pediatriia. 1988;(4):62-5.

[Clinical aspects and diagnosis of periodic disease in children].



[Article in Russian]

Astvatsatrian VA, Torosian EK.

PMID: 3205653 [Indexed for MEDLINE]

5418. Pediatriia. 1988;(4):58-61.

[Characteristics of the clinical course of periodic disease in children].

[Article in Russian]

Petrosian RE, Oboian SR.

PMID: 3205652 [Indexed for MEDLINE]

5419. Pediatriia. 1988;(6):94-5.

[Classification and terminology of periodic disease in children].

[Article in Russian]

Petrosian RE, Iboian SR.

PMID: 3186415 [Indexed for MEDLINE]

5420. Ter Arkh. 1988;60(6):93-5.

[Acetylation phenotype in patients with periodic disease].

[Article in Russian]

Podymov VK, Vinogradova OM, Kovaleva VL, Kochubeĭ LN, Galstian SM.

PMID: 2974645 [Indexed for MEDLINE]

5421. Biochemistry. 1987 Dec 15;26(25):8251-6.

Degradation and deposition of amyloid AA fibrils are tissue specific.

Prelli F(1), Pras M, Frangione B.

Author information:

(1)Department of Pathology, New York University Medical Center, New York 10016.

The complete amino acid sequences of two related AA proteins (Mr 9700 and 5300) derived from thyroid tissue from a patient, NOR, with the autosomal recessive disease familial Mediterranean fever were determined. Heterogeneity found at position 52 indicates these proteins are fragments of two allelic or isotypic SAA precursor molecules similarly degraded at unusual sites and deposited in the thyroid. Degradation appears to be tissue and/or enzyme(s) specific since the carboxy terminus of both fragments is Ala-Ala and is different from other AA amyloid fibrils extracted from various tissues in different patients. Electron micrographic studies reveal these fragments retain the characteristics of native amyloid fibrils under physiological conditions even after exposure to dissociating agents.

PMID: 3442653 [Indexed for MEDLINE]

5422. N Engl J Med. 1987 Dec 10;317(24):1542.

Complement in the pathophysiology of human disease.

Matzner Y.

PMID: 3683491 [Indexed for MEDLINE]

5423. Mayo Clin Proc. 1987 Dec;62(12):1095-100.

Autosomal dominant familial Mediterranean fever-like syndrome with amyloidosis.

Gertz MA(1), Petitt RM, Perrault J, Kyle RA.

Author information:

(1)Division of Hematology, Mayo Clinic, Rochester, MN 55905.

We report a pedigree in which a syndrome that resembled familial Mediterranean fever occurred in four family members over three successive generations. All four patients had systemic amyloidosis. Typically, patients with familial Mediterranean fever show an autosomal recessive inheritance pattern. The disorder commonly afflicts Sephardic Jews, Arabs, and persons of Turkish descent. Colchicine therapy dramatically reduces the attack rate of serositis. The family described herein is unique because of their European ethnicity and the autosomal dominant inheritance pattern. Unlike typical familial Mediterranean fever, colchicine had no influence on the attacks and did not prevent amyloidosis in the three patients who received this treatment.

PMID: 3682954 [Indexed for MEDLINE]

5424. Br J Obstet Gynaecol. 1987 Dec;94(12):1186-91.

Fertility and obstetric history in patients with familial Mediterranean fever on long-term colchicine therapy.

Ehrenfeld M(1), Brzezinski A, Levy M, Eliakim M.

Author information:

(1)Department of Medicine A, Hadassah University Hospital, Jerusalem, Israel.

The obstetric histories were examined for 36 women with familial Mediterranean fever (FMF) on long-term colchicine treatment followed for periods ranging between 3 and 12 years. Seven of 28 pregnancies (25%) associated with colchicine

therapy ended in miscarriage. Thirteen women (36%) had periods of infertility; these were due to ovulatory dysfunction in six women, to peritoneal adhesions in four and remained unexplained in three women. The rates for miscarriage and infertility are high but are similar to those reported for women with FMF before colchicine therapy was introduced. All 16 infants born to mothers who had taken colchicine during pregnancy were healthy. Currently, we do not advise discontinuation of colchicine before planned pregnancy but recommend amniocentesis for karyotyping and reassurance.

PIP: The obstetric histories of 36 women with familial Mediterranean fever (FMF) on longterm colchicine treatment were followed for periods ranging from 3-12 years and examined. 7 of 28 pregnancies (25%) associated with colchicine therapy ended in miscarriage. 13 women (36%) had periods of infertility; these were due to ovulatory dysfunction in 6 women, to peritoneal adhesions in 4, and were unexplained in 3 women. The rates for miscarriage and infertility are high but are similar to those reported for women with familial Mediterranean fever before colchicine therapy was introduced. All 16 infants born to mothers who had taken colchicine during pregnancy were healthy. Currently, it is not advised that colchicine be discontinued before a planned pregnancy but rather, amniocentesis is recommended for karyotyping and reassurance.

PMID: 3426990 [Indexed for MEDLINE]

5425. Am J Pathol. 1987 Dec;129(3):536-42.

Primary amyloidosis A. Immunohistochemical and biochemical characterization.

Picken MM(1), Pelton K, Frangione B, Gallo G.

Author information:

(1)Department of Pathology, New York University Medical Center, New York 10016.

Primary "idiopathic" amyloidosis is usually related to immunoglobulin light chain (AL) associated with immunocytic dyscrasias, while secondary "reactive" amyloidosis (AA) is related to serum amyloid A protein (SAA) and typically occurs with chronic inflammation, malignancy, or familial Mediterranean fever. In the present study, amyloid fibril protein extracted from frozen and paraffin-embedded tissue from a patient (CAR) with primary systemic amyloidosis proved to be AA

protein by immunohistochemical, immunochemical, and amino terminal sequence. Extracts from both frozen and formalin-fixed paraffin-embedded kidney and spleen yielded similar monomers and dimers of the AA protein. The additional high-molecular-weight bands and a distinct 12,000-dalton fragment in the amyloid protein extracted from the formalin-fixed paraffin-embedded lung suggest that different processing of proteins, ie, by polymerization and/or degradation, may occur in different organs.

PMCID: PMC1899827

PMID: 3425691 [Indexed for MEDLINE]

5426. Transfus Med Rev. 1987 Dec;1(3):171-81.

Neutrophil function studies in clinical medicine.

Matzner Y(1).

Author information:

(1)Hematology Unit, Hadassah University Hospital, Jerusalem, Israel.

A complete evaluation of neutrophil function including: chemotaxis; adhesion; aggregation; phagocytosis; granule content and degranulation; respiratory burst activity; and bacterial killing; is expensive and requires the services of a specialized laboratory. However, preliminary screening of a patient with a predisposition toward infection, can be carried out using simple and inexpensive methods. These include examination of blood films, which may prove helpful in the diagnosis of Chediak-Higashi syndrome and specific granule deficiency; the Rebut skin window test, which estimates chemotactic defects; the NBT test, which screens for chronic granulomatous disease patients; and peroxidase staining of the blood film in order to estimate the content of myeloperoxidase, when myeloperoxidase deficiency is suspected. For final diagnosis and determination of genetic transmission and radical treatment, ie, bone marrow transplantation, specific tests are indicated. Neutrophil function studies have also proved useful in detecting diseases in which defects in neutrophil function are secondary to the primary disorder. Indeed, increased neutrophil chemotaxis has been reported in the active phase of diseases such as: familial Mediterranean fever; psoriasis vulgaris, Behcet's syndrome and Sweet's syndrome. In these disorders the

neutrophil chemotaxis assay has aided in the diagnosis and follow-up, particularly in evaluating the response to antiinflammatory agents, such as colchicine.

PMID: 2980276 [Indexed for MEDLINE]

5427. J Biol Chem. 1987 Nov 15;262(32):15790-5.

Structure of a human serum amyloid A gene and modulation of its expression in transfected L cells.

Woo P(1), Sipe J, Dinarello CA, Colten HR.

Author information:

(1)Medical Research Council Clinical Research Centre, Harrow, Middlesex, United Kingdom.

The structure of a human serum amyloid A (SAA) genomic clone (SAAg9) has been analyzed and the nucleotide sequence of the coding regions is compared with that of the cDNA for apoSAA1. The leader and coding sequences of exons 2 and 3 are identical to SAA1. However, there are 10 nucleotide and 7 derived amino acid substitutions in exon 4. These changes are identical to the amino acid sequence of the amyloid protein associated with familial Mediterranean fever. In particular, the amino acid substitution (Thr to Phe) at residue 69 of SAA1 may have an important role in this type of hereditary amyloidosis. The genomic clone SAAg9 has been transfected into mouse L cells, and constitutive expression of human specific mRNA and protein were observed in stable transfected clones. The expression of both SAA mRNA and protein were increased by incubation of the transfected cells with purified human interleukin-1 (IL-1), both human and mouse recombinant IL-1, and recombinant human tumor necrosis factor alpha. The induction of SAA is pretranslational and is likely to be mediated by protein factor(s) since incubation with cycloheximide diminished IL-1-dependent increase in SAA mRNA.

PMID: 2890635 [Indexed for MEDLINE]

5428. Rev Med Chir Soc Med Nat Iasi. 1987 Oct-Dec;91(4):769-71.

[Recurrent polyserositis in the picture of systemic lupus erythematosus].

[Article in Romanian]

Clocotici O, Fierăstrău V, Demișcă I, Cernomaz O, Găină B.

PMID: 3452876 [Indexed for MEDLINE]

5429. Klin Med (Mosk). 1987 Oct;65(10):124-6.

[Experience using hyperbaric oxygenation in the treatment of periodic disease].

[Article in Russian]

Karapetian FV, Davtian DG, Shaginian EKh.

PMID: 3431040 [Indexed for MEDLINE]

5430. Am J Med. 1987 Oct;83(4):787-9.

Fulminant Kaposi's sarcoma complicating long-term corticosteroid therapy.

Koop HO(1), Holodniy M, List AF.

Author information:

(1)Department of Internal Medicine, Good Samaritan Medical Center, Phoenix, Arizona.

Cutaneous Kaposi's sarcoma occurs rarely in patients receiving long-term corticosteroid therapy. The case of a rapidly progressive form of Kaposi's sarcoma occurring in a 29-year-old Palestinian woman with steroid-dependent Crohn's disease and familial Mediterranean fever is reported. Despite an

extensive transfusion history, serologic and virologic studies failed to demonstrate exposure to the human immunodeficiency virus. Serologic and virologic evidence of concomitant cytomegalovirus infection, however, suggests possible pathogenic features similar to the acquired immunodeficiency syndrome-related form of Kaposi's sarcoma.

PMID: 2823601 [Indexed for MEDLINE]

5431. Jpn J Med. 1987 Aug;26(3):370-2.

Recurrent polyserositis (familial Mediterranean fever) in a Japanese.

Schwabe AD(1), Nishizawa A.

Author information:

(1)Department of Medicine, University of California, Los Angeles 90024.

A 36-year-old male of pure Japanese ancestry presented with a classical 20-year history of Recurrent Polyserositis manifested by self-limited attacks of fever plus pleuritis, peritonitis or arthritis. These attacks were completely suppressed by daily prophylactic colchicine, but recurred when the drug was briefly discontinued. For the past 10 years he has been on 1.2 mg of colchicine daily and has had no further febrile attacks. Although several cases of periodic or cyclic febrile disorders in patients of Japanese ancestry have been cited in the literature, the patient described here appears to satisfy the required criteria for a diagnosis of Recurrent Polyserositis in a Japanese.

PMID: 3694919 [Indexed for MEDLINE]

5432. J Pediatr. 1987 Aug;111(2):307.

Syndrome of periodic fever and pharyngitis.

Rubin LG, Kamani N.



PMID: 3612406 [Indexed for MEDLINE]

5433. Baillieres Clin Rheumatol. 1987 Aug;1(2):335-54.

Skin and nail changes in the arthritic foot.

Gilkes JJ.

The arthritic process is unlikely to be confined to the foot; similarly the cutaneous lesions associated with the arthritic foot are often widespread. Careful examination of the skin and nails, particularly the finger nails, may be helpful in the differential diagnosis when the patient presents with a painful foot joint. Conversely, certain cutaneous lesions may alert the physician to the possibility of joint disorders presenting at some later date. In this chapter, it is not possible to mention every skin lesion associated with an arthropathy. Some skin lesions are specific but many are non-specific and occur in several rheumatic diseases. The rheumatologist and dermatologist work in closest co-operation when managing patients with lupus erythematosus and psoriatic arthritis and it is for this reason there is particular emphasis on these two diseases. Patients with rheumatoid arthritis and gout usually come within the province of the rheumatologist, but there are often many characteristic dermatological features to these diseases. This chapter also includes some more esoteric diseases such as Familial Mediterranean fever, Behçet's syndrome, disseminated gonococcal infection and Lyme disease which may present a diagnostic problem to the general physician, rheumatologist or dermatologist.

PMID: 3331326 [Indexed for MEDLINE]

5434. Ned Tijdschr Geneeskd. 1987 Jul 4;131(27):1178-80.

[Periodic fever].

[Article in Dutch]

van der Meer JW.

PMID: 3614406 [Indexed for MEDLINE]

5435. Klin Med (Mosk). 1987 Jul;65(7):118-22.

[HLA antigens in periodic disease].

[Article in Russian]

Vinogradova OM, Zotikov EA, Kut'ina RM, Kochubeĭ LN, Kovalenko LV.

PMID: 3478515 [Indexed for MEDLINE]

5436. Ugeskr Laeger. 1987 Jun 8;149(24):1612-4.

[Familial Mediterranean fever. Continuous treatment with colchicine].

[Article in Danish]

Herlin T, Storm K, Ternowitz T.

PMID: 3603843 [Indexed for MEDLINE]

5437. Am J Med. 1987 Apr;82(4):829-32.

Panniculitis in familial Mediterranean fever. Case report with histopathologic findings.

Danar DA, Kwan TH, Stern RS, Kasdon EJ, Birnbaum PS, Brown RS.

A 79-year-old Armenian-born woman with stable, long-term familial Mediterranean fever had progression of chronic renal failure concurrently with two types of skin lesions. One lesion resembled erysipelas, which is quite common in familial

Mediterranean fever, whereas the other was panniculitis, only occasionally described in familial Mediterranean fever. The unique histopathologic features of the latter are presented. The onset of acute cutaneous disease in this patient coincided with worsening renal disease and preceded a flare of disease activity in other sites after a 14-year period of quiescence. The severe and unremitting pain from the skin lesions and their tendency to form nonhealing ulcers were substantial causes of morbidity in this patient with familial Mediterranean fever.

PMID: 3565436 [Indexed for MEDLINE]

5438. Br J Rheumatol. 1987 Apr;26(2):139-41.

Polyarteritis nodosa and familial Mediterranean fever.

Sachs D, Langevitz P, Morag B, Pras M.

A 22-year-old familial Mediterranean fever (FMF) patient was hospitalized for continuous fever, myalgia, hypertension, vertigo and a petechial rash. Laboratory findings revealed hyperglobulinaemia, thrombocytosis and a leukaemoid reaction. While on steroid therapy the patient sustained a haemorrhage into a renal aneurysm which responded to gel foam embolization. After 12 months of follow-up his condition remained stable under treatment with cyclophosphamide, prednisone and antihypertensive medications. This case provides the fourth example of polyarteritis nodosa associated with FMF.

PMID: 2881591 [Indexed for MEDLINE]

5439. Clin Chim Acta. 1987 Mar 16;163(2):199-205.

Preparative fractionation of amyloid proteins on a microgram scale by high-performance liquid chromatography and polyacrylamide gel electrophoresis.

Kaplan B, Pras M.

Preparative separation of amyloid proteins on a microgram scale is presented. Amyloid fibrils solubilized in aqueous 50% acetonitrile containing 0.1% trifluoroacetic acid, are fractionated by reverse-phase high-performance liquid chromatography. Fractionation of amyloids obtained from patients with familial Mediterranean fever allowed isolation of a protein identical with a conventionally isolated AA-protein. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis is used for preparative separation of AL-proteins. Two protein extraction procedures from Coomassie Blue stained gels are applied using elution in 0.1% sodium dodecyl sulfate containing buffer and 6 mol/l guanidine-HCl solution. The eluted proteins are concentrated and sodium dodecyl sulfate and dye are removed by acetonitrile precipitation of sample.

PMID: 3568424 [Indexed for MEDLINE]

5440. Presse Med. 1987 Feb 7;16(4):178-9.

[Acute intestinal occlusion in periodic disease (or familial Mediterranean fever)].

[Article in French]

Petit J, Testart J, Teniere P, Bourreille J, Oksenhendler G, Saour N, Ducable G.

PMID: 2950459 [Indexed for MEDLINE]

5441. Ann Rheum Dis. 1987 Feb;46(2):139-45.

Observer variation in grading sacroiliac radiographs might be a cause of 'sacroiliitis' reported in certain disease states.

Yazici H, Turunç M, Ozdoğan H, Yurdakul S, Akinci A, Barnes CG.

Radiological sacroiliitis in Behçet's syndrome (BS) has been a subject of controversy. We have examined pelvic radiographs of 38 patients with BS and 28 age and sex matched controls which we reported previously, and also 17 with

ankylosing spondylitis (AS), 27 with non-renal familial Mediterranean fever (FMF), and 33 with primary osteoarthritis (OA). Initially, five observers assessed radiographs on two different occasions according to the New York criteria for sacroiliitis in a blind protocol. Later, three of them examined the various possible abnormalities of the sacroiliac (SI) joints after training sessions. Although the inter- and intraobserver variation was quite high, all observers found the expected changes in patients with AS. The abnormalities detected in the other diseases were either mild, inconsistent, or both. Erosions were confined to patients with AS, and osteophytes and glenoid sulci to patients with OA. We conclude that high observer variation in interpreting a film of the anteroposterior (AP) view of the pelvis for sacroiliitis may be a major cause of reported 'sacroiliitis' in BS and FMF.

PMCID: PMC1002080

PMID: 3827336 [Indexed for MEDLINE]

5442. Arch Intern Med. 1987 Feb;147(2):378-9.

Recurrent pulmonary atelectasis as a manifestation of familial Mediterranean fever.

Brauman A, Gilboa Y.

Comment in

Arch Intern Med. 1989 Jul;149(7):1698.

Recurrent attacks of pulmonary atelectasis were the leading sign of familial Mediterranean fever in a young man of Jewish-Georgian extraction. His mother suffered from the more common manifestations of the disease. Treatment with colchicine caused a complete disappearance of his attacks. However, when challenged by discontinuing colchicine therapy for eight days, another, documented attack of pulmonary atelectasis occurred. To our knowledge, this is the first case of familial Mediterranean fever presenting with recurrent pulmonary atelectasis.

PMID: 3813759 [Indexed for MEDLINE]

5443. Chest. 1987 Feb;91(2):265-6.

Acute pleuritic chest pain with pleural effusion and plate atelectasis. Familial Mediterranean fever (periodic disease).

el-Kassimi FA.

PMID: 3802938 [Indexed for MEDLINE]

5444. Rev Rhum Mal Osteoartic. 1987 Feb;54(2):105-8.

[Muckle-Wells syndrome or association of joint pain attacks, urticarial outbreaks and sensory deafness?].

[Article in French]

Serratrice G, Pouget J.

The Muckle and Well's syndrome corresponding to a transmission of the autosomic dominant type, combines bouts of urticaria, episodes of arthralgias to a shrinking of the ear and a sensory deafness. Sometimes, it evolves into a renal amylosis. Sometimes, as the case presented here, it combines multiple malformations. Its place in nosology is imprecise. It is, at the same time, close to systemic urticaria, sensory deafness, amylosis and specially amylosis of the periodic disease. But the common link between the various elements of the syndrome remains undetermined, for the time being.

PMID: 3563375 [Indexed for MEDLINE]

5445. Transplant Proc. 1987 Feb;19(1 Pt 2):1544-5.

Cyclosporine toxicity in amyloidotic patients.

Siegal B(1), Zemer D, Shtrasburgh S, Pras M.

Author information:

(1)Transplant Unit, Sheba Medical Center, Tel Hashomer, Israel.

PMID: 3274378 [Indexed for MEDLINE]

5446. Schweiz Med Wochenschr. 1987 Jan 31;117(5):173-8.

[Familial Mediterranean fever. Study of a Swiss child].

[Article in German]

Federspiel B, Tönz O.

Familial Mediterranean fever (FMF) has been observed in a Swiss child without ethnic predisposition. The case is analyzed and the current literature briefly reviewed. Recurrent attacks of fever, accompanied by abdominal pain, colic and arthritic symptoms, and often by pleuritic pain and a transitory skin rash, are the hallmarks of FMF, which is predominantly seen in ethnic groups of the Mediterranean area, notably Sephardic Jews, Turks and Armenians. However, it rarely occurs among individuals without an ethnic predisposition. Its most ominous manifestation is amyloidosis, which leads to chronic renal failure within a matter of years. Thanks to colchicine treatment, which is now widely accepted, patients often lead normal lives, and it appears that amyloidosis can be prevented.

PMID: 3563445 [Indexed for MEDLINE]

5447. Ter Arkh. 1987;59(8):63-8.

[Comparative aspects of the course of periodic disease without and with amyloidosis (analysis of 437 case studies)].

[Article in Russian]

Vinogradova OM, Kochubei LN, Vasil'eva NA.

The paper is concerned with an analysis of a course of periodic disease (PD) without and with amyloidosis using also a method of the determination of survival rates in 437 patients followed up for 20 yrs. A course of PD without amyloidosis was benign and did not affect the patients' survival. In the development of amyloidosis the prognosis was unfavorable and determined by a degree of generalization of amyloidosis.

PMID: 3686448 [Indexed for MEDLINE]

5448. Vutr Boles. 1987;26(1):14-8.

[Successful therapeutic effect on periodic disease with the intermittent use of colchicine].

[Article in Bulgarian]

Maleev A, Naumov N.

The continuous application of colchicine reduces considerably the incidence of the paroxysms in patients with periodic disease. A patient is described, a Bulgarian, with periodic disease with a duration of 40 years (family Mediterranean fever), successfully treated with intermittent application of colchicine according to a schedule for the last 3 years. The evolution of the clinical manifestations was followed up as well as the absence of effect by the corticosteroid therapy applied before. The intermittent application of colchicine, in this case, prevents totally the paroxysms with high temperature and pain in abdomen, chest and joints with a considerable smaller amount of the drug applied. The intermittent application of colchicine should first be tried in the treatment of patients with periodic diseases.

PMID: 3590721 [Indexed for MEDLINE]



5449. Ter Arkh. 1987;59(2):26-8.

[Role of catecholamines in the development of gastric and duodenal mucosal lesions in patients with periodic disease].

[Article in Russian]

Arutiunian VM, Eganian GA, Virabian TL.

PMID: 3576473 [Indexed for MEDLINE]

5450. Acta Clin Belg. 1987;42(5):365-80.

Amyloidosis 1970-1985 with special reference to amyloid arthropathy. A discussion about 106 cases.

Huaux JP, Vandenbroucke JM, Noël H.

PMID: 3321813 [Indexed for MEDLINE]

5451. Ann Ital Med Int. 1987 Jan-Mar;2(1):1-5.

Familial Mediterranean fever.

Matzner Y.

PMID: 3079439 [Indexed for MEDLINE]

5452. Clin Ter. 1986 Nov 15;119(3):235-41.

[Familial Mediterranean fever (or recurrent polyserositis)].

[Article in Italian]

Piergiacomini G.

PMID: 3802735 [Indexed for MEDLINE]

5453. Arch Fr Pediatr. 1986 Nov;43(9):711-3.

[Cutaneous manifestations of periodic disease].

[Article in French]

Lachaux A, Hermier M, Cambazard F, Descos B, Collet JP.

The authors report the case of an 8 year-old girl admitted for an erysipelas-like rash of the lower limbs and an episode of Henoch-Schönlein purpura. These manifestations were subsequently attributed to familial mediterranean fever. This case report illustrates the polymorphism of cutaneous manifestations in this disease.

PMID: 3813802 [Indexed for MEDLINE]

5454. Biull Eksp Biol Med. 1986 Nov;102(11):561-3.

[Metabolism of arachidonic acid in the thrombocytes of patients with periodic disease].

[Article in Russian]

Panosian AG, Grigorian SV, Davtian DG, Gevorgian GA, Gabrielian ES.

Washed platelets of patients with familial Mediterranean fever (FMF) were incubated with I-14C arachidonic acid (AA). Only 10% of AA were transformed into thromboxane A<sub>2</sub>, 12(S)-12-hydroxy-5Z,8Z,10E,14Z-eicosatetraenoic acid (12-HETE) and 12(S)-12-hydroxy-5Z,8Z,10E-heptadecatrienoic acid (HHT), which strongly indicates the suppression of platelet lipooxygenase and cyclooxygenase or the

deficit in these enzymes in FMF. However, there were no noticeable alterations in AA platelet metabolism during attacks of fever and immediately after hyperbaric oxygenation used to relieve pain and fever. The data obtained suggest that arachidonic acid metabolism plays an important role in the pathogenesis of FMF.

PMID: 3096398 [Indexed for MEDLINE]

5455. Thromb Haemost. 1986 Oct 21;56(2):211-3.

Increased procoagulant response of monocytes from patients with familial Mediterranean fever.

Courillon-Mallet A, Bevilacqua M, Wautier JL, Dervichian M, Cattani D, Caen J.

Familial Mediterranean Fever (FMF) is an inherited disease of unknown etiology characterized by recurrent inflammatory episodes. Circulating fibrin was found in patients with FMF in absence of clinical manifestation of thrombosis and was statistically less frequently observed in patients treated with colchicine. These results suggest a cellular dysfunction. Therefore, we examined the procoagulant activity (PCA) of isolated mononuclear leukocytes and purified monocytes from FMF patients (n = 20). No PCA was detectable on freshly-isolated monocytes. After several hours of culture, FMF monocytes contained more PCA than control cells and the difference was more marked after endotoxin stimulation. Data obtained with coagulation factor-deficient plasma and anti-human apoprotein III antiserum indicated that the enhanced PCA in FMF monocytes is thromboplastin-like. Lysozyme and interleukin 1 production by monocytes were similar in patients and controls. The increased monocyte PCA appears to be due to an intrinsic and selective higher responsiveness of monocytes.

PMID: 3810556 [Indexed for MEDLINE]

5456. Nihon Naika Gakkai Zasshi. 1986 Oct;75(10):1423-8.

[A case of periodic fever resembling familial Mediterranean fever, suppressed effectively by colchicine].

[Article in Japanese]

Kuyama J, Nishida E, Tsubakio T, Kanayama Y, Tominaga N, Mineo I, Ogasawara S, Yamashita S, Yonezawa T, Tarui S.

PMID: 3805842 [Indexed for MEDLINE]

5457. *Pediatr Clin North Am*. 1986 Oct;33(5):1033-52.

Miscellaneous conditions associated with arthritis in children.

Cassidy JT.

Miscellaneous conditions associated with arthritis in children are reviewed as distinct entities in the differential diagnosis of the many types of juvenile arthritis reviewed here and in other articles.

PMID: 3763251 [Indexed for MEDLINE]

5458. *Rev Invest Clin*. 1986 Oct-Dec;38(4):389-93.

[Familial Mediterranean fever in Mexico City].

[Article in Spanish]

Halabe Cherem J, Lifshitz A, Mercado Atri M, Islas Andrade S, Mougrabi Mizrahi M, Lisker R.

PMID: 3563142 [Indexed for MEDLINE]

5459. *Lancet*. 1986 Sep 27;2(8509):724-5.

Colchicine in amyloidosis.

[No authors listed]

PMID: 2876192 [Indexed for MEDLINE]

5460. Presse Med. 1986 Sep 20;15(30):1422.

[Acute abdomen in familial Mediterranean fever. False or true surgical abdomen?].

[Article in French]

Feneyrou B, Courty P, Prioton JB.

PMID: 2947064 [Indexed for MEDLINE]

5461. Q J Med. 1986 Sep;60(233):837-47.

Familial Mediterranean fever (recurrent hereditary polyserositis) in Arabs--a study of 175 patients and review of the literature.

Barakat MH, Karnik AM, Majeed HW, el-Sobki NI, Fenech FF.

Recurrent hereditary polyserositis (RHP) or familial Mediterranean fever (FMF) is a chronic inherited illness of obscure aetiology. The disease is characterised by paroxysmal attacks of fever, peritonitis, pleuritis or arthritis, and predominantly affects Sephardic Jews, Arabs, Turks and Armenians. In this study, we report our 11-year experience of 175 Arab patients with this disease. As with other ethnic groups, the most common manifestation (93.7 per cent) was peritonitis. Arthritis (33.7 per cent) and pleurisy (32 per cent) were next in frequency. Adult patients in this series unlike those in other ethnic groups, rarely presented with arthritis. Similarly rare were amyloidosis, rashes, splenomegaly, hepatomegaly or lymphadenopathy. The aetiology of this disease is not clear but we suspect that abnormalities in catecholamine metabolism may be a factor in the pathogenesis.

PMID: 3306755 [Indexed for MEDLINE]

5462. Q J Med. 1986 Sep;60(233):819-23.

Periodic disease, recurrent polyserositis, familial Mediterranean fever, or simply 'FMF'.

Cook GC.

PMID: 3306754 [Indexed for MEDLINE]

5463. Rinsho Shinkeigaku. 1986 Aug;26(8):792-6.

[Periodic fever suppressed by colchicine--a case report].

[Article in Japanese]

Ota K, Sato T, Takahashi K.

PMID: 3802671 [Indexed for MEDLINE]

5464. Andrologia. 1986 Jul-Aug;18(4):420-6.

The effects of long-term colchicine therapy on male fertility in patients with familial Mediterranean fever.

Ehrenfeld M, Levy M, Margalioth EJ, Eliakim M.

Four out of 19 male patients suffering from familial Mediterranean fever (FMF) had fertility problems while on colchicine therapy (0.5-2.0 mg daily for as long as 11 years). Three of the patients had had children while off therapy but their wives could not conceive while they were on therapy. In one patient primary

sterility remained one year after cessation of colchicine. In this and two other patients the spermogram was normal but the sperm penetration test was pathological. The fourth patient had azoospermia. Patients should be informed about this possible risk of colchicine therapy. The need for continued follow-up and the value of the sperm penetration test in the detection of fertility problems in male patients on long-term colchicine therapy are stressed. It is concluded however, that overall the benefits outweigh the danger of long-term colchicine treatment in male patients with FMF.

PMID: 3752545 [Indexed for MEDLINE]

5465. J Comp Pathol. 1986 Jul;96(4):387-98.

Tissue distribution of amyloid deposits in Abyssinian cats with familial amyloidosis.

DiBartola SP, Tarr MJ, Benson MD.

The tissue distribution of amyloid deposits was studied in 15 related Abyssinian cats with familial amyloidosis. There was interstitial medullary amyloidosis in the kidneys of all 15 cats but only 11 had detectable glomerular involvement. The thyroid glands, stomach and colon were affected in all cats examined. Most of the cats also had amyloid deposits in the small intestine, spleen, heart, adrenals, pancreas, liver, lymph nodes and bladder. In 50 per cent or fewer of the cats examined, there was involvement of the parathyroids, lung and gonads. The central nervous system was not involved in any of the 3 cats evaluated. In 8 of the cats, no concurrent inflammatory disease could be detected. The tissue distribution of amyloid deposits resembled that found in other breeds of domestic cats with systemic amyloidosis. Despite the wide tissue distribution of amyloid deposits, clinical signs were related to renal amyloidosis. Familial amyloidosis in the Abyssinian cat may represent a valuable spontaneous animal model for the study of Familial Mediterranean Fever in man and the pathogenesis of reactive amyloidosis in general.

PMID: 3734172 [Indexed for MEDLINE]

5466. Minerva Pediatr. 1986 Jun 30;38(11-12):483-7.

[Familial Mediterranean fever. Presentation of a clinical case].

[Article in Italian]

Rottoli A, Riva E, Lista G, Bertassi F, Giovannini M.

PMID: 3736527 [Indexed for MEDLINE]

5467. Schweiz Med Wochenschr. 1986 Jun 21;116(25):851-5.

[Destructive arthropathy in familial Mediterranean fever].

[Article in German]

Kissling R, Brandenberg J, Papandreou A, Käppeli R.

Mediterranean fever, an autosomal recessive hereditary disease usually affecting closely circumscribed populations, is already characterized in early life by recurrent bouts of fever accompanied by polyserositis. One feared complication is amyloidosis, while the other, which is less frequent and almost unknown in Central Europe, is chronic destructive arthropathy. This partial aspect of familial Mediterranean fever is illustrated by the case of an Armenian born in 1960. The value of a theoretically conceivable basic therapy with colchicine is considered. Colchicine has apparently produced good results in the early stages of destructive arthropathy, although the mechanism by which this occurs is not yet understood. The positive effect described is likewise not evident in all cases.

PMID: 3738455 [Indexed for MEDLINE]

5468. Arch Intern Med. 1986 Jun;146(6):1243.



Liver sinusoidal dilatation in familial Mediterranean fever.

Clotet B, Navas J, Grifol M, Rubiés-Prat J, Foz M.

PMID: 3718121 [Indexed for MEDLINE]

5469. Transplantation. 1986 Jun;41(6):793-4.

Cyclosporine and familial Mediterranean fever amyloidosis.

Siegal B, Zemer D, Pras M.

PMID: 3520994 [Indexed for MEDLINE]

5470. Am J Clin Pathol. 1986 Jun;85(6):674-80.

Cardiac amyloid deposits in endomyocardial biopsies. Light microscopic, ultrastructural, and immunohistochemical studies.

Frenzel H, Schwartzkopff B, Kuhn H, Lösse B, Thormann J, Hort W, Linke RP.

In four patients with unexplained, abnormal thickening of the interventricular septum as demonstrated by echocardiography, right ventricular endomyocardial biopsy revealed unexpected cardiac amyloid deposits that resulted in increased myocardial thickness and rapidly progressive heart failure. Light microscopically, amyloid was observed in the subendocardial layer, interstitium, and walls of the intramural arterioles. Electron-microscopically, the amyloid fibrils were adjacent to the basement membranes of the heart muscle cells and the vascular smooth muscle cells. Immunohistochemical typing with specific antibodies against different amyloid fibril proteins on glutaraldehyde-fixed paraffin sections revealed different amyloid types. In two patients with generalized idiopathic amyloidosis and in two others with amyloidosis in multiple myeloma, the A-lambda form was diagnosed. In a fifth patient, AA-amyloidosis was found in familial Mediterranean fever with cardiac manifestation without thickening of the interventricular septum. The amyloid deposits were located almost exclusively

within the walls of the myocardial arterioles. The amount of amyloid as observed in the myocardial biopsies correlates with the rapidly progressive cardiac failure. It is suggested that in patients with abnormal thickening of the interventricular septum of unknown origin the diagnosis should be clarified by endomyocardial biopsy.

PMID: 3518402 [Indexed for MEDLINE]

5471. Rev Prat. 1986 Apr 21;36(23):1269-78.

[Periodic disease].

[Article in French]

Courillon-Mallet A, Dervichian M, Cattan D.

PMID: 3715347 [Indexed for MEDLINE]

5472. N Engl J Med. 1986 Apr 17;314(16):1001-5.

Colchicine in the prevention and treatment of the amyloidosis of familial Mediterranean fever.

Zemer D, Pras M, Sohar E, Modan M, Cabili S, Gafni J.

To determine whether colchicine prevents or ameliorates amyloidosis in patients with familial Mediterranean fever, we followed 1070 patients with the latter disease for 4 to 11 years after they were advised to take colchicine to prevent febrile attacks. Overall, at the end of the study, the prevalence of nephropathy was one third of that in a study conducted before colchicine was used to treat familial Mediterranean fever. Among 960 patients who initially had no evidence of amyloidosis, proteinuria appeared in 4 who adhered to the prophylactic schedule and in 16 of 54 who admitted non-compliance. Life-table analysis showed that the cumulative rate of proteinuria was 1.7 percent (90 percent confidence limits, 0.0 and 11.3 percent) after 11 years in the compliant patients and 48.9 percent (18.8

and 79.0 percent) after 9 years in the noncompliant patients (P less than 0.0001). A total of 110 patients had overt nephropathy when they started to take colchicine. Among 86 patients who had proteinuria but not the nephrotic syndrome, proteinuria resolved in 5 and stabilized in 68 (for more than eight years in 40). Renal function deteriorated in 13 of the patients with proteinuria and in all of the 24 patients with the nephrotic syndrome or uremia. We conclude that colchicine prevented amyloidosis in our high-risk population and that it can prevent additional deterioration of renal function in patients with amyloidosis who have proteinuria but not the nephrotic syndrome.

DOI: 10.1056/NEJM198604173141601

PMID: 3515182 [Indexed for MEDLINE]

5473. *Cutis*. 1986 Apr;37(4):290-2.

Bullous skin lesion in familial Mediterranean fever.

Ronnen M, Suster SM, Schewach-Millet M.

An unusual painful bullous skin lesion of the foot occurred in a 49-year-old woman as the only clinical manifestation of familial Mediterranean fever. The lesion preceded other symptoms of the disease by several years and responded only to treatment with colchicine. Recognition of this peculiar skin lesion may lead to an earlier diagnosis of the disease.

PMID: 3519101 [Indexed for MEDLINE]

5474. *Isr J Med Sci*. 1986 Mar-Apr;22(3-4):318-25.

Medical examination of Israeli 17-year-olds before military service as a national resource for health information.

Kark JD, Kedem R, Revach M.

At age 17 years Israelis undergo medical examination for the purpose of health classification for military service. The potential use of this extensive data

collection system for epidemiologic studies is illustrated for selected conditions. Trends in diagnosed disorders over a 25-year period are exemplified in the changing prevalence of tuberculosis, bronchial asthma, diabetes, epilepsy and heart defects. Within birth cohorts, cross-sectional analyses of height, body mass, blood pressure and disorders--such as bronchial asthma, allergic rhinitis, diabetes, psychiatric diagnoses and such genetic conditions as familial Mediterranean fever--point to clear ethnic differences. Educational level is strongly associated with measures of health status. Potential uses of this resource include: detecting groups in need of preventive, curative and rehabilitative care, assessing changing needs and priorities of health care, evaluation of intervention programs and health services provided in childhood, a wide spectrum of etiologic studies including assessment of health effects of social change, follow-up studies including the natural history of disorders, and developing data systems such as national registries of rare or important conditions. Issues relating to data reliability and validity, changing disease classification and nonexamination of groups exempted from military service limit interpretation of findings and restrict uses of this resource. Emphasis on standardization of data collection and diagnostic criteria, quality assurance and improved data management will be necessary.

PMID: 3744778 [Indexed for MEDLINE]

5475. Vrach Delo. 1986 Feb;(2):31-4.

[Periodic disease].

[Article in Russian]

Fombershteĭn KB.

PMID: 3705564 [Indexed for MEDLINE]

5476. Clin Ther. 1986;8(5):481, 586-7.

Therapeutic rounds. Colchicine therapy for familial Mediterranean fever.

Ben-Chetrit E, Levy M, Eliakim M.

PMID: 3768928 [Indexed for MEDLINE]

5477. Ter Arkh. 1986;58(7):123-5.

[Structural and functional changes in the parathyroid glands in patients with periodic disease].

[Article in Russian]

Arutiunian VM, Eganian GA, Grigorian GA.

The results obtained during radioimmunoassay, biochemistry and morphological studies in patients with periodic disease point to the development of hypoparathyroid hormonemia, reduction of the substrate of the parathyroid parenchyma, responsible for the synthesis of parathyroid hormone. These alterations became aggravated in the course of the development of amyloidosis. The latter is not always related to amyloidosis of the parathyroid glands themselves.

PMID: 3764728 [Indexed for MEDLINE]

5478. Z Rheumatol. 1986 Jan-Feb;45(1):26-30.

[Familial Mediterranean fever. Immunogenetic and rheumatologic aspects of the disease in a Turkish sibship].

[Article in German]

Langer HE, Robin-Winn M, Stangel W, Zeidler H.

A family study was performed in 24 members of a Turkish sibship with familial Mediterranean fever (FMF) with 5 patients affected in 3 generations. The

well-known autosomal-recessive inheritance of the disease was masked by a pseudodominant appearance, reflecting the striking frequency of congenial marriages. The immunogenetic investigation excluded a linkage between the expression of the disease and the HLA system. The arthritis of FMF was characterized typically by monarticular attacks in large joints of the lower limb. Frequently this manifestation led to diagnostic problems, particularly at the onset of the disease. No patient presented the clinical or radiological signs of sacroileitis. An observation of the disease process up to 3 years showed a benign prognosis of FMF-arthritis in 3 of 4 patients. Neither long-lasting functional impairment nor radiological signs of erosion had to be recognized. One patient suffered from a necrosis of the femoral head, possibly caused by the recurrent inflammation of the hip joint. Laboratory findings reflected the clinical picture of relapsing acute inflammation in an uncharacteristic manner. Their diagnostic significance exists mainly for the exclusion of other diseases.

PMID: 3705775 [Indexed for MEDLINE]

5479. Sov Med. 1986;(2):97-8.

[Association of peptic ulcer with periodic disease].

[Article in Russian]

Arutiunian VM, Eganian GA, Grigorian GA.

PMID: 3704771 [Indexed for MEDLINE]

5480. Epidemiol Rev. 1986;8:106-16.

Epidemiologic observations in familial paroxysmal polyserositis.

Armenian HK, Sha'ar KH.

PMID: 3533580 [Indexed for MEDLINE]

5481. Nephrologie. 1986;7(2):63-6.

[Kidney transplantation in a case of amyloidosis].

[Article in French]

Cuvelier R, Pirson Y, Cosyns JP, Squifflet JP, Alexandre GP, van Ypersele de Strihou C.

Renal transplantation was performed in five patients with various forms of amyloidosis (familial amyloidosis, Mediterranean fever and Crohn's disease). All grafts were functioning one year after the operation. Only one patient died of cardiac shock more than 10 years after transplantation; the other recipients are alive with a functioning graft from 12 to 67 (mean, 41) months after transplantation. No early severe infection was observed in any patient. Graft biopsy obtained in three patients disclosed amyloid deposits in only one: deposits initially (72 months post-transplantation) mild and perivascular, became more prominent in the vessels and extended into the mesangium 4 1/2 years later. Extrarenal amyloid involvement observed in four cases did not lead to serious clinical consequences during the follow-up period. Renal transplantation thus provides an effective treatment of terminal renal failure due to amyloidosis whatever its cause.

PMID: 3526167 [Indexed for MEDLINE]

5482. Trans Am Clin Climatol Assoc. 1987;98:128-34.

Familial Mediterranean fever--an update.

Goldfinger SE.

PMCID: PMC2279719

PMID: 3303616 [Indexed for MEDLINE]

5483. C R Seances Soc Biol Fil. 1986;180(1):10-21.

[Amyloidosis and familial Mediterranean fever].

[Article in French]

Pras M.

Familial Mediterranean Fever (F. M. F.) is an autosomal recessive disorder occurring most commonly in Sephardi Jews and Armenians. Two phenotypic features characterize the disease: brief episodic febrile attacks of peritonitis, pleuritis or synovitis recurring from childhood or adolescence and the development of systemic amyloidosis. Attacks are accompanied by striking elevations of acute phase proteins, including serum amyloid A protein. The amyloidosis of Familial Mediterranean Fever is of the AA type, and manifest clinically as a nephropathy that passes through proteinuria, nephrotic and uremic stages to renal death. Although there is ethnic variation in the incidence of amyloidosis of F. M. F. in our patient population--predominantly Sephardi Jews of North African extraction--an amyloidotic death at an early age is their genetic destiny. Since the introduction in 1972 of colchicine to prevent the febrile attacks, the drug has been proven and become the main stay of therapy. Today, colchicine has been shown to be effective in preventing amyloidosis as well as the febrile attacks in Familial Mediterranean Fever. End stage renal disease is not the end of the road for patients with F.M.F. because of improving outlook for dialysis and renal transplantation in these patients.

PMID: 2943362 [Indexed for MEDLINE]

5484. Dtsch Med Wochenschr. 1985 Nov 1;110(44):1695-700.

[Synovitis in familial Mediterranean fever].

[Article in German]

Langer HE, Huth F, Behfar S, Zeidler H.



Arthroscopy done on a 24-year-old turkish male with familial Mediterranean fever (FMF) and arthritis of the knee joint provided morphological data during the acute stage of FMF-arthritis. Main finding is a heavy granulocytic infiltration of the subsynovial stratum, similar to that seen in non-specific purulent inflammation, accompanied by marked ectasis and hyperaemia of the synovial vessels. In the microbiologically sterile synovial fluid cell counts and lactate values are found as in bacterial arthritis. The typical history and the characteristic course of the disease are indicators for the diagnosis. Serological, immunological and radiological findings are non-specific. The efficacy of prophylactic colchicine in symptomatic therapy could be verified but it is essential that the drug is taken regularly and that the patient is instructed accordingly. Investigation of other members of the family showed a high frequency of intermarriages and the presence of this autosomal-recessive inherited disease in three generations.

DOI: 10.1055/s-2008-1069072

PMID: 3876924 [Indexed for MEDLINE]

5485. Isr J Med Sci. 1985 Nov;21(11):883-5.

C3, BF and C4 polymorphisms in familial Mediterranean fever.

Davrinche C, Rivat C, Ollier-Hartmann MP, Hartmann L.

BF, C3 and C4 phenotyping were investigated in 34 patients with familial Mediterranean fever (FMF) and in 48 control subjects. Both groups included Sephardic Jews born in Tunisia, Algeria and Morocco. No linkage between BF, C3 and C4 polymorphisms and FMF was found.

PMID: 3852807 [Indexed for MEDLINE]

5486. Med Clin (Barc). 1985 Oct 5;85(10):430.

[Provocation test using metaraminol in familial Mediterranean fever].

[Article in Spanish]

Montalbán Gairín J, Alijotas Reig J, Ordi Ros J, Selva O'Callaghan A.

PMID: 4079500 [Indexed for MEDLINE]

5487. Rev Infect Dis. 1985 Sep-Oct;7(5):692-9.

Clinically benign fever of unknown origin: a personal retrospective.

Weinstein L.

The purpose of this discussion has been to bring to the attention of physicians the fact that all instances of etiologically undefined persistent fever are not associated with potentially serious or life-threatening organic disease, regardless of the height of the temperature. As has been pointed out, many patients with FUO clearly have disorders that are clinically benign, and the cause of these disorders is defined much more frequently on the basis of information obtained from a detailed historic inquiry than on the basis of findings made during the most meticulous physical examination and extensive laboratory studies. These individuals are usually seen first in an outpatient setting and seldom, if ever, require hospitalization because the cause of their FUO can, with uncommon exceptions, be identified as a physiologic or emotional dysfunction, a reaction to a drug or a chemical, or a disorder that is genetically determined. Failure to recognize that even a high elevation of the temperature can represent a clinically benign situation may lead to unnecessary hospitalization, during which the many investigations that are usually carried out may serve only to reinforce the patient's concern about a serious disease. It is most important for both patients and physicians to be aware that temperature, like all other physiologic and chemical measurements in humans, is expressed by a range of values and that a temperature of 98.6 degrees F is not normal for all persons. It must also be appreciated that "normal" temperature varies with age. The newborn infant may develop high-grade fever in the absence of disease because of marked instability of the vasomotor system.(ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 4059757 [Indexed for MEDLINE]

5488. Isr J Med Sci. 1985 Sep;21(9):757-8.

Familial Mediterranean fever: no association of HLA with amyloidosis or colchicine treatment response.

Fradkin A, Pras M, Zemer D, Gazit E.

PMID: 4055337 [Indexed for MEDLINE]

5489. Am J Ophthalmol. 1985 Aug 15;100(2):337-9.

Episcleritis associated with familial Mediterranean fever.

Scharf J, Meyer E, Zonis S.

PMID: 4025479 [Indexed for MEDLINE]

5490. J Clin Gastroenterol. 1985 Aug;7(4):296-300.

Crohn's ileitis complicated by amyloidosis: observations and therapeutic considerations.

Becker SA, Bass D, Nissim F.

We present a patient with clinically asymptomatic amyloidosis associated with Crohn's ileitis. A distinction should be made between immunocytic dyscrasia associated with amyloidosis (formerly primary or myeloma-associated amyloidosis) and acquired systemic amyloidosis (formerly secondary amyloidosis). We compare the natural course of amyloidosis complicating Crohn's disease with these complicating familial Mediterranean fever (FMF), and discuss the role of resection and the rationale behind colchicine therapy. Our patient is the first reported case in which colchicine therapy alone has been successful in the prophylactic treatment of amyloidosis complicating Crohn's ileitis.

PMID: 2864372 [Indexed for MEDLINE]

5491. Med Clin (Barc). 1985 Jul 6;85(6):213-6.

[Familial Mediterranean fever. Review of 16 cases].

[Article in Spanish]

López Vivancos J, Vilaseca J, Arnau JM, Bacardí R.

PMID: 4033280 [Indexed for MEDLINE]

5492. Harefuah. 1985 Jun 16;108(12):608-10.

[C5a inhibitor as a regulator of inflammation in serosal and synovial tissues--the significance of its deficiency in familial Mediterranean fever].

[Article in Hebrew]

Matzner Y.

PMID: 4065729 [Indexed for MEDLINE]

5493. J Rheumatol. 1985 Jun;12(3):603-4.

Cervical spine involvement in familial Mediterranean fever.

Sukenik S, Horowitz J, Boehm R, Bar-Ziv J.

We report a case of familial Mediterranean fever (FMF) complicated by nephrotic syndrome and renal failure due to amyloidosis. This case is unique in that the severity of joint involvement necessitated bilateral hip replacement and later caused cervical apophyseal joint fusion, the latter being a lesion not previously

described in the course of FMF.

PMID: 4045861 [Indexed for MEDLINE]

5494. Trop Geogr Med. 1985 Jun;37(2):167-70.

Renal amyloidosis in Jordan.

Amr SS, Hamzeh YS.

Twenty cases of renal amyloidosis were observed among 182 patients who underwent kidney biopsy at Jordan University Hospital (JUH) during the period 1979-1983. Eight cases were classified as primary amyloidosis while the remaining 12 were secondary to various underlying diseases, the most significant one was familial Mediterranean fever (FMF). Comparison of incidence of renal amyloidosis in kidney biopsy series from neighbouring countries is presented.

PMID: 4035783 [Indexed for MEDLINE]

5495. J Oral Maxillofac Surg. 1985 Jun;43(6):466-8.

Protracted temporomandibular joint arthritis in familial Mediterranean fever.

Tovi F, Barmeir E, Peist M, Bar-Ziv J.

PMID: 3858487 [Indexed for MEDLINE]

5496. Harefuah. 1985 May 1;108(9):437-9.

[Colchicine overdose].

[Article in Hebrew]

Lewinsohn G, Cohen N, Leonov Y.

PMID: 4029786 [Indexed for MEDLINE]

5497. Arch Dis Child. 1985 May;60(5):477-9.

Remission of progressive renal failure in familial Mediterranean fever during colchicine treatment.

Herlin T, Storm K, Hamborg-Petersen B.

Colchicine was administered to a 12 year old girl with familial Mediterranean fever and progressive renal insufficiency. There was immediate resolution of abdominal attacks together with a dramatic fall in the serum creatinine concentration and the degree of proteinuria. At the same time her severely impaired growth was stimulated.

PMCID: PMC1777329

PMID: 4015155 [Indexed for MEDLINE]

5498. Lab Invest. 1985 May;52(5):485-9.

Isolation and characterization of amyloid protein AA in the Abyssinian cat.

DiBartola SP, Benson MD, Dwulet FE, Cornacoff JB.

Amyloid fibrils were isolated by extraction in deionized water from the kidneys of an Abyssinian cat with familial renal amyloidosis. The fibrils were suspended in a buffer containing 6 M guanidine hydrochloride and reduced and alkylated using dithiothreitol and iodoacetic acid. The resulting amyloid fibril subunit protein was isolated by chromatography on a column of Sepharose CL6B. It was fragmented using cyanogen bromide, and the resultant peptides were separated by reverse phase high performance liquid chromatography. The protein was characterized by determination of the amino acid sequence of the cyanogen bromide fragments using a Beckman 890C sequencer. The primary structure of this amyloid

fibril subunit protein showed strong homology with amyloid protein AA found in man and animals with spontaneous and experimentally induced reactive systemic amyloidosis. This study confirms the reactive nature of familial renal amyloidosis in the Abyssinian cat and suggests that this disease may be a valuable spontaneous animal model for the study of familial Mediterranean fever in man.

PMID: 3990242 [Indexed for MEDLINE]

5499. Harefuah. 1985 Apr 15;108(8):386-7.

[Fever as the only manifestation of recurrent familial Mediterranean fever].

[Article in Hebrew]

Harats N.

PMID: 4043850 [Indexed for MEDLINE]

5500. Revmatologiya (Mosk). 1985 Apr-Jun;(2):61-4.

[Colchicine (problems of its pharmacokinetics, mechanism of action and use in therapeutic practice)].

[Article in Russian]

Kochubei LN, Tatevosian KG.

PMID: 3901198 [Indexed for MEDLINE]

5501. Presse Med. 1985 Mar 9;14(10):586-8.

[Familial paroxysmal polyserositis. Previously unpublished peritoneal

complications. A case].

[Article in French]

Bitar E, Rizk A, Nasr W, Gédéon EM, Tabbara W.

A young unmarried Lebanese woman presenting with periodic disease (familial paroxysmal polyserositis) since she was 3 months old developed recurrent abundant ascites at the age of 21 years. Several hundred millilitres of strongly eosinophilic fluid were evacuated. Exploratory laparotomy unexpectedly disclosed an encapsulating peritonitis with adhesions involving the small bowel and the ascending colon; there were masses of lipid-laden cells, clusters of cholesterol/crystals and marked mesoepithelial reaction. In view of the patient's dramatic response to colchicine 2 mg/day, these findings were regarded as being related to the periodic disease.

PMID: 3157938 [Indexed for MEDLINE]

5502. Nihon Naika Gakkai Zasshi. 1985 Mar;74(3):346-50.

[A case of periodic fever].

[Article in Japanese]

Oimomi M, Taki J, Inui A, Ishihara K, Saeki S, Yoshida Y, Baba S.

PMID: 4009018 [Indexed for MEDLINE]

5503. Pediatriia. 1985 Mar;(3):63-8.

[Current status of the question of periodic disease].

[Article in Russian]

Astvatsatrian VA, Torosian EKh.



PMID: 3889821 [Indexed for MEDLINE]

5504. Klin Monbl Augenheilkd. 1985 Feb;186(2):117-20.

[Television fluorescence angiography and image analysis: clinical use with a case example].

[Article in German]

Körber N, Jung F, Kieseewetter H, Wolf S, Prünke C, Stolze H, Reim M.

The clinical application of TV fluorescein angiography with subsequent image analysis as performed on a patient with familial Mediterranean fever (FMF), who was suffering from an arterial branch occlusion, is discussed. In addition, the diagnostic relevance of rheologic parameters to the diagnostic evaluation of retinal circulatory disorders is emphasized.

DOI: 10.1055/s-2008-1050888

PMID: 3999590 [Indexed for MEDLINE]

5505. Proc Natl Acad Sci U S A. 1985 Feb;82(4):1232-6.

Circulating hydroxy fatty acids in familial Mediterranean fever.

Aisen PS, Haines KA, Given W, Abramson SB, Pras M, Serhan C, Hamberg M, Samuelsson B, Weissmann G.

Episodes of fever, serositis, and arthritis in familial Mediterranean fever (FMF) suggested circulating mediators of acute inflammation (e.g., neutrophil activation). The mean serum neutrophil-aggregating activity of 51 FMF patients was  $2.5 \pm 0.2$  cm<sup>2</sup>/min, compared to  $1.0 \pm 0.1$  cm<sup>2</sup>/min in 20 normal controls ( $P$  less than 0.0002). Lipid extracts of FMF sera retained neutrophil-aggregating activity and had UV absorbance peaks at 269 and 279 nm, indicating the presence of lipids with a conjugated triene structure. Chromatography of extracts yielded peaks that were coeluted with reference dihydroxycosatetraenoic acids, had UV

absorbance peaks at 259, 269, and 279 nm, and possessed neutrophil-aggregating activity. The presence of leukotriene B<sub>4</sub> was excluded by chromatography following methyl-esterification. Monohydroxy compounds identified in FMF extracts by gas chromatography/mass spectrometry included 5-hydroxyicosatetraenoic acid, and 9- and 13-hydroxyoctadecadienoic acids. Hydroxy acids were present in 19 of 31 FMF sera and absent in extracts of sera from 8 patients with active systemic lupus erythematosus, 7 with fever from infection, and 12 normal controls. The finding of circulating mono- and dihydroxy fatty acids in FMF suggests that defects in the formation or elimination of these compounds might play a role in the pathogenesis of FMF.

PMCID: PMC397229

PMID: 3919389 [Indexed for MEDLINE]

5506. Vestn Akad Med Nauk SSSR. 1985;(11):32-9.

[Various indicators of the phagocytic activity of neutrophils in patients with periodic disease uncomplicated and complicated by amyloidosis].

[Article in Russian]

Kochubei LN, Vinogradova OM, Shovskaia TN.

PMID: 4090651 [Indexed for MEDLINE]

5507. Vutr Boles. 1985;24(5):93-6.

[Patient with familial Mediterranean fever and amyloidosis].

[Article in Bulgarian]

Atanasova P.

A patient is described, with genetic form of amyloidosis with family Mediterranean fever. The secondary amyloidosis, that developed as a complication,

has been preceded by attacks of acute articular and abdominal pains of several years. Elevated level of ethicholanolon in urine was established as well as extremely high values of serum fibrinogen, admitted to be pathognomonic signs of family Mediterranean fever. The eposition of amyloidosis is confirmed via rectal and renal punch biopsy. In spite of the diffuse character of the deposited amyloid in the renal tissue, there were still no signs of glomerular sclerosis and clinical--normal depuration renal function was observed, with normal creatinine clearance and normal nitrogenous bodies in serum. A favourable effect of colchicine therapy was observed in the patients both as regards the acute attacks of the disease and as regards the renal involvement.

PMID: 4090459 [Indexed for MEDLINE]

5508. Duodecim. 1985;101(24):2428-32.

[Mediterranean fever in Finland?].

[Article in Finnish]

Välimäki M, Anttila PM, Pentikäinen PJ, Törnroth T, Maury P, Nyman JA.

PMID: 4085375 [Indexed for MEDLINE]

5509. Harefuah. 1985 Jan 1;108(1):1-2.

[Effect of colchicine on the amyloidosis of familial Mediterranean fever].

[Article in Hebrew]

Zemer D, Sohar E, Pras M, Cabili S, Gafni J.

PMID: 3996948 [Indexed for MEDLINE]

5510. Proc Eur Dial Transplant Assoc Eur Ren Assoc. 1985;21:709-11.

The prevention of amyloidosis in familial Mediterranean fever with colchicine.

Cabili S, Zemer D, Pras M, Aviram A, Sohar E, Gafni J.

Colchicine has been used since 1972 to prevent the acute attacks of familial Mediterranean fever. The present study shows that colchicine is also effective in the prevention of amyloidosis. If initiated in patients without evidence of renal disease there is no appearance of proteinuria and no progression to renal insufficiency over long follow-up periods. Moreover, it ameliorates the course of the disease in patients with amyloid nephropathy and normal renal function. It does not alter the course of the disease if initiated after renal function is even mildly impaired. These findings suggest that colchicine prevents the new deposition of amyloid.

PMID: 3991564 [Indexed for MEDLINE]

5511. Vrach Delo. 1985 Jan;(1):20-2.

[Lesions of the gallbladder and biliary tract in periodic disease].

[Article in Russian]

Arutiunian VM, Eganian GA, Martirosian RS.

PMID: 3984317 [Indexed for MEDLINE]

5512. Ann Intern Med. 1985 Jan;102(1):71-2.

Serum amyloid A protein in familial Mediterranean fever.

Knecht A, de Beer FC, Pras M.

PMID: 3966749 [Indexed for MEDLINE]

5513. Ter Arkh. 1985;57(8):66-8.

[Comparative evaluation of the effects of colchicine and colchamine on the course of hereditary (in periodic disease) and experimental amyloidosis].

[Article in Russian]

Kochubeĭ LN, Vinogradova OM, Makarova OV, Chegaeva TV.

PMID: 3906997 [Indexed for MEDLINE]

5514. Vutr Boles. 1985;24(5):34-8.

[Colchicine: new therapeutic possibilities].

[Article in Bulgarian]

Chaldŭkov G, Vankov V.

PMID: 3879047 [Indexed for MEDLINE]

5515. Isr J Med Sci. 1985 Jan;21(1):83-5.

Henoch-Schönlein purpura and familial Mediterranean fever.

Schlesinger M, Rubinow A, Vardy PA.

PMID: 3871752 [Indexed for MEDLINE]

5516. Ann Rheum Dis. 1984 Dec;43(6):857.

Colchicine in systemic amyloidosis.

Akoğlu E, Akoğlu T, Erken E.

PMCID: PMC1001553

PMID: 6524989 [Indexed for MEDLINE]

5517. Tanpakushitsu Kakusan Koso. 1984 Dec;29(14):1770-82.

[Amyloidosis and amyloid protein].

[Article in Japanese]

Araki S.

PMID: 6398463 [Indexed for MEDLINE]

5518. Presse Med. 1984 Nov 10;13(40):2458.

[Can colchicine cure renal amylosis in periodic disease?].

[Article in French]

Lagrue G, Koeger AC, Sobel A.

PMID: 6239234 [Indexed for MEDLINE]

5519. Presse Med. 1984 Nov 3;13(39):2393.

[The curative effect of colchicine in renal amyloidosis cannot currently be held to have been proven].

[Article in French]

Méry JP.

PMID: 6239216 [Indexed for MEDLINE]

5520. Monatsschr Kinderheilkd. 1984 Nov;132(11):867-9.

[Familial Mediterranean fever].

[Article in German]

Schindera F, Löw R, Langer KH.

After 10 years of disease a Turkish boy and his sister were diagnosed to suffer from familial Mediterranean fever. Because an elder brother showed the symptoms of recurrent attacks of fever, abdominal pain, arthralgias and nephrotic syndrome due to amyloidosis. When these symptoms occur in residents of the Mediterranean area, the diagnosis "Familial Mediterranean Fever" has to be taken into account.

PMID: 6513948 [Indexed for MEDLINE]

5521. Eur J Clin Invest. 1984 Oct;14(5):398-401.

Degradation of amyloid A and serum amyloid A by red blood cell haemolysate in patients with familial mediterranean fever.

Shainkin-Kestenbaum R, Winikoff Y, Zimlichman S, Gorodischer R, Pras M.

Enzymatic activity for the degradation of serum amyloid A (SAA) and amyloid A (AA) was detected in erythrolysates of normal subjects and patients with familial mediterranean fever. A significant difference between the activity of normal subjects and patients was not found. Serum inhibited the SAA (but not the AA) haemolysate proteolytic activity. Interindividual variation in the susceptibility of SAA to degradation by RBC haemolysates was shown. The original digestible

fraction of SAA became gradually resistant to proteolytic cleavage over a 9 month period while the susceptibility of AA to degradation remained unchanged in this time period. These findings suggest that enzymatic degradation of SAA depends on the source of SAA, as well as inhibitory activity in serum.

PMID: 6437839 [Indexed for MEDLINE]

5522. Clin Exp Rheumatol. 1984 Oct-Dec;2(4):354-5.

Suppressor cell deficiency and elevated circulating immune complexes in familial Mediterranean fever.

Schlesinger M, Vardy PA, Handzel ZT, Ilfeld D, Kotkes P, Levin S.

PMID: 6241862 [Indexed for MEDLINE]

5523. Klin Med (Mosk). 1984 Sep;62(9):104-7.

[State of the stomach and duodenum in patients with periodic disease].

[Article in Russian]

Arutiunian VM, Eganian GA, Minasian GA.

PMID: 6492728 [Indexed for MEDLINE]

5524. N Engl J Med. 1984 Aug 2;311(5):325-6.

C5a-inhibitor deficiency--a role in familial Mediterranean fever?

Schwabe AD, Lehman TJ.

DOI: 10.1056/NEJM198408023110510



PMID: 6738643 [Indexed for MEDLINE]

5525. N Engl J Med. 1984 Aug 2;311(5):287-90.

C5a-inhibitor deficiency in peritoneal fluids from patients with familial Mediterranean fever.

Matzner Y, Brzezinski A.

Normal peritoneal fluid contains an inhibitor of neutrophil chemotaxis that acts by antagonizing the complement-derived chemotactic anaphylatoxin C5a. The inhibitor resembles a substance previously described in synovial fluids and is a protein with a molecular weight of approximately 40,000 as determined by gel filtration. In contrast, levels of inhibitory activity in peritoneal fluids from five patients with familial Mediterranean fever were decreased to less than 10 per cent of those found in normal subjects. Gel filtration of peritoneal and synovial fluids from these patients did not yield any fraction with inhibitory activity. We suggest that C5a-inhibitor deficiency in joint and peritoneal fluids from patients with familial Mediterranean fever may have a role in the pathogenesis of the inflammatory attacks characteristic of this disease.

DOI: 10.1056/NEJM198408023110503

PMID: 6738641 [Indexed for MEDLINE]

5526. Lancet. 1984 Jul 7;2(8393):41-2.

Diagnosing familial Mediterranean fever.

Barakat MH, El-Sobki NI, El-Khawad AO, Gumma KA, Fenech FF.

PMID: 6145957 [Indexed for MEDLINE]

5527. Tissue Antigens. 1984 Jul;24(1):65-6.

Familial Mediterranean fever: no linkage with HLA.

Schlesinger M, Ilfeld DN, Zamir R, Brautbar C.

PMID: 6484932 [Indexed for MEDLINE]

5528. Am J Med Sci. 1984 Jul-Aug;288(1):40-3.

Isolated adrenal mineralocorticoid deficiency due to amyloidosis associated with familial Mediterranean fever.

Agmon D, Green J, Platau E, Better OS.

A patient with familial Mediterranean fever (FMF) associated with renal amyloidosis, presented with hyperkalemia and acidosis which were excessive to his moderate degree of azotemia. The cause of this abnormality was isolated hypoaldosteronism with otherwise normal adrenal function and tubular capacity to transport potassium. This selective involvement of the zona glomerulosa stands in marked contrast to the usual sparing of the glomerulosa seen in post mortem studies of patients with FMF and amyloidosis reported from this country.

PMID: 6465194 [Indexed for MEDLINE]

5529. Lancet. 1984 Jun 30;1(8392):1463-4.

Hyperimmunoglobulinaemia D and periodic fever.

Reeves WG, Mitchell JR.

PMID: 6145896 [Indexed for MEDLINE]

5530. Presse Med. 1984 Jun 16;13(25):1578.

[Pericarditis in periodic disease].

[Article in French]

Adoue D, Arlet-Suau E, Couret B, Fedou R, Chiotasso P, Sassi JL.

PMID: 6234550 [Indexed for MEDLINE]

5531. Lancet. 1984 May 19;1(8386):1130-1.

Metaraminol provocation test for familial Mediterranean fever.

Cattan D, Dervichian M, Courillon A, Nurit Y.

PMID: 6144866 [Indexed for MEDLINE]

5532. Lancet. 1984 May 19;1(8386):1087-90.

Hyperimmunoglobulinaemia D and periodic fever: a new syndrome.

van der Meer JW, Vossen JM, Radl J, van Nieuwkoop JA, Meyer CJ, Lobatto S, van Furth R.

Six patients of Dutch ancestry with a long history of recurrent attacks of fever of unknown cause were found to have a high serum IgD level and a large number of plasma cells with cytoplasmic IgD in the bone marrow. Because the clinical picture in some ways resembled that of familial Mediterranean fever (FMF), sera of patients with FMF were also investigated; only one of eight such patients had a raised serum IgD.

PMID: 6144826 [Indexed for MEDLINE]

5533. Minerva Med. 1984 May 7;75(19):1147-52.

[Familial Mediterranean fever. Description of a case observed by us].

[Article in Italian]

Passiu G, Perpignano G, La Nasa G, Carcassi U.

Familial mediterranean fever (FMF) is an hereditary disorder characterized by attacks of febrile serosal inflammation involving pleura or peritoneum and synovium, followed usually by insidious onset of amyloidosis. In other patients amyloidosis of AA-type is the only finding of the disease. This disorder is common in Jews of Sephardi and Ashkenazi ancestry, Arabs, Armenians and Turks. In this work the clinico-biological features and the therapeutical aspects of a patient, suffering from FMF, of Italian ancestry are presented.

PMID: 6728265 [Indexed for MEDLINE]

5534. Akush Ginekol (Mosk). 1984 May;(5):54-5.

[Sexual development of girls with periodic disease].

[Article in Russian]

Akunts KB, Sarkisian RG, Igitian GV.

PMID: 6465453 [Indexed for MEDLINE]

5535. Isr J Med Sci. 1984 May;20(5):381-7.

Adrenal insufficiency in a general hospital over a 14-year period.

Shapiro M, Zalewski S, Steiner Z, Bernheim J, Nabriski D, Taragan R, Bruderman I, Shinkman L.

Over a 14-year period, 26 patients with adrenal insufficiency of multiple etiology were evaluated. Eight were diagnosed at autopsy, six of whom had acute

bilateral adrenal hemorrhage. Nine had chronic adrenal insufficiency. Of these, five were idiopathic and three had polyglandular disorders. Four others had tuberculosis. Six of nine patients with chronic adrenal insufficiency were hyperpigmented. Unusual manifestations of adrenal hypocorticism included hypercalcemia, flaccid paralysis, and joint contractures. The presence of multiple hormonal deficiencies focused the diagnosis on hypopituitarism. Two cases of isolated ACTH deficiency were detected. Patients with familial Mediterranean fever with amyloidosis commonly presented with reduced adrenal reserve rather than overt insufficiency. Metastatic cancer of the adrenal glands was a rare cause of reduced adrenal reserve.

PMID: 6088424 [Indexed for MEDLINE]

5536. J Assoc Physicians India. 1984 Apr;32(4):380-1.

Familial mediterranean fever in South India.

Singh DS.

PMID: 6746557 [Indexed for MEDLINE]

5537. Lancet. 1984 Mar 24;1(8378):656-7.

Metaraminol provocative test: a specific diagnostic test for familial Mediterranean fever.

Barakat MH, El-Khawad AO, Gumaa KA, El-Sobki NI, Fenech FF.

The diagnosis of familial Mediterranean fever has been one of exclusion. In a placebo-controlled, double-blind, cross-over study a challenge with a 10 mg dose of metaraminol infusion was followed within 48 h by a typical disease-like attack in all of 21 patients with familial Mediterranean fever but in none of 21 control subjects. The induced attacks were milder and of shorter duration than the spontaneous ones. The metaraminol-induced symptoms were similar to the natural disease attacks and could be prevented with prophylactic colchicine therapy. No

significant side-effects were observed.

PMID: 6142351 [Indexed for MEDLINE]

5538. Harefuah. 1984 Mar 1;106(5):232-3.

[Muscle pains in familial Mediterranean fever].

[Article in Hebrew]

Zemer D.

PMID: 6724421 [Indexed for MEDLINE]

5539. Harefuah. 1984 Mar 1;106(5):209-10.

[Familial Mediterranean fever presenting with recurrent severe myalgia].

[Article in Hebrew]

Kühnreich E, Naschitz JE, Kohn A, Yeshurun D.

PMID: 6724410 [Indexed for MEDLINE]

5540. Blood. 1984 Mar;63(3):629-33.

Diminished activity of a chemotactic inhibitor in synovial fluids from patients with familial Mediterranean fever.

Matzner Y, Partridge RE, Levy M, Babior BM.

Synovial fluids from patients with osteoarthritis contain a chemotactic inhibitor that acts by antagonizing the complement-derived chemotactic anaphylotoxin, C5a.

The activity of this inhibitor in synovial fluids from patients with several forms of inflammatory arthritis (rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, and gout) were comparable to the activity present in osteoarthritic synovial fluids. In contrast, levels of inhibitory activity in synovial fluids from 9 patients with familial Mediterranean fever were decreased to less than 20% of those found in osteoarthritis fluids. The possibility was considered that the diminished inhibitory activity in fluids from patients with familial Mediterranean fever plays a part in the pathogenesis of the inflammatory attacks characteristic of this disease.

PMID: 6365203 [Indexed for MEDLINE]

5541. Presse Med. 1984 Feb 25;13(8):475-7.

[Amyloidosis in periodic disease].

[Article in French]

Méry JP.

PMID: 6230628 [Indexed for MEDLINE]

5542. Biomed Pharmacother. 1984;38(9-10):448-55.

Inflammatory reaction in familial Mediterranean fever (FMF) before and with colchicine therapy.

Ollier-Hartmann MP, Godeau P, Hartmann L.

The familial mediterranean fever (FMF) is an inherited, autosomal, recessive disorder which occurs predominantly but not exclusively in Sephardic Jews. It is characterized by a total increase of blood complement components, particularly C4, without any molecular anomaly and associated with an increase in other inflammatory proteins. With colchicine therapy, the symptomatology observed regresses or diminishes and onset of amyloidosis is prevented but the

inflammatory and biochemical syndrome persists.

PMID: 6529602 [Indexed for MEDLINE]

5543. Ter Arkh. 1984;56(10):44-7.

[Immunomorphological evaluation of intestinal function in periodic disease patients].

[Article in Russian]

Mamikonian RS, Arutiunian VM, Eganian GA.

Based on clinico-endoscopic, x-ray, immunological and immunohistochemical studies the authors demonstrate the role of disorders in the components of humoral and cellular immunity in the development of intestinal inflammation and amyloidosis in patients with periodical disease. Circulatory disorders, congestive hyperemia, edema of the intestinal mucosa, and spasmodic intestinal dyskinesia that develop during an attack of periodical disease are the initial components in the pathogenesis of inflammatory intestinal lesions seen during periodical disease.

PMID: 6523360 [Indexed for MEDLINE]

5544. Adv Nephrol Necker Hosp. 1984;13:261-70.

Recent advances in familial Mediterranean fever.

Pras M, Gafni J, Jacob ET, Cabili S, Zemer D, Sohar E.

PMID: 6433668 [Indexed for MEDLINE]

5545. Bull Hosp Jt Dis Orthop Inst. 1984 Spring;44(1):82-5.



Traumatic intraosseous ganglion. A case report.

Kenan S, Robin GC, Floman Y.

The rapid development of an intraosseous ganglion following an intraarticular fracture of the distal radius in a patient suffering from familial Mediterranean fever is presented. The case supports the view that trauma may be an etiological factor in the genesis of intraosseous ganglia.

PMID: 6326910 [Indexed for MEDLINE]

5546. Pediatriia. 1983 Dec;(12):46-7.

[2 cases of periodic disease in children with severe symptomatology].

[Article in Russian]

Moreeva ZA.

PMID: 6672732 [Indexed for MEDLINE]

5547. Arthritis Rheum. 1983 Dec;26(12):1536.

Familial Mediterranean fever after recovery from Schönlein- Henoch syndrome.

Caglar MK.

PMID: 6651905 [Indexed for MEDLINE]

5548. Schweiz Med Wochenschr. 1983 Nov 26;113(47):1771-5.

[Familial Mediterranean fever].

[Article in German]

Brunner U, Streit H, Münch U.

The diagnosis of familial Mediterranean fever is often difficult. The typical symptoms of this disease have been observed in two Turkish patients. The diagnostic criteria are short attacks of fever recurring in varying intervals, and painful symptoms in the abdomen, chest, joints or skin. Since no specific test for familial Mediterranean fever is available, the diagnosis must be based on precise clinical criteria and a genetic disorder with autosomal recessive inheritance and predilection for people of Mediterranean stock, particularly sephardic Jews and Armenians. The therapeutic response to colchicine may confirm diagnostic accuracy. Amyloidosis is a major symptom of the disease and dominates the further clinical picture. Treatment with dimethyl sulfoxide (DMSO) may inhibit the progression of amyloidosis and improvement of renal function can be achieved.

PMID: 6658425 [Indexed for MEDLINE]

5549. Lijec Vjesn. 1983 Nov-Dec;105(11-12):466-8.

[Familial Mediterranean fever--report of a patient].

[Article in Croatian]

Domljan Z, Babić-Naglić D.

PMID: 6664205 [Indexed for MEDLINE]

5550. Am J Clin Pathol. 1983 Oct;80(4):511-4.

A case of familial Mediterranean fever with cutaneous vasculitis and immune complex nephritis: light, electron, and immunofluorescent study of renal biopsy.

Schlesinger M, Kopolovic J, Viskoper RJ, Ron N.

A 29-year-old patient suffering from familial Mediterranean fever developed severe myalgia and hematuria. Skin biopsy showed vasculitis. The kidney biopsy revealed diffuse proliferative and exudative glomerulonephritis. On immunofluorescent examination, IgM deposits accompanied by C3 were found in coarse granular peripheral distribution. Electron microscopy revealed glomerular subepithelial deposits. Familial Mediterranean fever with vasculitis and immune complex nephritis is discussed.

PMID: 6353905 [Indexed for MEDLINE]

5551. Clin Exp Immunol. 1983 Oct;54(1):73-9.

Effect of colchicine on immunoregulatory abnormalities in familial Mediterranean fever.

Schlesinger M, Ilfeld D, Handzel ZT, Altman Y, Kuperman O, Levin S, Bibi C, Netzer L, Trainin N.

The effect of colchicine on immunoregulatory T lymphocytes in children with familial Mediterranean fever (FMF) was studied. Concanavalin A (Con A)-induced suppressor cell function was significantly ( $P$  less than 0.0001) decreased in five untreated FMF patients ( $15 \pm 3\%$ , mean  $\pm$  s.e.) as compared to six age matched paediatric controls ( $46 \pm 3\%$ ) and eight healthy adults ( $49 \pm 4\%$ ). When the five untreated FMF patients' mononuclear cells were pre-incubated in vitro with Con A plus  $10^{-5}$  M colchicine, their suppressor cell function was significantly increased ( $52 \pm 10\%$ ,  $P$  less than 0.01). Similarly, oral colchicine treatment (0.5 mg twice daily) significantly ( $P = 0.02$ ) increased the five FMF patients' Con A-induced suppressor cell function to levels ( $34 \pm 6\%$ ) that were not significantly ( $P$  greater than 0.05) different than the paediatric controls or the healthy adults. The percentage of OKT8+ cells (but not OKT3+ or OKT4+ cells) was significantly ( $P$  less than 0.0001) decreased in 10 untreated FMF patients ( $16.0 \pm 0.9$ ) as compared to 10 paediatric controls ( $27.6 \pm 2$ ) or 10 healthy adults ( $25.7 \pm 0.6$ ). The 10 untreated FMF patients had a significant ( $P$  less than 0.002) increase in the OKT4/OKT8 ratio ( $2.41 \pm 0.13$ ) as compared to 10 FMF patients treated with 0.5 mg twice daily of colchicine ( $1.81 \pm 0.08$ ), 10 pediatric controls ( $1.47 \pm 0.2$ ), or 10 healthy adults ( $1.78 \pm 0.11$ ).

Colchicine appears to have corrected the FMF patients' elevated OKT4/OKT8 ratio by both decreasing the percentage of OKT4+ cells and increasing (but only partially correcting) the percentage of OKT8+ cells. Thus FMF patients have a suppressor cell deficiency in which colchicine treatment corrects their deficiency of Con A-induced suppressor cell function and their elevated OKT4/OKT8 ratio. This raises the possibility that colchicine might be potentially useful as an immunomodulating drug in treating patients with autoimmune or allergic diseases associated with a suppressor cell deficiency.

PMCID: PMC1536202

PMID: 6225583 [Indexed for MEDLINE]

5552. Klin Med (Mosk). 1983 Sep;61(9):119-21.

[Efficacy of lithium carbonate in patients with periodic disease].

[Article in Russian]

Arutiunian VM, Minasian GA, Eganian GA.

PMID: 6417403 [Indexed for MEDLINE]

5553. Exp Hematol. 1983 Sep;11(8):687-700.

Cyclic hematopoiesis: disorders of primitive hematopoietic stem cells.

Quesenberry PJ.

Utilizing both in vivo and in vitro techniques, a great deal of information has been obtained on the structure and regulation of the hematopoietic cell lineages. A number of hematopoietic stem cells and regulators have now been well characterized and their possible physiologic relevance at least in part established. More recently, new "alternative" or primitive stem cells have been described which may provide important insights into the nature of hematopoietic regeneration and regulation. These include late CFUs, high proliferative

potential colony-forming cells, colony-forming unit diffusion chamber and both bipotent and blast colonies assayed in in vitro culture systems. Regulators active at these stem cell levels are also under study and in large part appear to be produced by monocytes or lymphocytes. Cyclical hematopoiesis can be viewed as a genetic abnormality at the multipotent stem cell level with defective cell production. At present however, details of the defect await further investigation possibly including an evaluation of the role of primitive stem cells and their regulators.

PMID: 6354737 [Indexed for MEDLINE]

5554. Clin Exp Immunol. 1983 Sep;53(3):659-62.

The immune system in familial Mediterranean fever.

Melamed I, Shemer Y, Zakuth V, Tzehoval E, Pras M, Spirer Z.

Familial Mediterranean fever (FMF) is a genetic disorder with an obscure aetiology. In attempts to investigate a possible immunoregulatory imbalance involved in this disease we tested 24 FMF patients for suppressor T cell activity and for chemotaxis of mononuclear cells. The suppressor T cell activity and chemotaxis were decreased in untreated FMF patients as compared to colchicine treated patients or normal controls. Amyloid FMF patients manifested significantly increased chemotactic activity, while the suppressor T cell activity was normal. This finding may extend our knowledge concerning the immune mechanism involved in FMF.

PMCID: PMC1535657

PMID: 6225577 [Indexed for MEDLINE]

5555. Br J Clin Pharmacol. 1983 Aug;16(2):191-4.

The effect of long-term colchicine therapy in patients with recurrent polyserositis on the capacity of blood platelets to synthesize thromboxane A<sub>2</sub>.

Levy M, Eldor A, Zylber-Katz E, Eliakim M.

Thromboxane B<sub>2</sub> (TXB<sub>2</sub>) production during platelet activation was measured in 13 patients with recurrent polyserositis on long-term colchicine therapy and 10 healthy controls. Plasma colchicine concentration in patients ranged between 0.8-7.8 ng/ml (2.0-19.5 X 10<sup>-9</sup> M). Thromboxane production induced during aggregation by arachidonic acid or collagen and serum TXB<sub>2</sub> levels (clotted blood, 37 degrees C, 1 h) did not differ among patients and controls. Previous studies reporting platelet function defects including anomalous TXB<sub>2</sub> production, were performed in vitro using colchicine concentrations markedly exceeding the therapeutic range.

PMCID: PMC1427989

PMID: 6615693 [Indexed for MEDLINE]

5556. Australas J Dermatol. 1983 Aug;24(2):55-62.

Review of so-called aseptic neutrophilic dermatoses.

Moschella SL.

PMID: 6362643 [Indexed for MEDLINE]

5557. J Assoc Physicians India. 1983 Jul;31(7):464-6.

Familial Mediterranean fever (report of 3 Punjabi cases).

Mani MZ, Mathew M.

PMID: 6654812 [Indexed for MEDLINE]

5558. Infection. 1983 May-Jun;11(3):173-4.

Pneumococcal cellulitis.

Mujais S, Uwaydah M.

We are reporting a case of pneumococcal cellulitis with bacteremia in a patient with familial Mediterranean fever (FMF) and nephrotic syndrome. Four cases of pneumococcal cellulitis in adults have been reported in the literature. The potential etiologic role of *Streptococcus pneumoniae* in skin infections is pointed out, and possible predisposing factors and contributory conditions are described.

PMID: 6885177 [Indexed for MEDLINE]

5559. Rev Rhum Mal Osteoartic. 1983 Apr;50(4):303-6.

[Polyarthrititis with spinal involvement associated with psoriasis and periodic disease].

[Article in French]

Wendling D, Cassou M, Guidet M.

PMID: 6879099 [Indexed for MEDLINE]

5560. FDA Drug Bull. 1983 Apr;13(1):4.

Colchicine for familial Mediterranean fever.

[No authors listed]

PMID: 6343168 [Indexed for MEDLINE]

5561. Dtsch Med Wochenschr. 1983 Feb 11;108(6):210-5.

[Familial Mediterranean fever with amyloidosis. Recent pathogenetic and therapeutic aspects].

[Article in German]

Löffler HJ, Brass H, Thoenes W, Linke RP.

Familial Mediterranean fever was diagnosed in a 34-year-old Turkish patient with severe nephrotic oedema. Immunohistochemical classification of a biopsy specimen showed amyloidosis of the AA-type. There was a definite increase of serum amyloid-A-protein (SAA). The typical recurrent fever, attacks of abdominal pain with symptoms of subileus and joint swelling could be treated successfully with colchicine, the oedema with diuretics. The progression of renal failure and proteinuria as indicator of the degree of amyloid-induced renal damage remained unaffected by this treatment. With dimethyl-sulfoxide (DMSO) a marked improvement in renal function and a lowering of the SAA level could be achieved. Thus this treatment inhibits the progression of amyloidosis of the AA-type in Mediterranean fever and may be considered for other forms of AA-type amyloidoses. It is possible that the lowering of the SAA-serum concentration and the improvement of renal function is due to an antiphlogistic effect of DMSO, the mechanism of action of which is so far unknown.

DOI: 10.1055/s-2008-1069529

PMID: 6825596 [Indexed for MEDLINE]

5562. Exp Eye Res. 1983 Feb;36(2):181-6.

Immunohistochemical identification of the AA protein in lattice dystrophy.

Wheeler GE, Eiferman RA.

We examined the amyloid deposits of lattice dystrophy type I for common components of primary and secondary amyloid using the sensitive unlabelled antibody peroxidase-antiperoxidase technique. Tissue sections of formalin-fixed, paraffin-embedded specimens from three patients with lattice dystrophy were reacted with antisera specific for free immunoglobulin light chains, prealbumin, amyloid A (AA) protein, and amyloid P (AP) protein. The lattice amyloid was



positive for the AA protein associated with secondary amyloid. The deposits were also stained with the protein AP antiserum in each case. We were unable to detect the presence of immunoglobulin light chains associated with primary amyloid or prealbumin associated with another hereditary form of amyloid. Sera from two patients with lattice dystrophy were tested for the presence of the serum amyloid A related protein, the apparent precursor of AA amyloid, by immunoelectrophoresis and immunodiffusion. The sera showed no reaction with the AA antiserum with these techniques. Lattice amyloid differed from secondary systemic amyloid in the reaction with potassium permanganate. Congo red staining of lattice deposits was not abolished by treatment with potassium permanganate. Our findings suggest that the amyloid proteins in lattice dystrophy are antigenically similar to those of secondary amyloid and the hereditary form associated with familial Mediterranean fever.

PMID: 6337859 [Indexed for MEDLINE]

5563. Khirurgiia (Mosk). 1983 Feb;(2):38-40.

[Abdominal form of periodic disease].

[Article in Russian]

Ananikian PP, Grigorian SKh.

PMID: 6221147 [Indexed for MEDLINE]

5564. West J Med. 1983 Jan;138(1):43-6.

Colchicine use for familial Mediterranean fever. Observations associated with long-term treatment.

Peters RS, Lehman TJ, Schwabe AD.

Of 85 patients with familial Mediterranean fever receiving continuous prophylactic colchicine therapy, 62 (73 percent) have had a significant reduction

in the severity and frequency of their attacks. All 62 have been observed for three years or more, for a total of 4,680 patient-months and a mean duration of 75.5 months. Of the 85 patients, 23 (27 percent) did not complete three years of treatment for a variety of reasons. Diarrhea was the most common side effect, necessitating reduction of colchicine dosage in 12 patients, but discontinuation of treatment in only one. No other significant side effects were observed. Continuous, prophylactic colchicine therapy is effective in preventing the recurrent febrile paroxysms of familial Mediterranean fever and is indicated in those patients who are incapacitated by frequent attacks or who are at risk for amyloidosis developing.

PMCID: PMC1010626

PMID: 6837018 [Indexed for MEDLINE]

5565. Ter Arkh. 1983;55(6):110-4.

[The effect of colchicine on hereditary and experimental amyloidosis].

[Article in Russian]

Vinogradova OM, Kochubeĭ LN, Chegaeva TV, Kapinus LN.

PMID: 6612611 [Indexed for MEDLINE]

5566. Sov Med. 1983;(6):98-100.

[ACute abdomen syndrome in periodic disease].

[Article in Russian]

Tsorionov BI.

PMID: 6612490 [Indexed for MEDLINE]

5567. Ter Arkh. 1983;55(6):51-5.

[Cytochemical characteristics of the enzyme spectrum of peripheral blood leukocytes in patients with periodic disease and amyloidosis].

[Article in Russian]

Kochubeĭ LN, Vinogradova OM, Komissarova IA, Tatevosian KG, Shovskaia TN.

PMID: 6310810 [Indexed for MEDLINE]

5568. Klin Med (Mosk). 1983 Jan;61(1):43-5.

[Laparoscopy in the abdominal form of periodic disease].

[Article in Russian]

Ananikian PP, Grigorian SKh.

PMID: 6220176 [Indexed for MEDLINE]

5569. Can Med Assoc J. 1982 Dec 15;127(12):1163-4.

Long-term colchicine therapy for renal amyloidosis in familial Mediterranean fever.

Walker F, Bear RA.

PMCID: PMC1874754

PMID: 7139463 [Indexed for MEDLINE]

5570. Ann Rheum Dis. 1982 Dec;41(6):587-92.

Prolonged dimethylsulphoxide treatment in 13 patients with systemic amyloidosis.

Ravid M, Shapira J, Lang R, Kedar I.

Continuous oral dimethylsulphoxide (DMSO) treatment (7-15 g/day) was given to 3 patients with amyloidosis of familial Mediterranean fever (FMF), 3 patients with idiopathic amyloidosis, and 7 patients with secondary amyloidosis. The nephrotic syndrome and various degrees of renal insufficiency were the major clinical manifestation in all case. Renal function was used as the main parameter for evaluation of therapy. DMSO treatment for 7-16 months produced no effect in the FMF patients and in the patient with idiopathic amyloidosis; they all ran the predictable clinical course of their disease and either died of cardiac failure or have been maintained on chronic haemodialysis. In the 7 patients with secondary amyloidosis an unequivocal improvement of renal function was observed following 3-6 months of DMSO treatment. It was shown by a 30-100% rise of creatinine clearance and a decline in proteinuria. This new equilibrium has been maintained as long as DMSO was administered. No serious side effects of DMSO were encountered. Mild nausea and an unpleasant breath odour were the patients' main concern. We conclude that a therapeutic trial with oral DMSO is warranted in all patients with secondary amyloidosis. This treatment is unpleasant but bears no exceptional risks. It may significantly prolong life, though its effect on amyloid deposits themselves is doubtful.

PMCID: PMC1000989

PMID: 7149795 [Indexed for MEDLINE]

5571. J Am Vet Med Assoc. 1982 Nov 15;181(10):1097-101.

Mechanisms of immune deficiency diseases of animals.

Perryman LE.

PMID: 6757213 [Indexed for MEDLINE]

5572. *Pediatr Med Chir.* 1982 Nov-Dec;4(6):593-600.

[Childhood periodic syndromes and their long-term development].

[Article in Italian]

Cavazzuti GB, Ferrari P.

The long term development of periodic syndromes among children is little known. Our research has revealed that about one third of periodic headaches, two thirds of cyclic vomiting and half the cases of recurring abdominal pain disappear either before puberty or during adolescence. Other Authors have shown that this also happens in most cases of early-onset vertigo. The remaining headache cases develop into migraines in adults. When there is persistent cyclic vomiting, the collateral neurologic phenomena (headaches, vertigo, pallor, hypotonia, drowsiness) become more intense. This also happens in some cases of abdominal pain and paroxysmal vertigo which start in late childhood. Other sufferers from acute abdominal pain develop ulcers, gastroduodenitis and colitis as adults. Altogether, some infantile periodic syndromes (in particular the multi-symptomatic ones) have a common outcome, i.e. develop into more or less typical migraine syndromes. In these cases one can presume a common pathogenetic mechanism. In those cases where the outcome is favorable the pathogenesis may be different. These cases may often be spotted in early childhood on account of the monosymptomatic nature of the complaint or the absence of collateral neurologic symptoms as well as of the infrequency of critical episodes.

PMID: 6927413 [Indexed for MEDLINE]

5573. *Lakartidningen.* 1982 Oct 27;79(43):3906-7.

[Familial Mediterranean fever].

[Article in Swedish]

Järnerot G, Barr J, Rolny P.

PMID: 7154763 [Indexed for MEDLINE]

5574. Clin Exp Immunol. 1982 Oct;50(1):99-106.

Correction of a suppressor cell deficiency in four patients with familial Mediterranean fever by in vitro or in vivo colchicine.

Ilfeld D, Kuperman O.

PMCID: PMC1536837

PMID: 6217006 [Indexed for MEDLINE]

5575. Am J Med Sci. 1982 Sep-Oct;284(2):2-7.

Microtubules in PMNs from patients with familial Mediterranean fever.

Bar-Eli M, Wilson L, Peters RS, Schwabe AD, Territo MC.

Polymorphonuclear (PMN) cells derived from patients with Familial Mediterranean Fever (FMF) were evaluated in vitro for the function and concentration of their microtubules. Using the time-decay colchicine binding assay to determine the tubulin concentration in PMN cells, no difference was found in PMN cells derived from FMF patients in comparison with those from normal healthy subjects. Colchicine treatment had no effect on the detectable tubulin concentration in the cells. The mobility of fluorescent con A(F-con A)-receptor complexes on PMN membranes was used to test the function of the microtubules. PMNs from untreated FMF patients showed the same pattern of con A cap formation as seen in normal cells. PMNs derived from colchicine treated patients, however, showed 22-32% spontaneous cap formation. These cells also showed 10-30% more capping in comparison with normal or untreated FMF cells, for any given in vitro colchicine concentration, suggesting that at therapeutic doses, the colchicine does accumulate in the PMNs in vivo. We were unable to demonstrate a microtubule defect in the neutrophils from FMF patients in these studies.

PMID: 7124787 [Indexed for MEDLINE]

5576. Am J Med. 1982 Sep;73(3):426-8.

Amyloidosis associated with renal cell carcinoma of the AA type.

Pras M, Franklin EC, Shibolet S, Frangione B.

Amyloid fibrils were found at postmortem examination in a 70 year old woman with generalized amyloidosis associated with renal carcinoma (hypernephroma).

Clinically, her amyloid disease presented as nephrotic syndrome. It was demonstrated by electrophoretic and amino acid sequence analysis studies that the amyloid fibrils contained AA protein identical to that found in amyloidosis associated with chronic inflammatory and infectious diseases as well as in the genetic form of familial Mediterranean fever.

PMID: 7124769 [Indexed for MEDLINE]

5577. Medicine (Baltimore). 1982 Sep;61(5):269-92.

Fever of undetermined origin: diagnosis and follow-up of 105 cases, 1970-1980.

Larson EB, Featherstone HJ, Petersdorf RG.

PMID: 6287162 [Indexed for MEDLINE]

5578. Dig Dis Sci. 1982 Aug;27(8):723-7.

Gastrointestinal effects of long-term colchicine therapy in patients with recurrent polyserositis (familial mediterranean fever).

Ehrenfeld M, Levy M, Sharon P, Rachmilewitz D, Eliakim M.

Twelve patients with recurrent polyserositis (RP, familial Mediterranean fever) on colchicine prophylaxis (1.0-2.0 mg daily) for three years or more were

evaluated for the presence of gastrointestinal effects possibly attributable to the drug. Two patients had bulky stools, two others had transient diarrhea, and one had heartburn. Serum vitamin B12, calcium, and carotene levels were normal in all cases, and D-xylose absorption was normal in 11 of the 12. Three patients had mild steatorrhea (7.5, 7.9, and 9.9 g daily). Jejunal biopsies from these and a fourth patient with bulky stools but normal fecal fat excretion showed no abnormal histological changes. However, (Na + K)-ATPase activity was significantly decreased in all four cases. Colchicine had to be discontinued in only one of the 12 cases. It is concluded that mild steatorrhea and enzyme inhibition may occur in patients on long-term colchicine prophylaxis and that careful periodic observations for this and other adverse effects is imperative in such patients.

PMID: 6284460 [Indexed for MEDLINE]

5579. Rev Clin Esp. 1982 Jul 15-31;166(1-2):83-5.

[Familial Mediterranean fever and amyloidosis].

[Article in Spanish]

Mairata Bosch S, Alarcón Zurita A, Dalmau Diana M, Bestard Palmer J, Pizá Buñola C, Morey Molina A, Marco Franco JE.

PMID: 7146526 [Indexed for MEDLINE]

5580. Dtsch Med Wochenschr. 1982 Jul 2;107(26):1003-7.

[Recurrent fever of unknown etiology lasting more than 6 months. Report on 85 patients].

[Article in German]

Winckelmann G, Lütke A, Löhner J.



85 patients having recurrent fever of unclarified aetiology of more than 38.5 degrees C for more than 6 months were examined in a prospective study. Of these, 10 had an inflammation due to pathogens, 12 a malignant disease, 15 a collagenous or inflammatory vascular disease, while 9 had various diseases, 5 a familial Mediterranean fever and 18 a "periodic fever". In 16 patients, in most of whom the course of the disease extended over several years, the cause of the fever could not be clarified. Among the patients with polycyclic fever over many years or decades, alternating with symptom-free intervals, one can differentiate especially the systemic Still's syndrome, which also occurs in adults and which is identical with the so-called subsepsis allergica, the familial Mediterranean fever and the "periodic fever". There are no satisfactory pointers towards the existence of a relapsing fever of its own caused by an increase of unconjugated aetiocholanolone in the plasma ("aetiocholanolone fever").

DOI: 10.1055/s-2008-1070062

PMID: 7084067 [Indexed for MEDLINE]

5581. J Rheumatol. 1982 Jul-Aug;9(4):644.

Eye involvement in a patient with familial Mediterranean fever.

Yazici H, Pazarli H.

PMID: 7131467 [Indexed for MEDLINE]

5582. Arch Dermatol. 1982 Jul;118(7):453-7.

Colchicine. New uses of an old, old drug.

Malkinson FD.

PMID: 7046640 [Indexed for MEDLINE]

5583. Trop Geogr Med. 1982 Jun;34(2):189-91.

Familial mediterranean fever in Pondicherry (India).

Singh DS, Krishmenon D, Balasubramaniam R.

PMID: 7123652 [Indexed for MEDLINE]

5584. Trop Geogr Med. 1982 Jun;34(2):183-7.

Genetic and environmental factors in the aetiology of familial paroxysmal polyserositis. An analysis of 150 cases from Lebanon.

Armenian HK.

To assess the hypothesis that factors other than a single gene are involved in the aetiology of familial paroxysmal polyserositis (FPP) clinical and genetic data on 150 patients have been analyzed. The finding of a significantly lower number of observed-affected compared to the expected in the Lenz-Hogben method of analysis is not in favour for an autosomal recessive mode of inheritance. The absence of a significant difference in the proportion of affected offspring in families where one of the parents has the disease, compared to the families where the parents are normal, is further not consistent with an autosomal dominant mode of inheritance. The observation in the present study of the occurrence of the more severe forms of the disease in the familial cases compared to the non-familial, isolated cases, make a polygenic type of inheritance or an autosomal inheritance where the penetrance of the disease is influenced by extraneous factors, more likely models for the aetiology of FPP. The possible role of an atopic model for the aetiology of FPP is discussed.

PMID: 7123651 [Indexed for MEDLINE]

5585. Ann Intern Med. 1982 Jun;96(6 Pt 1):746-55.

Diffuse malignant mesothelioma. Prospective evaluation of 69 patients.

Chahinian AP, Pajak TF, Holland JF, Norton L, Ambinder RM, Mandel EM.

From 1974 to 1980, 69 patients with diffuse malignant mesothelioma were prospectively evaluated. The initial site of involvement was the pleura in 57 patients and the peritoneum in 12. Previous asbestos exposure was found in 53 patients (77%), with a shorter period of latency for peritoneal (mean, 28 years) than for pleural mesothelioma (mean, 35 years). Other associated exposure or diseases included talc, mica, familial Mediterranean fever, and diffuse lymphocytic lymphoma (one patient each). Thrombocytosis was common, as were thromboembolic episodes. Survival was significantly better for patients with an epithelial subtype, with pleural versus peritoneal mesothelioma, and for those under 65 years of age. Surgery was never curative, but its extent was correlated with survival and earlier diagnosis. Results of chemotherapy with doxorubicin and 5-azacytidine yielded a somewhat better survival rate than a combined program with doxorubicin and radiotherapy. Survival after chemotherapy was correlated with performance status, response to chemotherapy, and extent of previous surgery.

DOI: 10.7326/0003-4819-96-6-746

PMID: 7091938 [Indexed for MEDLINE]

5586. Minerva Med. 1982 May 12;73(20):1407-9.

[2 cases of familial mediterranean fever in subjects originating from the inland of the Marche region].

[Article in Italian]

Locatelli J, Vasta M, Guidi M, Donati L.

PMID: 7078816 [Indexed for MEDLINE]

5587. Riv Neurol. 1982 May-Jun;52(3):149-57.

[Periodic syndrome and headache in the preschool age].

[Article in Italian]

Raudino F, Federico V.

PMID: 7134755 [Indexed for MEDLINE]

5588. Vestn Dermatol Venerol. 1982 May;(5):15-9.

[Clinicomorphological characteristics of erysipelatous erythema in periodic disease].

[Article in Russian]

Ter-Kasparova MR, Danielian AE.

PMID: 7113426 [Indexed for MEDLINE]

5589. Chest. 1982 May;81(5):592-5.

Pericardial disease in familial Mediterranean fever: an echocardiographic study.

Dabestani A, Noble LM, Child JS, Krivokapich J, Schwabe AD.

We studied 30 randomly selected patients with familial Mediterranean fever (FMF) by M mode echocardiography to determine the frequency of pericardial involvement. There was no evidence of congestive heart failure, uremia, or any other illness known to be associated with pericardial disease in the study population. Eight of the 30 patients (27 percent) had echocardiographic evidence of pericardial disease. Two had pericardial effusions, two had pericardial thickening, and four either or both. Patients with pericardial involvement had a mean duration of FMF of 28.9 +/- 12.2 (SD) years vs 18.5 +/- 10.6 (SD) years for those without pericardial disease (P less than .02). We concluded that pericardial involvement is common in FMF and that its occurrence as detected by echocardiography increases with duration of illness.

PMID: 7075279 [Indexed for MEDLINE]

5590. J Lab Clin Med. 1982 May;99(5):693-700.

Degradation of amyloid by a serum component and inhibition of degradation.

Kedar I, Sohar E, Ravid M.

ADA of human serum was demonstrated and investigated with an agar gel diffusion technique using amyloid-impregnated agar plates. Sera of 20 healthy adults, 40 patients with AA-amyloidosis, and 86 nonamyloidotic patients were tested. The presence of an ADF, showing enzymatic properties and strongly bound to albumin, was demonstrated in normals and amyloidotic and nonamyloidotic patients. ADA in the serum of amyloidotic and cirrhotic patients was markedly decreased due to the presence of an inhibitor of ADF. ADA of amyloidotic sera was restored to normal by EDTA, citric acid, and ascorbic acid. The ADA of 16 FMF patients and four of 34 patients with rheumatoid arthritis without amyloidosis was intermediate between normal and amyloidotic values, indicating the presence of IADF at low concentrations in these patients. These findings suggest that amyloid is a normal protein metabolite, possibly with a high metabolic turnover. Accumulation of amyloid may be caused by decrease of the ADA of the serum by its inhibitor, rather than by accelerated production.

PMID: 6802914 [Indexed for MEDLINE]

5591. Med Hypotheses. 1982 May;8(5):477-80.

Familial Mediterranean fever - a congenital disorder of exaggerated response to endogenous interferon?

Aderka D, Weinberger A, Pinkhas J.

PMID: 6180285 [Indexed for MEDLINE]

5592. JAMA. 1982 Apr 2;247(13):1862-3.

Atypical monocytes in a patient with Hodgkin's disease.

Butler WM, Taylor HG, Hurwitz MA, Birx D.

PMID: 7062489 [Indexed for MEDLINE]

5593. Arthritis Rheum. 1982 Apr;25(4):471-2.

Correction of nonsuppressible responder cells by colchicine in familial Mediterranean fever.

Ilfeld D, Weil S, Kuperman O.

PMID: 7073779 [Indexed for MEDLINE]

5594. J Lab Clin Med. 1982 Apr;99(4):559-67.

Evidence for circulating fibrin in familial Mediterranean fever.

Mosesson MW, Wautier JL, Amrani DL, Dervichian M, Cattani D.

Cryofibrinogenemia was found in 10 of 24 plasma samples (42%) from subjects with FMF. This precipitate was found during active disease as well as during intervals between crises. We found a higher incidence of cryofibrinogenemia in subjects with mild to moderately severe disease not being treated with colchicine (six of eight) as compared with colchicine-treated subjects who were in partial or complete clinical remission (four of 16;  $p$  less than 0.02). All cryofibrinogen precipitates contained fibrin, as assessed by electrophoretic analyses showing the presence of multimeric crosslinked forms of fibrin(ogen) linked by gamma-dimers. This finding in clinical specimens supports the hypothesis that fibrin is an obligatory component of cryofibrinogen. Fibrin was also found in HPF (two of six specimens) prepared from cryofibrinogen-negative FMF plasmas, thus

showing that soluble forms of fibrin are even more prevalent in this disorder than is indicated by the frequent finding of cryofibrinogenemia.

PMID: 7061928 [Indexed for MEDLINE]

5595. Isr J Med Sci. 1982 Apr;18(4):495-8.

Unmasking of isolated hypoaldosteronism after renal allotransplantation in familial Mediterranean fever.

Silver J, Rosler A, Friedlander M, Popovtzer MM.

A patient with familial Mediterranean fever and renal amyloidosis was maintained on intermittent hemodialysis for chronic renal failure. After renal allotransplantation, he became weak, lost 12 kg in weight over 7 wk, and developed marked orthostatic hypotension. His symptomatic volume depletion responded dramatically to i.v. 0.9% NaCl. Metabolic balance studies showed that he was in negative Na balance (on a 44 mEq/24 h Na diet, he excreted 71 mEq/24 h in his urine), which was corrected by mineralocorticoid therapy.

Renin-aldosterone studies demonstrated a hyperreninemic hypoaldosteronism with normal glucocorticoid secretion. The patient probably suffered from amyloidosis selectively involving the glomerulosa zone of his adrenal cortices. While on dialysis he was anuric and therefore not volume depleted, but after successful renal allotransplantation the diuresis of the functioning kidney unmasked his mineralocorticoid deficiency which manifested as symptomatic volume depletion.

PMID: 7045036 [Indexed for MEDLINE]

5596. Arthritis Rheum. 1982 Feb;25(2):227-31.

Plasma colchicine concentration in patients with recurrent polyserositis (familial Mediterranean fever) on long-term prophylaxis.

Katz EZ, Ehrenfeld M, Levy M, Eliakim M.

PMID: 7066054 [Indexed for MEDLINE]

5597. Am J Pathol. 1982 Feb;106(2):141-4.

Demonstration of AA-protein in formalin-fixed, paraffin-embedded tissues.

Shtrasburg S, Pras M, Langevitch P, Gal R.

AA-protein was identified by SDS-acrylamide electrophoresis in amyloid fibrils fixed in formalin after isolation from fresh-frozen tissues obtained from patients with familial Mediterranean fever (FMF) amyloidosis and idiopathic AA-amyloidosis and, following deparaffination, rehydration and homogenization of embedded formalin-fixed tissues of old autopsy cases of the hereditary amyloidosis of FMF and amyloidosis acquired in association with tuberculosis, bronchiectasis, and rheumatoid arthritis. That AA-protein is unaltered by formalin was firmly established by agar gel diffusion using specific rabbit anti-AA serum. By contrast, AL proteins could not be demonstrated either in formalin-fixed amyloid fibrils derived from fresh-frozen tissues of a patient with presumably AL-amyloidosis dominated by cardiomegaly and one with AL-kappa amyloidosis or in blocks of cases of familial neuropathic amyloidosis, multiple myeloma, and idiopathic amyloidosis with cardiopathy. AA-protein is not denatured by formalin and retains its typical electrophoretic, chromatographic, and immunologic characteristics even 30 years after fixation and paraffin-embedding.

PMCID: PMC1916185

PMID: 7065112 [Indexed for MEDLINE]

5598. Arch Intern Med. 1982 Feb;142(2):378-9.

Periodic meningitis and familial Mediterranean fever.

Vilaseca J, Tor J, Guardia J, Bacardi R.

A 33-year-old man had had, since he was 20 years old, recurrent attacks of fever, rash, and aseptic lymphocytic meningitis. A nephrotic syndrome developed that was



found, on renal biopsy, to be due to amyloid deposit. After colchicine therapy, no further recurrence of fever and meningitis was observed. These findings suggest that aseptic periodic meningitis (Mollaret's syndrome) should be considered as an unusual manifestation of familial Mediterranean fever.

PMID: 7059265 [Indexed for MEDLINE]

5599. Rev Clin Esp. 1982 Jan 15;164(1):57-9.

[Familial Mediterranean fever with renal amyloidosis in a Gallacian family].

[Article in Spanish]

Ranero Díaz R, Vázquez Rodríguez O, Somoza Lázare J, Gómez Mendez P, Vazquez Martull E.

PMID: 7071405 [Indexed for MEDLINE]

5600. Q J Med. 1982;51(204):469-80.

Familial Hibernian fever.

Williamson LM, Hull D, Mehta R, Reeves WG, Robinson BH, Toghil PJ.

An Irish family with an unusual periodic syndrome is described. Attacks consist of fever with localized myalgia and painful erythema. Other features include abdominal pain and pleurisy, with leucocytosis and a high ESR. The syndrome resembles classical familial Mediterranean fever (FMF) but differs from it in its prompt response to steroids and its autosomal dominant pattern of inheritance. The disease appears to have a benign course and no patient has developed amyloid.

PMID: 7156325 [Indexed for MEDLINE]

5601. Ter Arkh. 1982;54(6):125-8.

[Colchicine treatment of periodic disease].

[Article in Russian]

Aïvazian AA, Bagdasarian GB, Zavgorodniaia AM, Abramian MK, Nazaretian EE.

PMID: 7112411 [Indexed for MEDLINE]

5602. Skeletal Radiol. 1982;8(2):157-9.

Case report 195: inflammatory synovitis due to familial Mediterranean fever (FMF) of left third metatarso-phalangeal joint.

Yagil Y, Mogle P, Ariel I.

PMID: 7100945 [Indexed for MEDLINE]

5603. Arthritis Rheum. 1982 Jan;25(1):42-7.

Schönlein-Henoch syndrome in patients with familial Mediterranean fever.

Flatau E, Kohn D, Schiller D, Lurie M, Levy E.

Ten episodes of Schönlein-Henoch purpura (SHP) in 8 patients with familial Mediterranean fever (FMF) were observed. Five episodes developed 3-14 days after penicillin injections, suggesting an etiologic association. FMF and SHP have clear clinical similarities, and if the frequency of association of the 2 diseases is indeed high, perhaps a common etiologic factor should be sought. An immune complex mechanism might be the link between these 2 disease entities.

PMID: 7066036 [Indexed for MEDLINE]

5604. Pediatriia. 1982 Jan;(1):44-7.

[Periodic disease in children].

[Article in Russian]

Riabova TV, Moreeva ZA.

PMID: 7063313 [Indexed for MEDLINE]

5605. Johns Hopkins Med J. 1982 Jan;150(1):22-6.

Variable incidence of amyloidosis in familial Mediterranean fever among different ethnic groups.

Pras M, Bronshpigel N, Zemer D, Gafni J.

PMID: 7054581 [Indexed for MEDLINE]

5606. Klin Med (Mosk). 1982 Jan;60(1):65-8.

[Pathogenesis of amyloidosis in periodic disease].

[Article in Russian]

Aĭvazian AA, Giulikekhvian NG, Zavgorodniaia AM, Abramian MK, Pashinian SA.

PMID: 6978969 [Indexed for MEDLINE]

5607. Nephron. 1982;30(4):333-5.

Maximal free water reabsorptive capacity in renal amyloidosis. Study of 4

patients with familial Mediterranean fever.

Tuma SN.

DOI: 10.1159/000182511

PMID: 6810188 [Indexed for MEDLINE]

5608. Ter Arkh. 1982;54(10):101-3.

[Treatment of periodic disease not complicated by amyloidosis].

[Article in Russian]

Vinogradova OM, Kochubeĭ LN, Tatevosian KG.

PMID: 6758164 [Indexed for MEDLINE]

5609. Arthritis Rheum. 1982 Jan;25(1):38-41.

Correction of a suppressor cell deficiency and amelioration of familial Mediterranean fever by hemodialysis.

Ilfeld D, Weil S, Kuperman O.

We tested the clinical and immunoregulatory effects of peritoneal dialysis and hemodialysis on a patient with familial Mediterranean fever (FMF), amyloidosis, and chronic renal failure. His frequency of FMF attacks during maintenance hemodialysis (no attacks in 21 months) was significantly less than during conservative medical therapy (10 attacks in 14 months,  $P$  less than 0.00002) or during intermittent peritoneal dialysis (3 attacks in 4 months,  $P$  less than 0.004). His mean ( $\pm$ SE) percentage suppressor cell function was significantly ( $P$  less than 0.001) higher during hemodialysis ( $53 \pm 5$ ) than during conservative medical therapy ( $4 \pm 3$ ) or during peritoneal dialysis ( $2 \pm 7$ ) and was similar to the healthy untreated volunteers ( $46 \pm 3$ ). This suggests that his suppressor cell deficiency may be associated with the pathogenesis of his disease. One possible mechanism by which hemodialysis ameliorates FMF may be the correction of

a suppressor cell abnormality.

PMID: 6461330 [Indexed for MEDLINE]

5610. Rev Clin Esp. 1981 Dec 31;163(6):373-6.

[Familial Mediterranean fever. Review of 15 cases].

[Article in Spanish]

Dalmau Diana M, Alarcón Zurita A, Piza C, Morey A, Marco J, Bestard J, Mairata S.

PMID: 7342197 [Indexed for MEDLINE]

5611. Rev Clin Esp. 1981 Dec 15;163(5):311-2.

[Treatment of familial Mediterranean fever with colchicine].

[Article in Spanish]

Alarcón Zurita A, Dalmau M, Morey A, Marco J, Bestard J, Pizá C, Mairata S.

PMID: 7342187 [Indexed for MEDLINE]

5612. Pediatrie. 1981 Dec;36(8):623-6.

[Eczematous rash and periodic disease: improvement by colchicine].

[Article in French]

Guillet G, Pinaquy JL, Mollard S, Guillet J, Massicot P, Maleville J.

PMID: 7335431 [Indexed for MEDLINE]

5613. Am J Hematol. 1981 Dec;11(4):387-95.

A neutrophil lysozyme leak in patients with familial Mediterranean fever.

Bar-Eli M, Territo MC, Peters RS, Schwabe AD.

Polymorphonuclear cells derived from the peripheral blood of patients with Familial Mediterranean Fever release more lysozyme in response to high temperature (42 degrees, 46 degrees C) than do control cells. No differences between the FMF and control cells were observed in the release of acid phosphatase, beta-glucuronidase, or lactoferrin. Colchicine treatment had no effect on the measurable release of the enzyme from PMNs derived from FMF patients. The increased release of lysozyme in response to high temperatures appears to be specific to FMF neutrophils, and was not found in PMNs from non-FMF patients with febrile or inflammatory diseases, nor was it seen in monocytes derived from the FMF patients. It is suggested that the increased release of lysozyme from the neutrophils may be of importance in the pathogenesis of FMF.

PMID: 7332647 [Indexed for MEDLINE]

5614. Kidney Int. 1981 Nov;20(5):676-85.

Familial Mediterranean fever and amyloidosis.

[No authors listed]

PMID: 7343715 [Indexed for MEDLINE]

5615. Srp Arh Celok Lek. 1981 Oct;109(10):1383-91.

[Familial mediterranean fever in a brother and sister treated with colchicine].

[Article in Serbian]

Jovanovski V.

PMID: 7345588 [Indexed for MEDLINE]

5616. Srp Arh Celok Lek. 1981 Oct;109(10):1373-81.

[Familial Mediterranean fever].

[Article in Serbian]

Jovanovski V.

PMID: 7345587 [Indexed for MEDLINE]

5617. Panminerva Med. 1981 Oct-Dec;23(4):249-52.

Periodic disease of twenty-five years' duration in an Italian subject. Efficacy of long-term colchicine prophylaxis.

Secchi GC, Negri E, Monti MA.

PMID: 7345398 [Indexed for MEDLINE]

5618. Monatsschr Kinderheilkd. 1981 Oct;129(10):593-4.

[The familial mediterranean fever (author's transl)].

[Article in German]

Bartram I, Bremer HJ.

PMID: 7335097 [Indexed for MEDLINE]

5619. Am J Gastroenterol. 1981 Oct;76(4):363-4.

Familial Mediterranean fever associated with menstruation. Efficacy of intermittent colchicine therapy.

Milano AM.

The majority of patients with familial Mediterranean fever have a random pattern of attacks without a clear prodrome. Continuous prophylaxis with colchicine has been shown to reduce the frequency of attacks. It is generally considered undesirable, however, to expose young patients to the potential adverse effects of continuous colchicine prophylaxis. The alternative of intermittent short courses of colchicine during acute attacks is often ineffective in patients without a clear prodrome. Case reports of patients with a pattern of attacks occurring 12-24 hours after the onset of menstrual bleeding have appeared. Such patients should be ideal candidates for intermittent colchicine therapy. A review of the literature reveals that a consistent pattern of attacks closely following the onset of menstruation is not uncommon. Such a patient is described who has responded completely to short courses of colchicine begun at the first sign of menstrual bleeding.

PMID: 7198867 [Indexed for MEDLINE]

5620. Clin Exp Immunol. 1981 Oct;46(1):77-81.

Correction of a suppressor cell deficiency in familial Mediterranean fever by colchicine.

Ilfeld D, Weil S, Kuperman O.

We have previously reported a suppressor cell deficiency in four patients with familial Mediterranean fever (FMF). Since colchicine prevents FMF attacks, we tested the effect of colchicine (1 mg twice daily) on the suppressor cell



function in three of these FMF patients. Proliferation of phytohaemagglutinin-stimulated responder cells co-cultured with concanavalin A-induced suppressor cells was measured. The three FMF patients' means ( $\pm$  s.e.m.) percentage suppression of normal responder cells was markedly low before treatment ( $6 \pm 2$ ) but significantly ( $P$  less than 0.001) increased during colchicine treatment ( $41 \pm 5$ ) to levels similar to normal volunteers' mean percentage suppression ( $44 \pm 3$ ). Colchicine corrected their suppressor cell deficiency and prevented FMF attacks during the 15 months of treatment. These findings support the hypothesis that there may be an association between these three patients' suppressor cell deficiency and the pathogenesis of their disease. Furthermore, colchicine may be potentially useful in treating patients with other diseases associated with a suppressor cell deficiency.

PMCID: PMC1536345

PMID: 6461454 [Indexed for MEDLINE]

5621. Medicine (Baltimore). 1981 Sep;60(5):339-54.

Internal potassium balance and the control of the plasma potassium concentration.

Sterns RH, Cox M, Feig PU, Singer I.

The plasma potassium concentration is determined both by external potassium balance and by the distribution of potassium between extracellular and intracellular fluid compartments, i.e., "internal potassium balance." Whenever external potassium balance is altered, the resultant change in the plasma potassium concentration is strongly influenced by concomitant alterations in internal potassium balance. Several factors alter internal potassium balance independently of changes in external balance. Acid-base disturbances produce shifts of potassium into or out of cells, but attempts to quantify these effects are not likely to be clinically useful. Hypertonicity produces a shift of potassium out of cells. Several hormones (insulin, aldosterone, catecholamines, glucagon, and growth hormone) may have roles in internal potassium balance. Digitalis and succinylcholine, by producing efflux of potassium from cells, may cause hyperkalemia. Potassium is released from skeletal muscle during exercise, causing an increase in the plasma potassium concentration. The periodic paralyses are associated with well-defined transient alterations in internal potassium

balance.

PMID: 6268928 [Indexed for MEDLINE]

5622. Tanpakushitsu Kakusan Koso. 1981 Aug;26(11):1789-97.

[Hereditary diseases accompanied with aberrant catecholamine metabolism, in special reference to catecholamine sensitive periodic fever and familial amyloid polyneuropathy (author's transl)].

[Article in Japanese]

Hayashi A, Suzuki T.

PMID: 6946522 [Indexed for MEDLINE]

5623. An Esp Pediatr. 1981 Jul;15(1):90-4.

[Collagenosis nephropathies].

[Article in Spanish]

Callís L.

Authors review their own experience in PAN, Lupus erythematosus and renal Amyloidosis. Two patients with PAN, both with arterial hypertension: one of them of macroscopic type, presenting great aneurysms localized in brain and in renal arteries; the other patient had microscopic type, with good response to corticotherapy after three years of follow-up. Four patients with lupus erythematosus nephritis; kidney biopsy was performed in three of them: two cases with membranoproliferative glomerulonephritis, and the last one with extramembranous glomerulonephritis. All of them had nephrotic syndrome, and arterial hypertension. Seven patients with renal amyloidosis, four related to rheumatoid arthritis, two related to mucoviscidosis and the last case was a patient with recurrent mediterranean fever.

PMID: 6119054 [Indexed for MEDLINE]

5624. Vestn Khir Im I I Grek. 1981 Jun;126(6):88-90.

[2 cases of "periodic disease"].

[Article in Russian]

Urman MG.

PMID: 7269159 [Indexed for MEDLINE]

5625. Arch Dis Child. 1981 Jun;56(6):464-7.

Amyloidosis in children with familial Mediterranean fever.

Ludomirsky A, Passwell J, Boichis H.

The clinical and laboratory findings of 35 children with familial Mediterranean fever who developed amyloidosis are described. The types, frequency, and severity of attacks of familial Mediterranean fever in these children were no different from patients with this disease without amyloidosis. Although amyloid was widely deposited in all tissues, the major clinical manifestations of the amyloidosis were proteinuria, the nephrotic syndrome, and progressive renal failure. Only 20% of the patients were alive 5 years after the first appearance of proteinuria.

PMCID: PMC1627456

PMID: 7259278 [Indexed for MEDLINE]

5626. Med Clin (Barc). 1981 May 10;76(9):405-7.

[Fever of unknown origin with a prolonged course (author's transl)].

[Article in Spanish]

Barbado Hernández FJ, Redondo C, Muñoz A, Gil A, Puig JA, Vázquez Rodríguez JJ.

Out of 110 cases of fever of unknown origin (FUO) that met Petersdorf and Beeson's criteria 15 patients were selected because of prolonged FUO with more than six months elapsed between admission and the final diagnosis. In this group of chronic FUO an etiological diagnosis was reached in 11 cases, distributed as follows: four cases with infections (two with toxoplasmosis, one with brucellosis, and another with a brain abscess); one with colon carcinoma; two with collagen-vascular diseases (systemic lupus erythematosus, temporal arteritis); and four with different diseases (two with familial mediterranean fever, one with idiopathic granulomatous disease, and another with factitious fever). In four cases no cause for the FUO could be determined. The procedures used to obtain the diagnosis were non-invasive in five cases (clinical course and serological tests), and invasive in another five (angiography, biopsies, and exploratory laparotomy). In one case the ethology could only be ascertained at autopsy. In the FUO with a prolonged course the peculiar etiological spectrum, the lesser yield of invasive procedures, and a mortality inferior to that of FUO in general all deserve special emphasis.

PMID: 7242170 [Indexed for MEDLINE]

5627. Hepatogastroenterology. 1981 Apr;28(2):81-3.

Hepatitis in exanthematous mediterranean fever.

Guardia J, Vilaseca J, Moragas A, Martinez-Vazquez JM, Bombi JA, Calders J, Bacardi R.

In 38 patients suffering from rickettsiosis caused by *Rickettsia conorii* (Mediterranean Exanthematous Fever), hepatic involvement was studied via laboratory tests and in 26 cases by means of liver biopsy. SGOT, SGPT and alkaline phosphatase were found to be elevated in more than half of the patients (SGOT 74.4 +/- 93 U.K., SGPT 82.2 +/- 93 U.K., a.p. 58 +/- 21 mU/ml). In 14 patients, liver biopsy showed the existence of inclusion corpules in Kupffer's

cells. Electron microscopic study demonstrated the existence of phagosomes inside the epithelioid cells, which, however, were difficult to categorize. The frequent existence of granulomatous hepatitis in this rickettsiosis was confirmed, while the presence of the infecting agent in the liver could not be established.

PMID: 7216150 [Indexed for MEDLINE]

5628. Rev Med Chil. 1981 Mar;109(3):239-41.

[Colchicine for familial Mediterranean fever (author's transl)].

[Article in Spanish]

Sacks S, Cordero G, Rojas P.

PMID: 7280408 [Indexed for MEDLINE]

5629. Clin Orthop Relat Res. 1981 Mar-Apr;(155):156-61.

Chronic destructive arthritis in familial Mediterranean fever: the predominance of hip involvement and its management.

Kaushansky K, Finerman GA, Schwabe AD.

Chronic destructive arthritis is a rare complication of Familial Mediterranean Fever (FMF). The hip joints are most commonly involved, but destructive changes may also occur in the knees, ankles, sacroiliac spine, shoulder, or temporomandibular joints. A 28-year-old man with bilateral advanced coxitis and FMF was successfully treated by total hip arthroplasty.

PMID: 7226609 [Indexed for MEDLINE]

5630. Br Med J (Clin Res Ed). 1981 Feb 28;282(6265):737.

Familial Mediterranean fever.

Bakir F, Martadha M.

PMCID: PMC1504521

PMID: 6781637 [Indexed for MEDLINE]

5631. Clin Immunol Immunopathol. 1981 Feb;18(2):261-7.

Immunoregulatory abnormalities in familial Mediterranean fever.

Ilfeld D, Weil S, Kuperman O.

PMID: 7471526 [Indexed for MEDLINE]

5632. Clin Exp Immunol. 1981 Feb;43(2):357-61.

Suppressor cell function in a family with familial Mediterranean fever.

Ilfeld DN, Weil S, Kuperman O.

Defective suppressor cell function has been demonstrated in several diseases but has not been tested in familial Mediterranean fever (FMF). We tested the ability of concanavalin A-activated suppressor cells from one family with FMF to inhibit the proliferation of phytohaemagglutinin-stimulated responder cells from normal volunteers. Four FMF patients tested between acute attacks had a mean ( $\pm$  s.e.) per cent suppression ( $5 \pm 2$ ) which was significantly ( $P$  less than 0.0005) less than an FMF patient tested during a spontaneous remission ( $47 \pm 3$ ), 10 healthy family members ( $41 \pm 6$ ) and eight normal volunteers ( $45 \pm 4$ ). Since FMF is inherited as an autosomal recessive disorder, deficient suppressor cell function is expressed in homozygotes between acute attacks, but not in a homozygote in spontaneous remission, homozygotes who are phenotypically normal, nor heterozygotes. This suggests that the suppressor cell abnormality in this family is probably related to the pathogenesis of FMF rather than representing a genetic

marker of FMF or non-specific depression by disease activity.

PMCID: PMC1537291

PMID: 6456097 [Indexed for MEDLINE]

5633. Am J Med Sci. 1981 Jan-Feb;281(1):15-8.

Leukocyte chemotaxis in recurrent polyserositis (familial Mediterranean fever).

Bar-Eli M, Ehrenfeld M, Levy M, Gallily R, Eliakim M.

Polymorphonuclear leukocyte chemotaxis was investigated in 35 patients with recurrent polyserositis during attacks and during spontaneous or colchicine-induced remissions. Chemotaxis was found to be unchanged in the attack-free period in untreated patients, increased by about 50% during attacks, and decreased by about 50% during colchicine treatment.

PMID: 7468635 [Indexed for MEDLINE]

5634. Ann Med Interne (Paris). 1981;132(7):493-5.

[Periodic arthralgia: teratogenicity of colchicine and its influence on pregnancy and sterility (author's transl)].

[Article in French]

Ghozlan R, Pras M, Bettoun A.

Pregnancy appears to exert a beneficial effect on periodic arthralgia, the frequency of episodes being reduced by a half. Sterility, probably of anavulatory rather than mechanical origin, occurs in one third of cases. Its frequency could be diminished by colchicine, which by its anti-inflammatory action can prevent the development of mechanical sequelae. Though colchicine appears to lack teratogenetic activity, it should be discontinued three months before pregnancy.

PMID: 7337327 [Indexed for MEDLINE]

5635. Ann Med Interne (Paris). 1981;132(7):487-9.

[Muscular manifestations of familial paroxysmal polyserositis: two cases in children (author's transl)].

[Article in French]

Nathanson M, Scart G, Perelman R.

PMID: 7337326 [Indexed for MEDLINE]

5636. Ann Med Interne (Paris). 1981;132(7):482-6.

[Familial Mediterranean fever and fatty liver. effect of a long time colchicine treatment on triglyceride storage (author's transl)].

[Article in French]

Moretti G, Le Bras M, Longy M, Veyret V, Bioulac P.

A 35-year-old man, sephardic jew, complains for the last eleven years of typical and frequent attacks of FMF. His liver is hypertrophic. Needle-biopsy reveals an extensive macrovacuolar triglyceride storage (60 per cent) and an active vascular congestion with erythrodiapedesis in the mild and centrolobular zone, without any necrosis, cellular infiltration nor fibrosis. Electron microscopy shows lipofuscin deposits and mild lesions of mitochondrias, endoplasmic reticulum. Blood triglycerides and apo B are rather low. After six weeks of colchicine treatment, needle biopsy shows no more active congestion nor erythrodiapedesis. Triglyceride storage lowers to 40 per cent. After seven months of colchicine treatment, triglyceride storage falls down to 12 per cent. FMF may be considered as a cause of fatty liver when there is not any cause else and only after deep decrease or disparition of triglyceride deposit by a long time colchicine treatment.



PMID: 7337325 [Indexed for MEDLINE]

5637. Ann Med Interne (Paris). 1981;132(7):480-1.

[Angiitis and periodic disease].

[Article in French]

Mongin M, Clauvel JP, Dor JF, Weiller PJ.

PMID: 7337324 [Indexed for MEDLINE]

5638. Ann Med Interne (Paris). 1981;132(7):475-9.

[Subacute and chronic joint involvement occurring during the course of familial Mediterranean fever (author's transl)].

[Article in French]

Brodsky A, Vinceneux P, Kahn MF, Bourgeois P, Gintzburger S, Kaplan G.

Subacute and chronic joint involvement occur in less than 5 p. cent of patients with familial mediterranean fever, whereas acute joint lesions are observed in approximately 3 out of 4 cases. The various aspects of these atypical forms are discussed in relation to 10 such cases. In most of these patients the lesions were merely due to the prolongation of the acute process, presenting as a subacute mono-arthritis lasting for several months before regression. X Rays show only regional demineralisation, sometimes predominating in the subchondral zone. Symptoms totally regress without sequelae. A time destructive arthropathy may however develop, especially in the hip. The presentation associates limitation of joint motion with, on X Rays, joint space narrowing and osteophytes. In 2 of our cases and one case reported in the literature, there was a progressive development of a chronic caxopathy without any previous acute involvement of this joint. At last, in some cases, familial mediterranean fever may be associated

with a known arthritidis, usually ankylosing spondylitis.

PMID: 7337323 [Indexed for MEDLINE]

5639. Ann Med Interne (Paris). 1981;132(7):472-4.

[Familial Mediterranean fever, complement, cryofibrinogen, colchicine (author's transl)].

[Article in French]

Wautier JL, Mosesson M, Dervichian M, Cattani D.

The components C1, C4, C2, C3 of the complement system were measured in a group of 24 patients with Familial mediterranean fever (F.M.F.). The presence of cryofibrinogen and its analysis was performed in the same patient. C4, C2, C3, were increased in the F.M.F. group. Cryofibrinogenemia was found in 42 p. 100 of the patients. The cryofibrinogen was composed of fibrin, fibrinogen and plasma fibronectin. The cryofibrinogen was less frequent in the group of patients treated by colchicine (p less than 0.02).

PMID: 7337322 [Indexed for MEDLINE]

5640. Ann Med Interne (Paris). 1981;132(7):511-3.

[Recurrence of amyloidosis on the kidney transplant despite colchicine therapy in a patient with familial Mediterranean fever (author's transl)].

[Article in French]

Touraine JL, Vital-Durand D, Malik MC, Blanc N, Traeger J.

PMID: 7039456 [Indexed for MEDLINE]

5641. Ann Med Interne (Paris). 1981;132(7):507-10.

[Kidney allograft in familial Mediterranean fever a case report and review of the literature (author's transl)].

[Article in French]

Giraud P, Adoue D, Durand D, Delsol G, That HT, Suc JM.

Chronic renal insufficiency in an Algerian patient with familial mediterranean fever and amyloidosis was treated by kidney transplantation. Diagnosis of the affection was confirmed by the onset of typical acute episodes during haemodialysis, and a bone marrow biopsy established the presence of amyloidosis. The transplant was unsuccessful at an early stage with infective complications. The incidence of similar complications and deaths (11 cases) was particularly high in the 23 previously reported patients in whom transplants had been performed, and no definite relationship was able to be established between the course of the disease and treatment by haemodialysis or transplantation. The functional prognosis of the transplant was apparently not adversely affected by the recurrence of amyloidosis in 3 cases.

PMID: 7039455 [Indexed for MEDLINE]

5642. Ann Med Interne (Paris). 1981;132(7):501-6.

[Familial paroxysmal polyserositis: modern therapeutic possibilities (author's transl)].

[Article in French]

Mignon F, Méry JP, Cuvelier R, Delons S, Meyrier A, Rottembourg J.

Prognosis of familial paroxysmal polyserositis is primarily related to the presence of renal insufficiency due to the amyloidosis. Current treatment of terminal renal failure--haemodialysis and renal transplantation--has increased survival in these patients, but prognosis remains relatively poor because of the

extrarenal, mainly cardiac deposits which have had time to develop. Preventive treatment is therefore all that can be hoped for, and initial results of the use of colchicine in this amyloid affection, by Israelian authors, appear encouraging.

PMID: 7039454 [Indexed for MEDLINE]

5643. Ann Med Interne (Paris). 1981;132(7):496-500.

[Colchicine treatment of renal amylosis in familial paroxysmal polyserositis (author's transl)].

[Article in French]

Lagrue G, Koeger AC, Benaym JC, Sobel A.

Mortality in familial paroxysmal polyserositis results mainly from renal amylosis, the outcome, until recently, being always fatal. Continuous colchicine administration prevents acute relapses, but certain recent observations have demonstrated that this treatment may be able to prevent the onset of amyloid disease. It could even provoke its regression, at least if administration is during the early stages before the development of renal insufficiency. The mechanism of this preventive action against amyloid disease occurrence is discussed as a function of current knowledge of amyloidogenesis.

PMID: 7039453 [Indexed for MEDLINE]

5644. Ann Med Interne (Paris). 1981;132(7):461-6.

[Familial Mediterranean fever].

[Article in French]

Pras M, Zemer D, Revach M, Shemer Y, Cabili S.

PMID: 7039452 [Indexed for MEDLINE]

5645. Ann Med Interne (Paris). 1981;132(7):490-2.

[Familial Mediterranean fever in childhood (author's transl)].

[Article in French]

Harpey JP.

Most cases of familial mediterranean fever (periodic disease) begin in childhood. However reports of this disorder in the pediatric literature are rare. This diagnosis is too often missed in pediatric practice. His symptomatology is the same as in adulthood with some particularities. Familial history is often the corner-stone of the diagnosis. Assessment of C'4 fraction of complement seems of good help for the diagnosis. The frequent occurrence of premonitory symptoms heralding the attacks allows us in many cases to start an intermittent colchicine therapy. Long term colchicine therapy should be used very cautiously in children and should be restricted to those children whose activities are disrupted by crisis occurring without alarm or to cases associated with amyloidosis.

PMID: 6978102 [Indexed for MEDLINE]

5646. Ann Med Interne (Paris). 1981;132(7):467-71.

[The complement system in familial Mediterranean fever: studies in 41 families (author's transl)].

[Article in French]

Ollier-Hartmann MP, Godeau P, Gouet E, Hartmann L.

A total increase of blood complement components, particularly C4, is found in subjects with familial Mediterranean fever both before and after colchicine therapy. This effect differs from the serum haptoglobin and orosomucoïd

concentration decreases detected after identical therapy, conferring diagnostic value to this inflammatory syndrome. This could be of both hepatic and extrahepatic origin. For the latter, it is possible that up take of circulating monocytes, macrophage precursors, by the connective tissue of the serum sub-mesothelial layer is responsible for the lesion.

PMID: 6978101 [Indexed for MEDLINE]

5647. Eur J Nucl Med. 1981;6(6):277-80.

Renal uptake of <sup>67</sup>Ga-citrate in renal amyloidosis due to familiar Mediterranean fever.

Banzo-Marraco J, Nerin-Mora E, Abos-Olivares MD, Nerin de la Puerta I, Iribar-Ibabe MC, Prats-Rivera E, Banzo-Marraco JI, Teijeiro-Vidal J.

Renal uptake of <sup>67</sup>Ga-citrate is described in a patient with biopsy-proven amyloidosis of the kidneys, due to Familial Mediterranean Fever. After administration 150 MBq (4 mCi) <sup>67</sup>Ga-citrate, scans were done at 48, 72, and 120 h. Intense uptake was noted in both kidneys. A renal biopsy done 5 days after the <sup>67</sup>Ga-citrate scan revealed a pattern typical of amyloidosis. Gallium scanning can be useful in patients with fever of unknown origin. Renal amyloidosis can be considered when renal uptake of <sup>67</sup>Ga-citrate associated with nephrotic syndrome is observed.

PMID: 6940754 [Indexed for MEDLINE]

5648. Sem Hop. 1980 Dec 18-25;56(47-68):2041-4.

[Cutaneous manifestations of mediterranean periodic disease. Concerning an observation. Review of the literature (author's transl)].

[Article in French]

Devaux J, Belaube P, Garcin G, Gamby T, Privat Y.

Méditerranean Periodic Disease is frequently encountered in non-aschenazic Jews and in Armenians. Aside from the classic triad of pseudo-palustral febrile crises, paroxysms of abdominal and articular pain, and a biological syndrome of inflammation; cutaneous manifestations were noted in 25 to 35% of the cases according to various authors. The most commonly encountered lesions consisted of erysipiel-like plaques and subcutaneous nodules. We observed the case of a 47 years old Armenian male, afflicted with Mediterranean Periodic Disease for 30 years in which the dermatologic symptoms are quite classic aside from a vitiligo having progressively appeared since 15 years. Possibly a coincidental association, but to the best of our knowledge, which has not as yet been reported.

PMID: 6256918 [Indexed for MEDLINE]

5649. J Rheumatol. 1980 Nov-Dec;7(6):886-90.

Circulating immune complexes in recurrent polyserositis. (Familial mediterranean fever, periodic disease).

Levy M, Ehrenfeld M, Levo Y, Fischel R, Zlotnick A, Eliakim M.

Increased levels of circulating immune complexes (CIC) were demonstrated by the Clq binding assay in 22 (27%) out of 81 patients with recurrent polyserositis. The prevalence of increased CIC was significantly higher in Jewish patients of North African origin (42%) than in subjects of other ethnic groups (6%). North African patients also manifested an increased familial incidence, earlier onset of symptoms and a higher frequency of arthritis. There was no correlation between increased CIC levels and disease activity. These findings suggest that the immune response of North African patients differs from that of subjects of other ethnic groups and that this difference is possibly genetically determined.

PMID: 7205826 [Indexed for MEDLINE]

5650. An Esp Pediatr. 1980 Sep;13(9):785-8.

[Familial Mediterranean fever (FMF) (author's transl)].

[Article in Spanish]

Ribó Golovart MA, Gassó Campos M, Esteban Velasco B, Castellá Ribó MA, Pulido Bosch R.

Authors present an Andalusian family, affected by FMF with a dominant autosomal inheritance. The number of members affected by phenotype II (40%) and the cases of bad prognosis (1/3 died before 34 years of age) was higher than those found by other authors. A new clinical finding: the presence of prodromic ocular symptoms (constant in this family), and the presence of Park's transverse lines in the skeletal X-rays, not previously reported, are referred. An increasing pediatric interest in this disease is pointed out.

PMID: 7469195 [Indexed for MEDLINE]

5651. Akush Ginekol (Mosk). 1980 Sep;(9):44-6.

[Characteristics of the course of periodic disease in women who use hormonal contraceptives].

[Article in Russian]

Akunts KB, Pogolian GK, Arutiunian MM.

PMID: 7435847 [Indexed for MEDLINE]

5652. Lancet. 1980 Jul 12;2(8185):91.

Treatment of familial Mediterranean fever.

Berlyne GM.



PMID: 6105277 [Indexed for MEDLINE]

5653. Br Med J. 1980 Jul 5;281(6232):2-3.

Familial Mediterranean fever.

[No authors listed]

PMCID: PMC1713742

PMID: 7407479 [Indexed for MEDLINE]

5654. Clin Pharmacol Ther. 1980 Jul;28(1):82-7.

Colchicine kinetics in patients with familial Mediterranean fever.

Halkin H, Dany S, Greenwald M, Shnaps Y, Tirosh M.

Serum colchicine levels were determined by radioimmunoassay after a 1-mg bolus injected intravenously in 4 patients with familial Mediterranean fever and in 6 normal subjects. Mean elimination half-life ( $t_{1/2}$ ) ( $\pm$  SEM) was  $157 \pm 20$  min in the patients and  $65 \pm 15$  min in the normal subjects ( $p$  less than 0.005). Total clearance was  $239 \pm 50$  ml/min in the patients and  $601 \pm 155$  ml/min in the normal subjects ( $p$  less than 0.05). Volume of distribution ( $V_d$ ) was  $76 \pm 16$  and  $49 \pm 91$  and did not differ significantly. In 8 patients receiving colchicine prophylactically with good clinical response, serum colchicine ranged from 0.3 to 2.4 ng/ml after daily doses of 1 mg orally. In 2 responding patients 2-mg doses orally induced levels from 4 to 10 ng/ml, and in one (a nonresponder) a 3-mg dose induced levels of 7.5 to 13 ng/ml. Of 3 patients receiving 2 mg daily with unsatisfactory clinical responses, serum levels were not detectable in one and in the low range of 1.5 to 5.4 ng/ml in the others. It is suggested that lack of response to colchicine orally in some nonresponders could result from inadequate absorption or altered disposition of colchicine.

PMID: 7389258 [Indexed for MEDLINE]

5655. Biomedicine. 1980 Jul-Aug;33(4):95-6.

Absence of interferon activity during acute attacks of familial Mediterranean fever.

Aderka D, Pras M, Bino T, Rosenberg H, Weinberger A, Pinkhas J.

The pharmacokinetics of interferon, the symptoms caused by its administration, the decreased prevalence of viral diseases in FMF patients and the fact that colchicine, the drug of choice in the prevention of FMF attacks is an interferon antagonist, raised the question whether interferon may have a role in the pathogenesis of FMF attacks. An interferon activity was not detected in sera obtained at the height of FMF attacks in 8 patients, six of them under colchicine treatment. It is possible that the interferon activity has to be searched at the very beginning of FMF attacks, since at their height it already disappeared from the serum, while the symptoms of the attack are further mediated by other interferon-induced lymphokines.

PMID: 6159009 [Indexed for MEDLINE]

5656. Minerva Med. 1980 Jun 23;71(25):1801-13.

[Amyloidosis. II. Current pathogenetic and clinico-nosographic aspects].

[Article in Italian]

Lovisetto P, Frascisco M, Gilardi E, Marchi L, Mairano D.

Amyloidosis is due to the overproduction of a precursor protein and its conversion into products capable of polymerisation into fibrils. The primary form, or that associated with multiple myeloma or Waldenström's macroglobulinaemia, marked by the presence of protein AL, includes the overproduction of Ig light chains followed by conversion on the part of lysosome enzymes. The forms can thus be classified as immunoproliferative diseases (plasma-cell dyscrasias). Secondary amyloidosis is primarily associated with

neoplasia or chronic inflammation. Its biochemical label is the AA protein. Initially, there is overproduction of protein SAA, while the formation of AA-amyloid fibrils may theoretically be attributed to a variety of factors: changes in the amount of circulating SAA, the presence of amyloidogenic SAA, variations in the activity of SAA catabolic systems, insufficient removal of accumulated fibrils. The way in which the immunocompetent system intervenes is a controversial subject. Lesser forms of amyloidosis are known in which there are local deposits of amyloid: AL-amyloidosis, amyloidomas. In some forms, the features of systemic accumulation are maintained, but only one organ is primarily involved. They are rarely of clinical significance (e.g. senile amyloidosis). Current biochemical techniques enable a clinical and nosographic distinction to be drawn between an Ig (AL)-amyloidosis and non-Ig (AA, AL and AS) forms.

PMID: 6774298 [Indexed for MEDLINE]

5657. N Engl J Med. 1980 Jun 5;302(23):1283-92.

Amyloid deposits and amyloidosis. The beta-fibrilloses (first of two parts).

Glenner GG.

DOI: 10.1056/NEJM198006053022305

PMID: 6154243 [Indexed for MEDLINE]

5658. AJR Am J Roentgenol. 1980 Jun;134(6):1293-4.

Pediatric case of the day. Case 1. Familial Mediterranean fever.

Gilsanz V, Stanley P.

DOI: 10.2214/ajr.134.6.1293

PMID: 6446230 [Indexed for MEDLINE]

5659. Med J Aust. 1980 May 17;1(10):494.

Familial Mediterranean fever in Australia.

Robinson BW, Joske RA.

PMID: 7412686 [Indexed for MEDLINE]

5660. Kardiologiia. 1980 May;20(5):35-7.

[Heart lesion in amyloidosis].

[Article in Russian]

Vinogradova OM, Mukhin NA, Khasabov NN, Zubareva VN, Savitskiĭ SN.

PMID: 7392380 [Indexed for MEDLINE]

5661. J Pediatr Surg. 1980 Apr;15(2):186-7.

Intestinal obstruction caused by primary adhesions due to Familial Mediterranean Fever.

Tal Y, Berger A, Abrahamson J, Horowitz I, Winter ST.

Repeated acute abdominal episodes of Familial Mediterranean Fever can lead to peritoneal bands. These may cause mechanical obstruction of the bowel, requiring surgical intervention. Three such cases are reported, including one fatality.

PMID: 7373498 [Indexed for MEDLINE]

5662. Nouv Presse Med. 1980 Mar 12;9(17):1246.

[Biliary acids in familial mediterranean fever (author's transl)].

[Article in French]

Heim M, Bereziat G, Dimas D, Gauthier A, Olmer M, Bouvenot G, Simonin R.

PMID: 7454563 [Indexed for MEDLINE]

5663. Am J Med. 1980 Feb;68(2):291-4.

AA protein in a case of "primary" or "idiopathic" amyloidosis.

Pras M, Zaretzky J, Frangione B, Franklin EC.

Amyloidosis constitutes a group of diseases in which extracellular fibrils with a characteristic appearance are deposited in a variety of tissues. Several different proteins have been identified as the major subunits of the fibrils. In the primary and myeloma-associated type, the amyloid fibrils consist of immunoglobulin light chain fragments, whereas in the secondary type and the amyloid associated with familial Mediterranean fever the major component is the AA protein. In this report a 21 year old man of Yemenite extraction with no underlying disease and no family history of amyloidosis was found to have amyloid deposits composed of AA protein. Although clinically this might be classified as primary amyloidosis, the absence of light chain fragments makes that diagnosis unlikely. Therefore, it is suggested that whenever possible the clinical classification be supplemented by a description of the biochemical nature of the fibrils.

PMID: 6766664 [Indexed for MEDLINE]

5664. Med J Aust. 1980 Jan 26;1(2):77-8.

Familial Mediterranean fever in Australia.

Smith MD, Angove RC.

A case of familial Mediterranean fever is presented, which is, as far as it could

be ascertained, the first reported case of this condition in Australia. The difficulties encountered in making this diagnosis are discussed along with diagnostic criteria necessary to substantiate a diagnosis of familial Mediterranean fever. The importance of this condition both to physicians and to surgeons is emphasized.

PMID: 7360092 [Indexed for MEDLINE]

5665. Ter Arkh. 1980;52(10):121-3.

[Treatment of amyloidosis and periodic disease with colchicine].

[Article in Russian]

Vinogradova OM, Kochubei LN.

PMID: 7444772 [Indexed for MEDLINE]

5666. Vestn Akad Med Nauk SSSR. 1980;(6):8-12.

[Pathogenesis of periodic disease].

[Article in Russian]

Kochubei LN, Komissarova IA, Vinogradova OM, Kozlovskaya LV, Tatevosian KG.

PMID: 7405385 [Indexed for MEDLINE]

5667. Sov Med. 1980;(4):67-70.

[Use of colchamine in periodic disease].

[Article in Russian]

Vinogradova OM, Kochubei LN, Tatevosian KG.

PMID: 7384884 [Indexed for MEDLINE]

5668. Medicine (Baltimore). 1980 Jan;59(1):66-77.

Familial Mediterranean fever: report of a large family, review of the literature, and discussion of the frequency of amyloidosis.

Meyerhoff J.

Familial Mediterranean Fever is a rare disease which usually begins in childhood and occurs primarily among persons of Mediterranean ancestry. It is characterized by short, self-limited, febrile episodes that may occur alone or with inflammation of serosal surfaces. Some individuals may exhibit an erysipilas-like erythema, almost always on the lower extremities. These attacks are associated with considerable morbidity and may lead to unnecessary surgery, but this disease does not appear to be associated with an increased mortality, except in those individuals who develop amyloid nephropathy. For those patients death usually occurs below the age of 40 years although longer survival has been reported. This complication occurs frequently in Turks and Sephardic Jews, but only rarely in individuals of other ethnic origins. A rare patient may develop destructive changes in a joint that has been subjected to a protracted attack. Recent data indicate that either daily or intermittent colchicine will effectively reduce the severity and frequency of attacks; in some individuals these regimens have induced a complete remission. Preliminary data suggest that colchicine may also reduce the degree of nephropathy associated with amyloidosis. Diagnosis of this disease depends, in the absence of any objective markers, on the recognition of the symptoms in a susceptible individual. Despite the name of the disease, it may occur without a family history and in non-Mediterranean individuals. Most of the attacks, however, are associated with a rise in temperature although the fever spike may be more transient than the associated symptoms. Any individual with suggestive symptoms who is significantly disabled by the attacks should have a therapeutic trial of colchicine.

PMID: 6986010 [Indexed for MEDLINE]

5669. Rev Rhum Mal Osteoartic. 1980 Jan;47(1):61-2.

[Rheumatic pelvispondylitis and periodic disease (separately attacking two brothers in the same family)].

[Article in French]

Caroit M, Darbon L, Villiaumey J.

PMID: 6966811 [Indexed for MEDLINE]

5670. Pediatr Pol. 1979 Dec;54(12):1487-91.

[Differential diagnosis of familial Mediterranean fever and systemic connective tissue diseases in children].

[Article in Polish]

Gutowska-Grzegorzczak G, Polowiec Z.

PMID: 534151 [Indexed for MEDLINE]

5671. Isr J Med Sci. 1979 Dec;15(12):1011-3.

Dialysis requirements in Israel.

Eliahou HE, Iaina A.

Chronic dialysis is available in Israel to almost all patients who require it. During the last four years the mean number of new patients/million population per year was 44.5 (range, 39.5 to 48.6), excluding patients with systemic diseases such as diabetes mellitus and lupus erythematosus. This number is close to that



estimated in a previous study--53/million per year for the years 1965-66--and the discrepancy is probably methodological in nature. The stage of equilibrium for Israel, when the net gain in patients per year approaches zero, as forecast by the European Dialysis and Transplant Association, will be reached in 1983 with 261 dialysis patients/million population. At present, the number is about 171. Inadequately treated hypertension was found to considerably affect long-term survival.

PMID: 528183 [Indexed for MEDLINE]

5672. Int J Dermatol. 1979 Dec;18(10):824-7.

Cutaneous manifestations of periodic diseases.

Reimann HA.

PMID: 528105 [Indexed for MEDLINE]

5673. Clin Endocrinol (Oxf). 1979 Dec;11(6):595-601.

Amyloid goitre in familial Mediterranean fever.

Danovitch GM, Le Roith D, Sikuler SE, Straus R.

Three patients known to suffer from familial Mediterranean fever (FMF), systemic amyloidosis and chronic renal failure developed large amyloid goitres. Amyloid goitre is an extremely rare complication of systemic amyloidosis not previously described in FMF. The clinical and pathological features of these three cases were similar to those previously described in amyloid goitre. In two of the patients abnormalities in thyroid function were consistent with those documented in chronic renal failure. There was evidence of hypothyroidism in a third patient. There was no evidence of amyloid induced dysfunction of other endocrine organs.

PMID: 119593 [Indexed for MEDLINE]

5674. Ugeskr Laeger. 1979 Oct 15;141(42):2903-4.

[A case of familial Mediterranean fever].

[Article in Danish]

Hansen BA, Iversen J.

PMID: 505605 [Indexed for MEDLINE]

5675. Klin Med (Mosk). 1979 Oct;57(10):77-82.

[Puncture biopsy in the early diagnosis of renal pathology in periodic disease].

[Article in Russian]

Ter-Kasparova MR, Tevosian TG.

PMID: 502400 [Indexed for MEDLINE]

5676. Am J Pathol. 1979 Oct;97(1):43-58.

The potassium permanganate method. A reliable method for differentiating amyloid AA from other forms of amyloid in routine laboratory practice.

van Rijswijk MH, van Heusden CW.

Alterations in affinity of amyloid for Congo red after incubation of tissue sections with potassium permanganate, as described by Wright et al, were studied. The affinity of amyloid for Congo red after incubation with potassium permanganate did not change in patients with myeloma-associated amyloidosis, familial amyloidotic polyneuropathy, medullary carcinoma of the thyroid,

pancreatic island amyloid, and cerebral amyloidosis. Affinity for Congo red was lost after incubation with potassium permanganate in tissue sections from patients with secondary amyloidosis and amyloidosis complicating familial Mediterranean fever (consisting of amyloid AA). Patients with primary amyloidosis could be divided into two groups, one with potassium-permanganate--sensitive and one with potassium-permanganate--resistant amyloid deposits. These two groups correlated with the clinical classification in typical organ distribution (presenting with nephropathy) and atypical organ distribution (presenting with cardiomyopathy, nephropathy, and glossopathy) and the expected presence of amyloid AA or amyloid AL. Potassium permanganate sensitivity seems to be restricted to amyloid AA. The potassium permanganate method can be important in dividing the major forms of generalized amyloidosis in AA amyloid and non-AA amyloid. This can be used for differentiating early stages of the disease and cases otherwise difficult to classify. It is important to define patient groups properly, especially in evaluating the effect of therapeutic measures. (Am J Pathol 97:43--58, 1979).

PMCID: PMC2042379

PMID: 495695 [Indexed for MEDLINE]

5677. Arch Intern Med. 1979 Oct;139(10):1135-8.

Renal transplantation in the amyloidosis of familial Mediterranean fever.  
Experience in ten cases.

Jacob ET, Bar-Nathan N, Shapira Z, Gafni J.

Ten patients with familial Mediterranean fever (FMF) and histologically confirmed amyloidosis received cadaver kidney transplants for treatment of terminal renal disease. Colchicine, 1 mg daily, was included in the routine postoperative regimen from 1974 for amyloidotic patients. Graft and patient survival were compared with ten nonamyloidotic recipients of renal grafts matched for age, sex, type of allograft, and HLA compatibility. In the FMF group, five of ten grafts have survived from 20 to 64 months; in the control group, six of ten. While only recipients with functioning grafts survived in the FMF group, patient survival in the control group is eight of ten after one year. In all five FMF survivors, graft function is satisfactory, proteinuria is absent, and blood creatinine

levels are normal. Amyloid involvement of an allograft was documented 16 months after transplantation in the only patient whose maintenance colchicine dosage had been reduced to 0.5 mg daily.

PMID: 384952 [Indexed for MEDLINE]

5678. Nihon Rinsho. 1979 Sep 10;37(9):3158-64.

[Amyloid fibrils. Biochemistry of proteins and precursor substances].

[Article in Japanese]

Tawara S.

PMID: 118276 [Indexed for MEDLINE]

5679. West J Med. 1979 Sep;131(3):193-5.

Amyloidosis and periodic peritonitis (familial mediterranean Fever).

Bakir F(1), Murtadha M, Issa N.

Author information:

(1)Department of Medicine, College of Medicine, University of Baghdad and Medical City, Baghdad, Iraq.

Some reports indicate that amyloidosis is a rare occurrence in persons with periodic peritonitis (familial Mediterranean fever), while others seem to show it occurs relatively frequently. Two cases were seen among 80 patients in Iraq. Twenty-one consecutive rectal biopsies were negative for amyloidosis. The variation in reported incidence is partly real and partly apparent. Amyloidosis occurs frequently in certain ethnic groups, and it is possible that there are two traits, one for periodic peritonitis and the other for amyloidosis.

PMCID: PMC1271767

PMID: 18748466

5680. Clin Orthop Relat Res. 1979 Sep;(143):76-83.

The seronegative spondyloarthropathies of childhood.

Schaller JG.

Most chronic arthritis in childhood is seronegative. Within "JRA" several distinct subgroups exist: one of these (pauciarticular disease type II) affects predominantly boys more than 8 years of age. It is clearly associated with sacroiliitis, HLA-B27, family history of spondyloarthropathy, and subsequent ankylosing spondylitis in an as yet underfined percentage of patients. This type of disease is probably classified appropriately with the spondyloarthropathies, although patients often may fulfill diagnostic criteria for "JRA" in the first years of their disease, and accounts for about 15% of "JRA." The other JRA subgroups do not appear to have features of seronegative spondyloarthropathy. Reiter's syndrome and psoriatic arthritis exist in children, but appear to be rare. The arthritis of inflammatory bowel disease in childhood resembles that in adulthood. The recognition of spondyloarthropathy in children, particularly the sizable group of patients with "JRA" pauciarticular disease type II, is of practical importance to permit proper therapy, follow-up and prevention of deformity.

PMID: 509839 [Indexed for MEDLINE]

5681. Harefuah. 1979 Aug;97(3-4):55-7.

[Circulating immune complexes in familial Mediterranean fever, systemic lupus erythematosus and HBsAg carriers].

[Article in Hebrew]

Zlotnick A, Levo Y, Fishel R, Ehrenfeld M, Levy M, Shouval D, Eliakin M.

PMID: 540822 [Indexed for MEDLINE]

5682. Am J Psychiatry. 1979 Aug;136(8):1082-3.

Lithium prophylaxis in familial Mediterranean fever.

Christodoulou GN, Madianos MG, Stefanis CN, Loukopoulos DL.

DOI: 10.1176/ajp.136.8.1082

PMID: 464138 [Indexed for MEDLINE]

5683. N Engl J Med. 1979 Jul 19;301(3):142-4.

Amelioration of familial Mediterranean fever during hemodialysis.

Rubinger D, Friedlaender MM, Popovtzer MM.

DOI: 10.1056/NEJM197907193010306

PMID: 377075 [Indexed for MEDLINE]

5684. Rev Rhum Mal Osteoartic. 1979 Jul-Sep;46(7-9):487-90.

[Severe muscular manifestations during periodic disease with ankylosing spondylitis. Effect of colchicine].

[Article in French]

Delcambre B, Defrance D, Duquesnoy B, Deremaux JJ, d'Eshougues JR.

PMID: 504951 [Indexed for MEDLINE]

5685. Am J Med Sci. 1979 Jul-Aug;278(1):77-81.

Fatal colchicine poisoning in a boy with familial Mediterranean fever.

Stahl N, Weinberger A, Benjamin D, Pinkhas J.

PMID: 484593 [Indexed for MEDLINE]

5686. Arch Intern Med. 1979 Jul;139(7):781-3.

Periodic peritonitis. Present management and future prospects.

Bakir F.

Thirty-three patients with periodic peritonitis were treated with colchicine for 863 patient-months of observation (average, 27 months). There is a personal optimum dose, and the daily requirement varies at 1 or 1.5 mg. All patients responded to treatment. Episodes were precipitated in all patients who stopped their medications. No side effects were noticed. Four normal full-term infants were born to patients taking colchicine during the study.

PMID: 454065 [Indexed for MEDLINE]

5687. Rep Rheum Dis. 1979 Jul;(69):1-2.

Rheumatic diseases in immigrants.

Eade A, Richardson G.

PMID: 316162 [Indexed for MEDLINE]

5688. Lille Med. 1979 Jun-Jul;24(6):445-9.

[Periodic disease with ankylosing spondylarthritis and severe muscular manifestations : study of the action of colchicine and a family survey].

[Article in French]

Delcambre B, Duquesnoy B, Defrance D, Deremaux JJ, D'Eshougues JR.

PMID: 502733 [Indexed for MEDLINE]

5689. Nouv Presse Med. 1979 May 26;8(23):1927-9.

[Spontaneous perirenal haematoma occurring during 1 familial mediterranean fever.  
3 cases (author's transl)].

[Article in French]

Dor JF, Clauvel JP, Degos L, Mongin F.

A perirenal haematoma, associated with the presence of renal micro-aneurysms, developed in three patients with periodic syndrome. In one of the cases, the histology of a subcutaneous nodule confirmed the diagnosis of periarteritis nodosa. This emphasies the importance of vascular lesions in familial mediterranean fever.

PMID: 37484 [Indexed for MEDLINE]

5690. N Engl J Med. 1979 May 17;300(20):1160-1.

Cyclic nucleotides in familial Mediterranean fever.

Paykoc Z, Sümer N, Ertan A, Akit A.

DOI: 10.1056/NEJM197905173002010

PMID: 219343 [Indexed for MEDLINE]

5691. Med Hypotheses. 1979 Mar;5(3):365-78.



Multiple sclerosis: the rational basis for treatment with colchicine and evening primrose oil.

Horrobin DF.

Multiple sclerosis (MS) is a disease with no known treatment. In view of this and of its distressing nature patients are attracted by any new concepts. As a reaction to this neurologists are sometimes excessively sceptical and fail to consider new approaches seriously. Recent attempts have been made to treat multiple sclerosis with polyunsaturated fatty acids and with colchicine. This approach is not arbitrary and is firmly grounded in fundamental basic scientific concepts. In patients with multiple sclerosis there is evidence of both an abnormality in essential fatty acid metabolism and an abnormality in lymphocyte function. It is now apparent that the fatty acid abnormality may cause the lymphocyte abnormality and that both may be improved by dietary manipulation. There is also evidence that the demyelination may be associated with recurrent inflammatory episodes and with entry of calcium into the cytoplasm. In vitro colchicine has been shown to have actions compatible with regulation of cytoplasmic calcium and in two diseases characterised by intermittent inflammatory episodes (Behçets syndrome and familial Mediterranean fever) it has been found to prevent or to reduce the severity of such episodes. Preliminary results suggest that combined therapy with evening primrose oil and colchicine may be of considerable value.

PMID: 313499 [Indexed for MEDLINE]

5692. Am Fam Physician. 1979 Feb;19(2):131-9.

Arthritis of the temporomandibular joints.

Marbach JJ.

The most common disease of the temporomandibular joint (TMJ) is osteoarthritis. Rheumatoid arthritis and psoriatic arthritis may also involve this joint. Other diseases that may occasionally affect the TMJ include familial Mediterranean fever, systemic lupus erythematosus, gout, Sjögren's syndrome and infectious

arthritis. Many cases of TMJ syndrome are labeled as idiopathic facial pain syndrome, a category that probably represents a number of different entities. The role of dental malocclusion has been greatly overemphasized in the past.

PMID: 760437 [Indexed for MEDLINE]

5693. Akush Ginekol (Mosk). 1979 Feb;(2):46-8.

[Hypophyseal luteinizing hormone excretion in women suffering from periodic disease].

[Article in Russian]

Pogosian GK.

PMID: 426221 [Indexed for MEDLINE]

5694. Klin Med (Mosk). 1979 Feb;57(2):11-5.

[Difficult to diagnose and rare diseases in gastroenterological practice].

[Article in Russian]

El'shtein NV.

PMID: 370451 [Indexed for MEDLINE]

5695. Oral Surg Oral Med Oral Pathol. 1979 Feb;47(2):123-6.

Temporomandibular joint synovitis with effusion in familial Mediterranean fever.

Cooksey DE, Girard K.

A unique case of TMJ synovitis with effusion associated with FMF is described. This effusion was treated by aspiration, once the diagnosis was established. It is believed that aspiration is the most effective way of avoiding aseptic necrosis and should be carried out as soon as the diagnosis is established. The posterior portion of the compartment is easier to find with the aspirating needle. The use of a corticosteroid in conjunction with aspiration is of questionable benefit in FMF but may play a more important part in effusion from other causes.

PMID: 284274 [Indexed for MEDLINE]

5696. Clin Ter. 1979 Jan 15;88(1):89-95.

[A case of recurrent arthro-peritonitis (familial Mediterranean fever) with Raynaud's syndrome].

[Article in Italian]

Vellucci A, Filocamo G, Galanti G, De Petrillo V, Conti S.

PMID: 436380 [Indexed for MEDLINE]

5697. J Iowa Med Soc. 1979 Jan;69(1):11-3.

Familial Mediterranean fever.

Rappaport K, Larson D, Overton RW.

PMID: 759513 [Indexed for MEDLINE]

5698. Zh Nevropatol Psikhiatr Im S S Korsakova. 1979;79(7):912-7.

[Neurologic manifestations of periodic disease].

[Article in Russian]

Fedorova ML.

Results of comprehensive neurological examinations of 4 patients suffering from periodic disease have shown that the latter may be not only a disease entity, but also a syndrome characterizing some organic affections of the brain. The abdominal and other crises of the periodic disease included cerebrovascular disturbances which manifested hemipareses, syncopes, and migraine-like cephalgia. EEG and REG examinations have revealed dysfunction of the mesodiencephalic structures which, probably, underlies the pathogenesis of the periodic disease. The knowledge of the formerly almost unexplored neurological manifestations of the periodic disease will contribute to improvement of the therapy of this rare ailment.

PMID: 465161 [Indexed for MEDLINE]

5699. Ann Clin Lab Sci. 1979 Jan-Feb;9(1):16-7.

Periodic peritonitis, amyloidosis and colchicine.

Reimann HA.

PMID: 420508 [Indexed for MEDLINE]

5700. Arch Anat Cytol Pathol. 1979;27(6):348-56.

[Digestive localization of generalized amyloidosis: attempt at differentiating primary and secondary amyloidosis (author's transl)].

[Article in French]

Lavergne A, Galian A.

PMID: 400223 [Indexed for MEDLINE]

5701. Adv Exp Med Biol. 1979;121B:341-50.

Phagocyte functions in familial Mediterranean fever.

Bar-Eli M, Levy M, Ehrenfeld M, Eliakim M, Gallily R.

Monocytes derived from peripheral blood of patients with familial Mediterranean fever (F.M.F.) demonstrated lower phagocytic capacity for *Shigella flexneri* and depressed bactericidal activity against *S. albus* when compared to monocytes from healthy individuals. Treatment of patients with colchicine did not alter these functions. On the other hand, chemokinesis of PMN of F.M.F. patients was enhanced especially during attacks. Colchicine treatment decreased significantly the PMN chemotactic migration.

PMID: 397753 [Indexed for MEDLINE]

5702. JAMA. 1978 Dec 15;240(25):2733.

Familial mediterranean fever (periodic peritonitis)

[No authors listed]

PMID: 713001 [Indexed for MEDLINE]

5703. Indian Pediatr. 1978 Dec;15(12):1051-4.

Familial Meditteranean fever in India.

Taneja A, Yohanan MD.

PMID: 751944 [Indexed for MEDLINE]

5704. Akush Ginekol (Mosk). 1978 Dec;(12):53-5.

[Gynecological aspects of periodic disease].

[Article in Russian]

Akunts KB, Sarkisian RG, Pogolian GK.

PMID: 736236 [Indexed for MEDLINE]

5705. Am J Dis Child. 1978 Dec;132(12):1209-10.

Familial Mediterranean fever. A case report.

Nichols EA, Reder RF.

A case of familial Mediterranean fever in a young girl presented typical diagnostic dilemmas. Although intermittent proteinuria was noted, a rectal biopsy specimen failed to demonstrate the presence of amyloidosis. Treatment consisted of supportive therapy and colchicine, to which she responded. In a cosmopolitan population, familial Mediterranean fever should be considered in the differential diagnosis of fever of unknown origin.

PMID: 717337 [Indexed for MEDLINE]

5706. Hosp Pract. 1978 Nov;13(11):113-5, 120-3.

Familial mediterranean fever: a status report.

Wolff SM.

The recent discovery that an age-old drug, colchicine, can control this

enigmatic, often unrecognized, recurrent disease means that most affected individuals can now lead virtually normal lives. The research leading to this advance is described, as are the essentials of diagnosis, colchicine's possible mechanisms of action, and the relative merits of chronic vs intermittent colchicine therapy in the abortion of impending attacks.

PMID: 738709 [Indexed for MEDLINE]

5707. J Pediatr. 1978 Nov;93(5):876-8.

Long-term colchicine therapy of familial Mediterranean fever.

Lehman TJ, Peters RS, Hanson V, Schwabe A.

Familial Mediterranean fever is a disorder characterized by recurrent fever and polyserositis. Continuous prophylactic colchicine therapy has been effective in suppressing attacks in affected adults. From 30 children with FMF, 14 were selected for colchicine therapy. Eight children continued prophylactic colchicine therapy for 29 months (mean) and experienced a marked decrease in the frequency of attacks. Six other children did not comply with the treatment regimen. Although no deleterious side effects were noted, the safety of long-term colchicine administration in childhood is unknown.

PMID: 712499 [Indexed for MEDLINE]

5708. Minerva Chir. 1978 Oct 15;33(19):1325-38.

[False acute abdomen].

[Article in Italian]

Quarti-Trevano GM, Pagani M, Poma S, Bruni M, Lochis D, Bracale M, Salvini A.

PMID: 692915 [Indexed for MEDLINE]

5709. Minerva Med. 1978 Sep 15;69(42):2849-53.

[Familial Mediterranean fever. Evidence of its autoimmune pathogenesis].

[Article in Italian]

Savi M, Asinari G, Gaudio V, Neri TM.

Immunological disturbances in FMF have not been previously reported. In present case, positivity for RA and Waaler-Rose test as well as increase of plasma IgG and IgM immunoglobulins during an episode of acute peritonitis is described. These findings, in association with very high levels of urinary FDP, suggest an autoimmune pathogenesis of the disease.

PMID: 692939 [Indexed for MEDLINE]

5710. Ned Tijdschr Geneesk. 1978 Sep 2;122(35):1284-8.

[Colchicine therapy in familial Mediterranean fever].

[Article in Dutch]

Hoefnagel CA, Nauta EH.

PMID: 692754 [Indexed for MEDLINE]

5711. Ned Tijdschr Geneesk. 1978 Sep 2;122(35):1281-3.

[Fever, acute abdomen and painful joints in migrants from the Mediterranean sea area].

[Article in Dutch]



van den Berg B, Frenkel M.

PMID: 692753 [Indexed for MEDLINE]

5712. Fertil Steril. 1978 Jun;29(6):667-8.

Testicular function in patients with familial Mediterranean fever on long-term colchicine treatment.

Levy M, Yaffe C.

Sperm counts and hormonal studies were carried out in six patients with familial Mediterranean fever who were receiving long-term colchicine therapy. The duration of therapy ranged between 7 and 31 months. In all subjects, spermograms, testosterone, follicle-stimulating hormone, luteinizing hormone, and prolactin levels were within normal limits.

PMID: 658478 [Indexed for MEDLINE]

5713. Lakartidningen. 1978 May 17;75(20):2046-7.

[Recurrent fever, abdominal pain of unknown origin among immigrants].

[Article in Swedish]

Torstensson S.

PMID: 661432 [Indexed for MEDLINE]

5714. Rev Clin Esp. 1978 Apr 15;149(1):97-8.

[Prolonged remission with colchicine in a case of familial mediterranean fever].

[Article in Spanish]

Vilardell F.

PMID: 674762 [Indexed for MEDLINE]

5715. Arch Intern Med. 1978 Apr;138(4):644-5.

Unusual immunologic findings in familial Mediterranean fever.

Savi M, Asinari G, Gaudiano V, Olivetti G, Neri TM.

Familial Mediterranean fever (FMF) is an inherited disease of unknown etiology. We report a case in which, during an acute febrile attack, rheumatoid factor and immunoglobulin levels rose, and the levels of complement components fell. The level of urinary fibrinogen degradation products also increased, and all results of tests returned to normal at the end of the acute attack. This suggests that an immunologic phenomenon may play a substantial role in the etiology of FMF.

PMID: 637649 [Indexed for MEDLINE]

5716. Vrach Delo. 1978 Mar;(3):56-60.

[Periodic disease associated with rheumatoid arthritis].

[Article in Russian]

Burdeinyĭ AP, Akimova TF.

PMID: 645038 [Indexed for MEDLINE]

5717. Pediatrics. 1978 Mar;61(3):423-6.

HLA-B27-negative sacroiliitis: a manifestation of familial Mediterranean fever in childhood.

Lehman TJ, Hanson V, Kornreich H, Peters RS, Schwabe AD.

Familial Mediterranean fever is a polysystemic disease seen most frequently in persons of Mediterranean ancestry. Arthritis is one of the common manifestations. Both symptomatic and asymptomatic sacroiliitis have been reported in adults. We report on two children with familial Mediterranean fever with radiographic abnormalities similar to those described in adults. Although sacroiliitis is strongly correlated with the presence of HLA-B27 in most arthropathies, these children were HLA-B27-negative. The diagnosis of familial Mediterranean fever was delayed in both patients because the association of sacroiliitis with familial Mediterranean fever in childhood was not recognized.

PMID: 643416 [Indexed for MEDLINE]

5718. Proc Eur Dial Transplant Assoc. 1978;15:506-14.

Familial Mediterranean fever and nephrotic syndrome in Turkey.

Erek E, Onen K, Müftüoğlu A, Ulkü U, Akokan G.

PMID: 740682 [Indexed for MEDLINE]

5719. Ter Arkh. 1978;50(6):57-60.

[Diagnosis of primary amyloidosis].

[Article in Russian]

Vinogradova OM, Chernokhvostova EV, Batalova TN, Mukhin NA, Nikolaev Alu.

PMID: 675539 [Indexed for MEDLINE]

5720. Clin Pediatr (Phila). 1978 Jan;17(1):14-5.

Colchicine therapy in familial Mediterranean fever. Prophylactic benefit in 6 childhood patients.

Branski D, Gross-Kieselstein E, Abrahamov A.

DOI: 10.1177/000992287801700102

PMID: 618694 [Indexed for MEDLINE]

5721. Nouv Presse Med. 1977 Dec 24;6(44):4140.

[Biliary acids in periodic disease].

[Article in French]

Mamou H, Mamou JE.

PMID: 600764 [Indexed for MEDLINE]

5722. Can Med Assoc J. 1977 Dec 17;117(12):1416-7.

Colchicine therapy for nephrotic syndrome due to familial Mediterranean fever.

Skrinskas G, Bear RA, Magil A, Lee KY.

PMCID: PMC1880423

PMID: 589544 [Indexed for MEDLINE]

5723. Rev Rhum Mal Osteoartic. 1977 Dec;44(12):703-8.

[HL-A and periodic disease].

[Article in French]

Chaquat Y, Tormen JP, Hors J, Dausset J.

In the department of Professor Dausset 41 cases of periodic disease referred by 7 clinics in Paris were examined. Two studies were carried out. A series of 31 not related patients was tested with 30 locus A and B antigen and the frequencies observed were compared with the frequencies in a French and Yemenite Jew population. No statistically valid increase of an HLA gene indicative of a relationship between periodic disease and HLA was found. In 5 cases of amyloidosis HLA A 28 was present and it is possible that this gene is related to the amyloid complication. A family study on 12 families, 7 of which included at least 2 affected children, confirmed the recessive hereditary character of the disease, but not in relation to the HLA system. A parallel clinical study was made, which corroborated the previous studies as regards the frequency of clinical signs. The therapeutic study proved the value of long-term colchicine treatment with or without antihistaminics. The frequency of pain and abdominal crises was reduced, but there was little effect on the articular manifestations.

PMID: 609874 [Indexed for MEDLINE]

5724. Biomedicine. 1977 Dec;26(6):416-24.

An investigation of the complement system in patients with periodic disease (results from 29 cases).

Hartmann L, Lego-Crescioni A, Brecy H, Ollier MP, Herreman G, Mouthon JM, Godeau P.

The complement system was investigated in 29 patients suffering from authentic periodic disease. A statistically significant increase in C4, also in total complement and C3 could be demonstrated. It is possible that the increase in C4 was due to the macrophages which are always present in the infiltrates of periodic disease. This biological observation is of clear practical importance for the diagnosis of the condition both before and after colchicine therapy.

PMID: 304745 [Indexed for MEDLINE]

5725. JAMA. 1977 Nov 14;238(20):2183-8.

Fever of unknown origin. An algorithmic approach.

Vickery DM, Quinnell RK.

PMID: 578837 [Indexed for MEDLINE]

5726. Can Fam Physician. 1977 Nov;23:132-6.

Benign paroxysmal peritonitis: the principal manifestation of familial mediterranean Fever.

Kronld AV.

Two cases of familial mediterranean fever are presented. Several other members of the family were probably affected by the same disease. The etiopathogenesis, ethnic origin and clinical symptomatology are discussed in detail. The importance of history and clinical investigation in differential diagnosis is emphasized, in comparison with the non-specific results of laboratory tests. Finally, therapeutic measures are reviewed, of which only colchicine appears promising at present.

PMCID: PMC2379266

PMID: 21304802

5727. Ann Intern Med. 1977 Nov;87(5):568-70.

Prolonged colchicine treatment in four patients with amyloidosis.

Ravid M, Robson M, Kedar I.

The natural clinical course of four patients with systemic amyloidosis was favourably altered by continuous colchicine therapy. One patient had primary amyloidosis, and the other three suffered from amyloidosis of familial Mediterranean fever. All had a nephrotic syndrome, and one showed features of intestinal malabsorption. The institution of colchicine therapy was followed by a gradual remission of the nephrotic syndrome, a rise of serum albumin to normal values, a slight improvement of renal function, and regression of the intestinal malabsorption. This pattern has remained steady during an observation period of 30 months.

PMID: 921085 [Indexed for MEDLINE]

5728. Isr J Med Sci. 1977 Nov;13(11):1102-8.

Renal amyloidosis: immunofluorescence and electron microscopy studies.

Müftüoğlu AU, Erben T, Harman M, Karayel T, Gürsoy E, Tahsinoğlu M.

Renal biopsy specimens of 15 patients with renal amyloidosis were studied by immunofluorescence microscopy. The amyloidosis was associated with chronic pulmonary disease in five, rheumatoid arthritis in one, chronic lymphocytic leukemia in one, and familial Mediterranean fever in five patients. In three patients no associated condition could be determined although the pattern of organ involvement resembled that of secondary amyloidosis. IgG and complement (C3) were demonstrated in the glomerular capillary walls and in the mesangium in all patients. The pattern of the deposits was neither granular nor linear. Ig and C3 appeared as large confluent masses or broad ribbon-like segments. In the six patients studied by electron microscopy the fibrillary formation of amyloid was seen in the mesangium and the glomerular capillary walls corresponding to the Ig deposits. No immunofluorescence or ultrastructural differences were observed among the patients with secondary, inherited and leukemia-associated amyloidosis included in this study.

PMID: 591304 [Indexed for MEDLINE]

5729. Am J Med Sci. 1977 Nov-Dec;274(3):265-70.

Monocyte function in familial Mediterranean fever.

Bar-Eli M, Gallily R, Levy M, Eliakim M.

Monocytes derived from the peripheral blood of patients with familial Mediterranean fever (FMF) demonstrated a consistently lower phagocytic capacity (38-44%) for 125I-labelled *Shigella flexneri* when compared to monocytes from healthy subjects. Phagocytosis of both viable and killed *Staphylococcus albus* was similar in patients and controls. However, FMF monocytes had a two- to eight-fold depressed bactericidal capacity against *S. albus* in comparison to normal monocytes. Acid phosphatase and beta-glucuronidase monocyte activities were similar in patients and controls. It is suggested that the defects in monocyte function may be of importance in the pathogenesis of FMF. Colchicine had no effect on any of the indices studied.

PMID: 345807 [Indexed for MEDLINE]

5730. Ann Intern Med. 1977 Nov;87(5):579-80.

Amyloidosis in a renal allograft in familial Mediterranean fever.

Jones MB, Adams JM, Passer JA.

PMID: 335941 [Indexed for MEDLINE]

5731. Nouv Presse Med. 1977 Oct 8;6(33):2949-53.

[HLA markers and periodic disease [familial Mediterranean fever (F.M.F.)]  
(author's transl)].

[Article in French]



Chaouat Y, Tormen JP, Godeau P, Camus JP, Kahn MF, Ryckewaert A, Laula JE, Menkes CJ, Schmid M, Hors J.

Thirty-one unrelated patients, 15-52 years old, were typed by microlymphocytotoxicity for 27 alleles of the HLA system. In addition, 12 families including 1 or more patient were also analysed. This criteria for diagnosis were those of Sohar et al. (Am. Intern. Med., 1967, 43, 227-253). All patients were of Israelite-Sephardin origin except two (Armenian and French); they were from North-Africa (Tunisia, Morocco and Algeria) and Israël. The results were compared to the antigen frequencies of 3 reference normal populations. The frequencies of the studied alleles do not differ from those of controls, except for HL-A28 and B14 slightly increased when compared to the normal frequencies. The study of 7 families with at least two sibs suffering from FMF shows a random distribution of the genotypes : 2 HLA identical, 6 different and 10 haploidentical diseased sibs. This distribution differs significantly ( $p$  less than 0.01) from that expected in the case of a recessive inheritance. These data do not support the hypothesis of a linkage between genes controlling FMF and HLA genes.

PMID: 593830 [Indexed for MEDLINE]

5732. Br Med J. 1977 Sep 24;2(6090):808.

Long-term colchicine prophylaxis in familial Mediterranean fever.

Levy M, Eliakim M.

PMCID: PMC1631975

PMID: 912334 [Indexed for MEDLINE]

5733. Am J Med Sci. 1977 Sep-Oct;274(2):147-52.

A cytogenic evaluation of long-term colchicine therapy in the treatment of Familial Mediterranean fever (FMF).

Cohen MM, Levy M, Eliakim M.

Thirty-eight patients suffering from Familial Mediterranean Fever (FMF) and undergoing colchicine therapy for periods varying from one week to three years were examined cytogenetically. Preparations were derived from short-term lymphocyte cultures; mitotic rate, percent tetraploidy, and chromosome breakage rates were determined. Twenty-one patients were examined prior to treatment, 22 during treatment and 5 both before and during treatment. No statistically significant differences were observed in the parameters studied between ten controls and the patient groups. An in vitro experiment indicated a direct correlation between increased colchicine concentration and mitotic rate. However, tetraploidy or chromosome damage showed no such association with colchicine concentration. Among the patient group, pregnancy occurred in four patients while under treatment; three pregnancies resulted in the birth of normal children while the fourth has not yet been completed. In one pregnancy, cultured fetal amniotic fluid cells demonstrated no effect of colchicine on the cytogenetic parameters investigated. These results indicate no untoward effects on long-term colchicine treatment in FMF with respect to fertility, teratogenicity and chromosomal damage.

PMID: 602955 [Indexed for MEDLINE]

5734. Am J Pathol. 1977 Sep;88(3):679-98.

The relationship of a serum protein, C1t, to a common nonfibrillar constituent of amyloid (P component) as revealed by immunohistochemical studies.

Katz A, Weicker-Thorne J, Painter RH.

C1t, a serum protein isolated by affinity chromatography on Sepharose bears a remarkable ultrastructural and physicochemical resemblance to P component, a common constituent of amyloid. This study provides further evidence for their similarity by the demonstration of immunologic identity and by the presence of C1t in amyloid deposits of various types using immunoperoxidase and immunofluorescent techniques. In addition, subcomponents of C1, as well as C3, C4, C5, and properdin, were demonstrated to a limited extent. The possible role of C1t/P component in amyloidogenesis is discussed in the light of recent

advances in our knowledge of the nature of amyloid substance.

PMCID: PMC2032378

PMID: 329683 [Indexed for MEDLINE]

5735. Br J Ophthalmol. 1977 Jul;61(7):496-7.

Colchicine suppression of corneal healing after strabismus surgery.

Biedner BZ, Rothkoff L, Friedman L, Geltman C.

Two patients who had previously undergone uneventful operations for strabismus showed healing of corneal dellen and erosion after withdrawal of colchicine therapy. It is suggested that the exhibition of colchicine therapy for familial Mediterranean fever in these two cases was responsible for initial persistence of these two postoperative complications.

PMCID: PMC1043020

PMID: 889763 [Indexed for MEDLINE]

5736. West J Med. 1977 Jul;127(1):40-1.

Familial Mediterranean fever--a progress report.

Goldfinger SE.

PMCID: PMC1237686

PMID: 878472 [Indexed for MEDLINE]

5737. West J Med. 1977 Jul;127(1):15-23.

Familial Mediterranean fever. Recent advances in pathogenesis and management.

[No authors listed]

The success of colchicine therapy in the management of familial Mediterranean fever has provided new direction to investigations into the pathogenesis of this disease. Examination of HLA antigen frequencies in 53 patients with familial Mediterranean fever and appropriate controls, as well as various immunologic studies have yielded no significant differences. However, B lymphocyte typing and assays for immune complexes, lymphokines and prostaglandins may be of potential interest. Preliminary studies indicate that leukocytes of patients with familial Mediterranean fever release increased amounts of lysozyme ( $P < 0.01$ ), when subjected to high temperatures, and of both lysozyme and myeloperoxidase at low osmotic concentrations. The known and potential effects of colchicine on leukocyte and cellular metabolism, and the current status of colchicine prophylaxis are reviewed. In patients receiving an optimum colchicine dose of 1.5 to 1.8 mg per day, side effects have been minimal and the frequency of attacks has been decreased significantly.

PMCID: PMC1237671

PMID: 878470 [Indexed for MEDLINE]

5738. Infirm Fr. 1977 Jul;(187):19-21.

[Periodic disease (Cattan-Mamou disease)].

[Article in French]

Robert JF.

PMID: 587104 [Indexed for MEDLINE]

5739. Ann Intern Med. 1977 Jul;87(1):31-4.

Amyloid deposition in a renal transplant in familial Mediterranean fever.

Benson MD, Skinner M, Cohen AS.

A patient with familial Mediterranean fever and amyloidosis who received a cadaver renal transplant 6 1/2 years ago was studied to determine the relation of the serum precursor of secondary amyloid (SAA) to the clinical course and to the deposition of amyloid in the transplant. Amyloid fibrils extracted from the patient's kidneys contained protein AA as a major constituent, which identified the amyloid as secondary. Protein AA antiserum was used in an indirect immunofluorescent technique to stain amyloid deposits in sections of the original kidney. A renal biopsy at 2 years showed no amyloid, but a renal biopsy at 4 years showed amyloid. Serum levels of SAA from 3 years before transplant to 6 years after transplant were elevated throughout most of the course.

PMID: 327890 [Indexed for MEDLINE]

5740. Lancet. 1977 May 28;1(8022):1140-1.

Colchicine in familial Mediterranean fever.

[No authors listed]

PMID: 68234 [Indexed for MEDLINE]

5741. Fortschr Med. 1977 May 26;95(20):1329-32.

[Amyloidosis].

[Article in German]

Franklin EC.

Recent studies have clearly indicated that amyloid is a generic term which includes a number of different substances, all of which have a beta-pleated sheet structure and a characteristic fibrillar appearance in the electron microscope. The most common types are made of immunoglobulin light chain (AL) fragments in the primary and myeloma-associated type, and of the AA protein in the secondary

and some familial forms. It seems probable that other localized types are composed of prohormones or other tissue proteins. In systemic amyloidosis, the fibrils seem to be derived from a soluble circulating precursor; immunoglobulin light chains give rise to AL, and the SAA protein, which behaves as an acute phase reactant yields AA, presumably by proteolysis. It is not known whether the disease is due to overproduction or a defect in degradation. Though effective therapeutic agents are still lacking, colchicine has proved useful in preventing or ameliorating the amyloid in Familial Mediterranean Fever and in several experimental forms of the disease. It deserves careful study as a possible therapeutic agent on other types of amyloidosis.

PMID: 406184 [Indexed for MEDLINE]

5742. Cas Lek Cesk. 1977 May 6;116(18):564-7.

[Some newer biological properties of colchicine and its derivatives].

[Article in Czech]

Trnavský K, Trnavská Z, Mikulíková D.

PMID: 880594 [Indexed for MEDLINE]

5743. Rheumatol Rehabil. 1977 May;16(2):102-6.

Protracted arthritis in familial Mediterranean fever.

Sneh E, Pras M, Michaeli D, Shanin N, Gafni J.

A review of the files of familial Mediterranean fever (FMF) confirmed the rarity of patients suffering protracted arthritic attacks and the propensity of the joints, in general, to recover. While 70% of those afflicted suffered bouts of synovitis, only 57 patients (5% of the FMF-population) experienced protracted attacks involving a total of 84 joints, 36 of them knees and 25 hips. Functional and, usually, anatomical integrity was regained in all but 27 joints. Of the 27

joints producing residual incapacity, 21 were hips. Seven hips showed roentgenologically typical aseptic necrosis of the femoral head and 14 only sclerosis and narrowing of the joint space. Eight hips eventually required total prosthetic replacement. We suggest that the poor prognosis of the hip, in contrast to other joints affected by protracted FMF-arthritis, is related not directly to the metabolic aberration underlying the disease but to attenuation of the arterial blood supply of the femoral head by synovial exudation. Early aspiration of exudate could alter the prognosis by preventing the complication of aseptic necrosis.

PMID: 866903 [Indexed for MEDLINE]

5744. J Lab Clin Med. 1977 May;89(5):1092-1104.

Immunochemical studies on the nature of the serum component (SAA) related to secondary amyloidosis.

Ignaczak TF, Sipe JD, Linke FP, Glenner GG.

The relative occurrence of the amyloid-related serum protein SAA in various disease states and in healthy subjects has been compared by both solid phase radioimmunoassay ((RIA) and immunodiffusion techniques which employ antibodies to purified amyloid fibril protein AA of homogeneous size and charge. SAA levels were elevated above normal in certain categories of neoplastic, inflammatory, and infectious diseases as well as in secondary amyloidosis. The lowest median value, 8 ng./ml., was observed for approximately 150 normal sera, with no age-related increase in subjects ranging in age from 16 to 70 years. The results are consistent with several recent observations that SAA is normal acute phase reactant, and hence the RIA for SAA has no prognostic or diagnostic significance for secondary amyloidosis. The sensitivity of RIA for the detection of SAA is lower than would be expected when AA cross-reactivity values for sera are correlated with their reaction with anti-AA antibodies in immunodiffusion. This observation, along with others reported elsewhere suggests that those determinants which cross-react with anti-AA antibodies are relatively hidden in native SAA. Myeloma sera were less reactive than other groups of pathologic sera in immunodiffusion, although they were similar to other patients' sera when analyzed by RIA. Antibodies to highly purified AA were also used to investigate

the structure of SAA by a double-antibody immunoprecipitation method. Precipitated SAA was partially dissociated during sodium dodecyl sulfate-urea-polyacrylamide gel electrophoresis to a 12,500 molecular weight moiety designated, SAAL. Multiple radiolabeled species of molecular weight intermediate to SAA and SAAL were also detected and appeared to represent incompletely dissociated SAA. The results suggest the SAA is an aggregate of several SAAL chains.

PMID: 404372 [Indexed for MEDLINE]

5745. Tissue Antigens. 1977 May;9(5):273-5.

HLA antigen in familial mediterranean fever.

Gazit E, Orgad S, Pras M.

PMID: 70085 [Indexed for MEDLINE]

5746. Q J Med. 1977 Apr;46(182):243-58.

Renal vein thrombosis as the major cause of renal failure in familial Mediterranean fever.

Reuben A, Hirsch M, Berlyne GM.

Eighteen out of 57 patients (31.6 per cent) suffering from Familial Mediterranean Fever (FMF) were found to have the nephrotic syndrome, histologically proven amyloidosis and progressive renal failure. In 14 cases renal function deteriorated rapidly after the first appearance of significant proteinuria, and 12 cases (66.7 per cent) required regular haemodialysis. Seven of these patients, seen in the early stages of renal impairment, were subsequently diagnosed clinically as probably having developed renal vein thrombosis. There was radiological proof of intrarenal or major renal vein occlusion in five which in one patient progressed to inferior vena cava obstruction. Treatment with heparin, plasminogen activators and fibrinolytic agents was disappointing although renal function has stabilized in one patient on long term oral anticoagulant



therapy. It is suggested that renal vein thrombosis is common in FMF with renal amyloidosis and usually causes rapid deterioration of function and irreversible renal failure requiring dialysis. Renal phlebography may delineate clot in the main renal veins or indicate areas of reduced blood flow due to thromboses in intrarenal venules. Treatment is only partially satisfactory but there is some evidence to suggest that renal phlebography should be undertaken promptly when renal function begins to fall followed by anticoagulant therapy to prevent further thromboembolic complications.

PMID: 866577 [Indexed for MEDLINE]

5747. JAMA. 1977 Mar 7;237(10):960-1.

Mollaret meningitis.

Reimann HA.

PMID: 576245 [Indexed for MEDLINE]

5748. Zdravookhr Kirg. 1977 Mar-Apr;(2):48-52.

[Hypothalamic visceropathy in the clinical aspects of internal diseases].

[Article in Russian]

Bazhanov BG.

PMID: 17978 [Indexed for MEDLINE]

5749. Rev Clin Esp. 1977 Feb 28;144(4):297-9.

[Study of a Spanish family with familial Mediterranean fever].

[Article in Spanish]

Siso C, Vinyes-M A, Badrinas F, Carrera M.

PMID: 847266 [Indexed for MEDLINE]

5750. Rev Clin Esp. 1977 Feb 28;144(4):243-50.

[Familial, mediterranean fever].

[Article in Spanish]

Siso C, Vinyes-M A, Badrinas F, Fernandez-Nogues F.

PMID: 847259 [Indexed for MEDLINE]

5751. Ann Intern Med. 1977 Feb;86(2):162-5.

Efficacy of intermittent colchicine therapy in familial Mediterranean fever.

Wright DG, Wolff SM, Fauci AS, Alling DW.

Nine patients with familial Mediterranean fever (FMF) were admitted to a controlled, double-blind trial to determine if there are patients with this disease who are able to abort their acute episodes of pain and fever with short courses of colchicine taken at the onset of attacks. Five patients completed their treatment assignments, and colchicine was significantly effective in aborting the attacks of three but was ineffective in two. The remaining four patients could not be assessed because of insufficient numbers of courses. During the 10 months of the trial, 28 courses of colchicine and 31 of placebo were taken during the early stages of FMF attacks. Twenty-one (75%) colchicine courses were followed by attacks considered to have been aborted, compared to only three (10%) placebo courses. This trial shows that patients can recognize the prodrome of their FMF attacks and that some patients can consistently abort their attacks with short courses of colchicine taken at the very onset of symptoms.

PMID: 319724 [Indexed for MEDLINE]

5752. Klin Med (Mosk). 1977 Feb;55(2):91-7.

[Immunogenesis of periodic disease].

[Article in Russian]

Aĭvazian AA, Zavgorodniaia AM, Abramian MK, Pashinian SA, Bagdasarian GB.

PMID: 300821 [Indexed for MEDLINE]

5753. Ter Arkh. 1977;49(8):33-8.

[Human transplantation antigens and diseases. Current state of the problem].

[Article in Russian]

Zaretskaia IuM.

PMID: 929391 [Indexed for MEDLINE]

5754. Nouv Rev Fr Hematol Blood Cells. 1977;18(2):275-83.

Genes and geography.

Waldenstrom JG.

The author discusses a number of genetically determined diseases, such as hemoglobinopathies, acute intermittent porphyria, familial Mediterranean fever and so-called acquired hypogammaglobulinemia from the geographical point of view. Possible factors explaining localized increases in incidence are discussed. The

importance of isolates for the development of such foci is stressed.

PMID: 917829 [Indexed for MEDLINE]

5755. Isr J Med Sci. 1977 Jan;13(1):55-8.

Constrictive pericarditis in familial Mediterranean fever.

Zemer D, Cabili S, Revach M, Shahin N.

Fibrosing peritonitis and constrictive pericarditis occurred in an 18-year-old patient who manifested the classic features of familial Mediterranean fever (FMF). Pericardial calcification had been present in chest X-rays taken when the patient was five years old. Intermittent intestinal obstruction and congestive heart failure were relieved by appropriate surgical intervention, but attacks of FMF subsided only after colchicine therapy. This is the first instance of nonuremic pericarditis in our experience with over 1,000 FMF patients. Critical analysis of the reported cases in which pericarditis was attributed to FMF strengthens our belief that the occurrence of pericarditis in a patient with FMF probably represents a fortuitous intercurrent disease.

PMID: 838571 [Indexed for MEDLINE]

5756. Bull Rheum Dis. 1977-1978;28(2-3):932-9.

Disorders of the axial skeleton which are lesser known, poorly recognized or misunderstood.

Resnick D.

PMID: 618560 [Indexed for MEDLINE]

5757. Zh Eksp Klin Med. 1977;17(1):37-44.

[Humoral and cellular factors of immunogenesis in periodic disease].

[Article in Russian]

Aivazian AA, Zavgorodniaia AM, Abramian MK, Pashinian SA, Bagdasarian GB.

PMID: 329624 [Indexed for MEDLINE]

5758. Isr J Med Sci. 1977 Jan;13(1):33-8.

Probability of survival in hypertensive and nonhypertensive patients on maintenance hemodialysis.

Eliahou HE, Iaina A, Reisin E, Shapira J.

The actuarial survival rate for 58 unselected patients who entered a program of maintenance hemodialysis and transplantation was found to be 43.0 +/- 8.3 (SE)% for the six-year period of observation. The survival rate was considerably lower in hypertensive patients as well as in patients with familial Mediterranean fever with amyloidosis, all of whom were nonhypertensive. When the patients with familial Mediterranean fever were excluded from the non-hypertensive group, the expected survival rate of this group became greater than that of the hypertensive group, the difference being about 25% in five years and about 50% in six years. This difference in the survival rate approaches that between normotensive subjects and untreated severely hypertensive patients in the general population. It is concluded that hypertension is a serious limiting factor in the survival of patients on chronic hemodialysis, and that the difference in survival between the hypertensive and the non-hypertensive patients is attributable to hypertension.

PMID: 320159 [Indexed for MEDLINE]

5759. Arch Maragliano Patol Clin. 1977;33:61-70.

[The clinical problem of periodic fever].

[Article in Italian]

Arcuri F, Pagano G.

PMID: 263680 [Indexed for MEDLINE]

5760. Nouv Presse Med. 1976 Oct 9;5(9 Oct 76):2151-2.

[Treatment of periodic disease with colchicine].

[Article in French]

Mamou H, Mamou JE, Grout F.

PMID: 980775 [Indexed for MEDLINE]

5761. Nouv Presse Med. 1976 Sep 25;5(31):1969-73.

[Gastrointestinal amyloidosis].

[Article in French]

Lévy A, Lender M.

A series of 29 cases of amyloidosis of the alimentary tract is reported. Five cases (17%) were primary amyloidosis; 14 cases (48%) were amyloidosis secondary to other diseases (such as chronic inflammatory and neoplastic diseases); 10 cases (35%) were amyloidosis of the heredo-familial type connected with Familial Mediterranean Fever. In 23 patients (79%) the diagnosis was established by biopsies, and in 6 more cases on autopsy. Gastrointestinal involvement was found in all age groups. Gastro-enterologic complications observed in the present series include: diarrhea, malabsorption, ileus and gastrointestinal bleeding. In addition other conditions such as jaundice (3 cases), esophagitis and acute hemorrhagic pancreatitis were observed. In 22 patients proteinuria was observed

and in 13 patients the nephrotic syndrome. Among 17 patients, in 11 the clinical picture before death was that of terminal renal failure. The survival after diagnosis among 14 patients reached 4 years in 9 cases, and 19 years in one case. The diagnostic value of the rectal biopsy is emphasized.

PMID: 185589 [Indexed for MEDLINE]

5762. Nouv Presse Med. 1976 Sep 11;5(29):1834-5.

[Hemolysis with course of periodic disease].

[Article in French]

Laurens A, Duriez R, Halpert J, Martoia P.

PMID: 967663 [Indexed for MEDLINE]

5763. Minerva Pediatr. 1976 Aug 18;28(26):1650-3.

[Familial mediterranean fever (periodic disease). Description of a case].

[Article in Italian]

Gemme G, Ruffa G, Bonioli E, Mangiante G.

PMID: 1012200 [Indexed for MEDLINE]

5764. Br Med J. 1976 Jul 31;2(6030):284.

Detection of urinary amyloid in familial Mediterranean fever.

Nimoityn P, Lasker N, Soriano RZ.

PMCID: PMC1687860

PMID: 953566 [Indexed for MEDLINE]

5765. Harefuah. 1976 May 2;90(9):440-2.

[Continuous colchicine therapy in familial mediterranean fever].

[Article in Hebrew]

Zemer D, Pras M, Sohar E, Gafni J.

PMID: 939460 [Indexed for MEDLINE]

5766. Pediatrics. 1976 May;57(5):810-2.

Familial Mediterranean fever with temporomandibular joint arthritis.

Simon G, Marbach JJ.

PMID: 940726 [Indexed for MEDLINE]

5767. Arthritis Rheum. 1976 May-Jun;19(3):618-22.

Effect of prophylactic colchicine therapy on leukocyte function in patients with familial Mediterranean fever.

Dinareello CA, Chusid MJ, Fauci AS, Gallin JJ, Dale DC, Wolff SM.

Patients with familial Mediterranean fever (FMF) who were part of a double-blind trial of daily colchicine as prophylaxis for their disease had leukocyte functions studied while receiving colchicine or placebo. Leukocytes taken from these patients while on prophylactic doses of colchicine produced normal quantities of leukocytic pyrogen, ingested bacteria normally, and migrated



normally in chemotactic chambers. In addition these patients had normal numbers of circulating T and B lymphocytes as well as normal blastogenic responses of their peripheral lymphocytes to mitogenic stimuli. The patients on colchicine, however, had significantly fewer neutrophils and monocytes accumulating at skin-window sites 24 hours after the initial abrasion. Because the early phase of the skin-window response was normal in these patients, the decreased late response may be related to a failure to amplify the initial inflammatory reaction. The reduced capacity to generate a normal inflammatory response may account for the failure of these patients to develop full attacks while taking colchicine.

PMID: 779797 [Indexed for MEDLINE]

5768. Rev Rhum Mal Osteoartic. 1976 Apr;43(4):267-72.

[Periodic disease (familial paroxysmal polyseritis). 52 cases].

[Article in French]

Bitar E, Naffah J, Nasr W, Khoury K.

On the basis of well defined diagnostic criteria, the authors conclude that periodic disease affects males in particular. It commences before the age of 20 years in 80 percent of cases. In particular it occurs in Armenian and Shiite communities. Its evolution is normally benign ; amyloidosis is found in only 8 percent of cases. Joint manifestations are found in 48 percent of cases and may take on different aspects and occur in several different sites : myalgia or arthralgia, monoarthritis, oligoarthritis, polyarthritis, neck or sacroiliac pain. The authors have not noted prolonged peripheral joint episodes. No cases of amyloidosis were diagnosed before the appearance of the clinical signs of the disease. An autosomal, dominant heredity with incomplete penetration seems to be the most likely hypothesis.

PMID: 1273476 [Indexed for MEDLINE]

5769. Arch Intern Med. 1976 Apr;136(4):449-51.

Dialysis in renal failure caused by amyloidosis of familial Mediterranean fever.  
A report of ten cases.

Ari JB, Zlotnik M, Oren A, Berlyne GM.

Ten unselected patients with renal failure caused by amyloidosis associated with FMF were treated by regular hemodialysis therapy from 1969 to 1974. They were compared to age-matched control patients treated by hemodialysis in the same unit during the same period, who were suffering from renal failure caused by other disease. Mortality in FMF and control patients was 30% with no significant difference in mean survival, shunt life, serum albumin or hemoglobin levels between the two groups. There was no significant difference in blood pressure measured predialysis or postdialysis in patients with FMF or in controls. The synthetic ACTH stimulation test showed adequate or elevated adrenocortical function. It is concluded that life can be prolonged up to 3 1/2 years by hemodialysis in renal failure caused by amyloidosis complicating FMF, and that renal failure caused by FMF is not a contraindication to regular hemodialysis therapy.

PMID: 178285 [Indexed for MEDLINE]

5770. Lancet. 1976 Mar 13;1(7959):592.

Letter: Periodic fever suppressed by reserpine.

Hayashi A, Suzuki T, Shimizu A, Yamamura Y.

PMID: 55872 [Indexed for MEDLINE]

5771. Arch Dermatol. 1976 Mar;112(3):364-6.

Cutaneous manifestations of familial Mediterranean fever.

Azizi E, Fisher BK.

Familial Mediterranean fever (FMF) is frequently accompanied by erysipelas-like attacks. These should alert the physician to the correct diagnosis of this systemic disease. Several other nonspecific skin lesions may be seen in FMF. To our knowledge, histologic findings in erysipelas-like skin rashes seen in FMF are not reported elsewhere in the literature.

PMID: 1259449 [Indexed for MEDLINE]

5772. Dtsch Med Wochenschr. 1976 Feb 6;101(6):200-4.

[Amyloidosis in familial mediterranean fever: clinical and renal-biopsy features (author's transl)].

[Article in German]

Brass H, Klein H, Buss H, Lapp H, Heintz R, Angelkort B.

In two Turkish female patients, aged 14 and 29 years, with familial mediterranean fever amyloidosis of the perireticular type was found. The disease was characterized by feverish bouts, abdominal colics, and joint involvements. The younger patient had the diagnosis confirmed at an early stage by renal biopsy, and under heparin and azathioprine the clinical signs, especially the nephrotic syndrome, regressed over a period of seven months. The second patient died of treatment-resistant shock in acute renal failure, due to rapidly progressing renal amyloidosis.

PMID: 1248398 [Indexed for MEDLINE]

5773. Rev Prat. 1976 Jan 21;26(5):235-40, 43-4, passim.

[The therapeutic year].

[Article in French]

Dry J.

PMID: 775603 [Indexed for MEDLINE]

5774. N Engl J Med. 1976 Jan 15;294(3):170-1.

Letter: Colchicine in familial Mediterranean fever.

Zemer D, Pras M, Sohar E, Gafni J.

DOI: 10.1056/NEJM197601152940327

PMID: 1244524 [Indexed for MEDLINE]

5775. Ann Pediatr (Paris). 1976 Jan 2;23(1):11-6.

[Macroscopic hematuria in infants and children. Report of 103 cases].

[Article in French]

Lasfargues G, Baudon JJ, Bégué P, Omanga U.

PMID: 16104245 [Indexed for MEDLINE]

5776. Trans R Soc Trop Med Hyg. 1976;70(1):90.

Letter: Colchicine and periodic peritonitis.

Farid Z, Hassan A, Trabolsi B.

PMID: 1265831 [Indexed for MEDLINE]

5777. Rocky Mt Med J. 1976 Jan-Feb;73(1):25-30.

Glomerulitis and factor vii deficiency in Familial Mediterranean fever.

Miller EE, Bowerman DL.

PMID: 1246584 [Indexed for MEDLINE]

5778. Ter Arkh. 1976;48(11):119-20.

[Case of periodic disease associated with Bechterew's disease].

[Article in Russian]

Kovalev VF, Vherepanov SP.

PMID: 1021885 [Indexed for MEDLINE]

5779. Med Chir Dig. 1976;5(7):345-7.

[Familial Mediterrean fever. Apropos of 7 Greek cases].

[Article in French]

Economopoulos P, Gabriel P, Kandylas J, Zevgolatis C.

PMID: 1018528 [Indexed for MEDLINE]

5780. Am J Hematol. 1976;1(3):307-11.

Leukocyte function in familial Mediterranean fever.

Territo MC, Peters RS, Cline MJ.

Neutrophilic leukocytes of patients with familial Mediterranean fever and of normal control subjects were studied in vitro. FMF neutrophils were found to be morphologically normal by light and electron microscopy and to have normal quantities of the lysosomal enzyme lysozyme. FMF cells demonstrated a slight decrease in their ability to migrate randomly in capillary tubes, this was primarily seen in Armenian patients and in those experiencing an acute attack. The leukocytes of these patients functioned normally in regard to their chemotactic and Candida-killing activity.

PMID: 998618 [Indexed for MEDLINE]

5781. Zh Eksp Klin Med. 1976;16(5):70-3.

[Correlation of cellular immunity data with blood plasma globulin fractions in periodic disease].

[Article in Russian]

Zavgorodniaia AM, Guiumdzhian IO.

PMID: 66826 [Indexed for MEDLINE]

5782. J Med Genet. 1975 Dec;12(4):317-26.

Genetic factors in amyloidosis.

Thomas PK.

In the absence of biochemical distinctions, the nosography of the inherited amyloidoses must at present depend largely upon clinical subdivisions. In the broad classification adopted here, the disorders have for convenience been grouped according to the anatomical system that is predominantly affected. It is evident that the amyloid syndromes display considerable heterogeneity. However, they overlap. Thus in the Iowa type classified with the hereditary amyloid neuropathies (van Allen et al, 1969; Gimeno et al, 1974), renal involvement was

frequent and was the usual cause of death. In the English (Zalin et al, 1974) and Scandinavian (Andersson, 1970) families with neuropathy as the predominant feature, cardiac involvement was a common finding. In certain of the conditions discussed, such as medullary carcinoma of the thyroid and Down's syndrome, amyloid deposition is merely an incidental aspect of the disorder. In those conditions in which generalized or localized amyloid deposition occupies a more central position in the clinical syndrome, an autosomal dominant inheritance has been established or suggested in the majority. An autosomal recessive inheritance has so far only been recognized in familial Mediterranean fever. In the family with hereditary amyloid heart diseases reported by Fredricksen et al (1962), the disorder was confined to a single sibship, raising the possibility of recessive inheritance. This could also be true in sporadic examples of primary amyloidosis. The dominantly inherited amyloidoses comprise a number of geographically widely scattered families with clinical pictures that do not show consistent differences between some families. The families that do not show consistent differences are not necessarily harbouring mutations at the same locus, or the same mutation at any particular locus. However, many of these dominantly inherited clinical syndromes are sufficiently different from each other and the clinical manifestations of each sufficiently consistent to indicate that separate main genes are likely to be involved...

PMCID: PMC1013309

PMID: 176361 [Indexed for MEDLINE]

5783. *Nouv Presse Med.* 1975 Nov 29;4(41):2949-50.

[Letter: Association of periodic disease and ankylosing spondylitis].

[Article in French]

Lejeune E, Daumont A, Deplante JP.

PMID: 1219614 [Indexed for MEDLINE]

5784. *Lancet.* 1975 Nov 8;2(7941):932-3.

Letter: Mollaret's meningitis.

Melendro JC.

PMID: 53417 [Indexed for MEDLINE]

5785. Ann Clin Lab Sci. 1975 Nov-Dec;5(6):417-20.

Rhythms and periodicity in health and disease.

Reimann HA.

Biorhythms longer than the circadian that influence reactions of people and characterizes some diseases have not received much medical attention. The lay press describes cycles of 23, 28 and 33 days said to regulate moods, intellectual ability and efficiency, respectively. Whether or not three overlapping cycles actually regulate three different vague reactions may be questioned. Of interest, however, are rhythms of similar tempo which control mensis, cyclic changes in male hormones and a number of periodic diseases. Although reports of more than 2500 cases of periodic diseases have been published, physicians generally are skeptical on the subject. Incorrect diagnosis leads to unnecessary testing, surgical exploration and medication.

PMID: 1200616 [Indexed for MEDLINE]

5786. Ann Intern Med. 1975 Oct;83(4):581.

Letter: Remission in renal amyloidosis.

Méry JP, Mostefa S.

PMID: 1167003 [Indexed for MEDLINE]



5787. Virchows Arch A Pathol Anat Histol. 1975 Sep 18;367(4):263-72.

Synovitis of familial mediterranean fever. A histologic and ultrastructural study.

Stein H, Yarom R, Makin M.

The microscopic and ultrastructural features seen in the synovium of twelve patients affected by the protracted arthritis variety of FMF is described. It would appear that the small vessels of the synovial membrane are the principle target organ in this articular pathology. Intra articular injections of colloidal radioactive gold, or hydrocortisone, do not alter the histologic and ultrastructural appearance of the affected synovia. Neither do these findings change in the regenerated synovia, growing after a surgical synovectomy. The implications of these findings are discussed.

PMID: 809910 [Indexed for MEDLINE]

5788. J Med Soc N J. 1975 Sep;72(9):735-6.

The use of colchicine for the treatment of familial Mediterranean fever.

Cheung MW, Pugliese AC.

PMID: 1059788 [Indexed for MEDLINE]

5789. Br Med J. 1975 Jul 12;3(5975):60.

Editorial: Colchicine in familial Mediterranean fever.

[No authors listed]

PMCID: PMC1673619

PMID: 1095131 [Indexed for MEDLINE]

5790. S Afr Med J. 1975 May 10;49(20):813-7.

Amyloidosis of the kidneys. Review of patients and literature.

Lender M, Rosenblueth M.

The clinical findings in 49 patients (27 males) who had histologically confirmed amyloidosis of the kidney, are reviewed. In 28 patients, the diagnosis was arrived at by percutaneous renal biopsy, and in 21 patients it was made at autopsy. The youngest patient was diagnosed at the age of 16 years. In 11 patients (22,5%) no associated disease was found, in a further 11 patients the amyloidosis was of the type connected with familial Mediterranean fever, and in 27 patients (55%) the amyloidosis was of the secondary type. Forty-six patients (94%) presented with proteinuria at some stage of their disease. Twenty-one patients developed the nephrotic syndrome. Thirty-two patients died, and in 18 instances uraemia was the cause of death. In 18 patients there was evidence of renal pathology other than amyloidosis, and in some patients this may have contributed to the impairment of renal function and the appearance of proteinuria.

PMID: 1154134 [Indexed for MEDLINE]

5791. Nouv Presse Med. 1975 Apr 5;4(14):1031-3.

[Gentic study of paroxystic familial polyseritis. 72 cases].

[Article in French]

Naffah J, Bitar E, Nasr W, Khoury K.

Study of the mode of hereditary transmission of familial paroxystic polyseritis in Lebanon led us to conclude that the disease was transmitted in a dominant fashion. In almost one third of our families, dominant transmission was certain or probable. In the other families, dominant heredity was not excluded if the

hypothesis, supported by many facts, of incomplete penetrance is accepted. The possibility that certain forms of the disease are dominant and others recessive cannot be rejected, but in the absence of biological proof of this genetic heterogeneity it cannot be confirmed. The majority of the patients, as is usual in the disease, were male. The highest risk groups in the Lebanese population are Armenians and Shiite Moslems

PMID: 1129060 [Indexed for MEDLINE]

5792. J Clin Microbiol. 1975 Apr;1(4):363-5.

Antibodies to Epstein-Barr virus in patients with cryptococcosis.

Levine PH, Diamond RD, Reisher JL.

Antibody levels to the Epstein-Barr virus, the etiological agent for heterophile-positive infectious mononucleosis, have been demonstrated in high titer in a number of lymphomas as well as infectious mononucleosis. Recent reports have suggested that the elevated antibody levels to Epstein-Barr virus may be the nonspecific result of disordered cell-mediated immunity. This study of patients with cryptococcosis was therefore undertaken to examine another disorder of known etiology associated with a defect in cell-mediated immunity. In this study we found that antibody levels in cryptococcosis patients, including a group specifically demonstrated to be anergic to a series of skin test antigens, were no different than those in matched normal controls. At the present time, therefore, it is unlikely that elevated antibody levels can be explained solely on the basis of depressed cellular immunity.

PMCID: PMC275093

PMID: 170312 [Indexed for MEDLINE]

5793. Nouv Presse Med. 1975 Mar 22;4(12):887-8.

[Letter: Treatment of periodic disease (familial Mediterranean fever) by colchicine].

[Article in French]

Cattan D, Dervichian M, Wargon H, Vesin P.

PMID: 1094778 [Indexed for MEDLINE]

5794. Ann Intern Med. 1975 Mar;82(3):433.

Letter: Nomenclature: familial Mediterranean fever and periodic peritonitis.

Reimann HA.

PMID: 1115493 [Indexed for MEDLINE]

5795. J Bone Joint Surg Am. 1975 Mar;57(2):265-7.

Articular damage in familial Mediterranean fever. Report of four cases.

Herness D, Makin M.

Four cases of familial Mediterranean fever have been reported in which the disease produced organic damage to a joint. The diagnosis was confirmed by clinical and family history and a typical course which included attacks of recurrent joint synovitis. The laboratory findings, while typical, were not specific. The main involvement was in the lower limbs. The findings at operation were of a non-specific synovitis with destruction of cartilage. It is emphasized that in the majority of cases of familial Mediterranean fever the joint involvement is transient and only uncommonly does damage to the joint become permanent. The fact that organic joint damage occurs is not widely recognized, which is the reason for our report of these four cases.

PMID: 1112853 [Indexed for MEDLINE]

5796. Radiology. 1975 Feb;114(2):331-3.

Radiographic changes in the sacroiliac joints in familial Mediterranean fever.

Brodey PA, Wolff SM.

In a series of 43 patients with familial Mediterranean fever, six were found to have radiographic changes in the sacroiliac joints consisting of loss of normal cortical definition, sclerosis on both sides of the joint with or without erosions, and fusion. These changes were noted despite the absence of clinically symptomatic joint disease. The explanation for these findings is unknown.

DOI: 10.1148/114.2.331

PMID: 1110999 [Indexed for MEDLINE]

5797. JAMA. 1975 Jan 6;231(1):64-6.

Colchicine for periodic peritonitis.

Reimann HA.

After 25 years of unsuccessful therapeutic trials, colchicine suppressed episodes of periodic peritonitis (recurrent polyserositis, familial Mediterranean fever) in most reported cases after 1972 and in 12 of 14 patients in this study. Dosage of 0.65 mg daily was continuous, but intermittent therapy timed in accordance with predicted episodes is under trial. Suppression of episodes by the drug serves as the only diagnostic test available.

PMID: 1243571 [Indexed for MEDLINE]

5798. Vestn Akad Med Nauk SSSR. 1975;(6):21-5.

[Periodic disease--disease of the leukocytic granules].

[Article in Russian]

Tareev EM, Piruzian LA, Rogovin VV, Murav'ev RA, Vinogradova OM.

PMID: 1227105 [Indexed for MEDLINE]

5799. J Egypt Med Assoc. 1975;58(3-4):205-15.

A trial of diphenylhydantoin in periodic disease (familial Mediterranean fever) in Egyptian children.

Hamed MA, Abdel-Aal HM, Abdel-Aziz TM, Nassar SK, Sweify SM, Atta SM, el-Awady SM, el-Aref M, el-Garf TA.

PMID: 1223200 [Indexed for MEDLINE]

5800. Trans R Soc Trop Med Hyg. 1975;69(1):111-7.

Periodic peritonitis. Report of 41 cases without amyloidosis.

Bakir F, Murtadha M.

PMID: 1145707 [Indexed for MEDLINE]

5801. Arkh Patol. 1975;37(2):70-5.

[Clinico-morphologic characteristics of periodic disease].

[Article in Russian]

Vinogradova OM, Serov VV, Sivakov AE.

The article deals with clinico-anatomical characteristics of two observations over periodical disease. Peculiar features of the developing in this case of

genetic amyloidosis, which is considered as a disease of accumulation, are analysed.

PMID: 1131061 [Indexed for MEDLINE]

5802. Reumatologia. 1975;13(1):9-15.

[Pathogenesis of amyloidosis in the light of our observations].

[Article in Polish]

Szpilman H, Płachecka-Gutowska M, Polowiec Z, Pazdur J, Kopec M.

PMID: 1118693 [Indexed for MEDLINE]

5803. Sov Med. 1975 Jan;(1):25-7.

[Characteristics of changes in myeloperoxidase in the blood serum of patients with periodic disease].

[Article in Russian]

Vinogradova OM, Komissarova IA, Kozlovskaja LV, Kaplan BS.

PMID: 1114372 [Indexed for MEDLINE]

5804. Nurs Mirror Midwives J. 1974 Dec 19;139(25):50-1.

Risks that follow childhood vomiting.

Hammond JE.

PMID: 4498283 [Indexed for MEDLINE]

5805. Ann Intern Med. 1974 Dec;81(6):792-4.

Prophylactic colchicine therapy in familial Mediterranean fever. A controlled, double-blind study.

Goldstein RC, Schwabe AD.

PMID: 4611296 [Indexed for MEDLINE]

5806. Am J Med Sci. 1974 Nov;268(5):291-4.

Heredofamilial amyloidosis: incidence in familial Mediterranean fever: A report of two families.

Lender M.

PMID: 4458445 [Indexed for MEDLINE]

5807. Medicine (Baltimore). 1974 Nov;53(6):453-62.

Familial Mediterranean Fever in Armenians. Analysis of 100 cases.

Schwabe AD, Peters RS.

PMID: 4437392 [Indexed for MEDLINE]

5808. N Engl J Med. 1974 Oct 31;291(18):934-7.

Colchicine therapy for familial mediterranean fever. A double-blind trial.



Dinareello CA, Wolff SM, Goldfinger SE, Dale DC, Alling DW.

DOI: 10.1056/NEJM197410312911804

PMID: 4606353 [Indexed for MEDLINE]

5809. N Engl J Med. 1974 Oct 31;291(18):932-4.

A controlled trial of colchicine in preventing attacks of familial mediterranean fever.

Zemer D, Revach M, Pras M, Modan B, Schor S, Sohar E, Gafni J.

DOI: 10.1056/NEJM197410312911803

PMID: 4606109 [Indexed for MEDLINE]

5810. N Engl J Med. 1974 Sep 26;291(13):681-2.

Letter: Gouty arthritis and colchicine.

[No authors listed]

DOI: 10.1056/NEJM197409262911320

PMID: 4852795 [Indexed for MEDLINE]

5811. J Bone Joint Surg Am. 1974 Sep;56(6):1317-8.

Letter: Palindromic rheumatism.

Ehrlich GE.

PMID: 4548064 [Indexed for MEDLINE]

5812. J Trop Med Hyg. 1974 Sep;77(9):208-10.

The role of the nephrotic syndrome in familial mediterranean fever.

Nik-Akhtar B, Hanjani A, Khakpour M, Rashed MA.

PMID: 4416479 [Indexed for MEDLINE]

5813. Orv Hetil. 1974 Aug 11;115(32):1863-6.

[Periodic diseases].

[Article in Hungarian]

Barta I.

PMID: 4858619 [Indexed for MEDLINE]

5814. Arch Intern Med. 1974 Jul;134(1):125-6.

Cryofibrinogen in familial Mediterranean fever.

Shamir H, Pras M, Sohar E, Gafni J.

PMID: 4833940 [Indexed for MEDLINE]

5815. Turk J Pediatr. 1974 Jul;16(3):116-23.

Familial Mediterranean fever in an Iraqi family.

Nouri L, Nagi NA.

PMID: 4471231 [Indexed for MEDLINE]

5816. Nouv Presse Med. 1974 Jun 29;3(26):1657-60.

[Inflammatory and anti-inflammatory steroids in periodic disease].

[Article in French]

Mamou H, Mamou JE.

PMID: 4845417 [Indexed for MEDLINE]

5817. Nouv Presse Med. 1974 May 25;3(21):1363-4.

[Periodic disease and the Muckle-Wells syndrome].

[Article in French]

Mamou H, Mamou JE, de Regnault DM.

PMID: 4849369 [Indexed for MEDLINE]

5818. Arch Intern Med. 1974 May;133(5):868-9.

Letter: Estrogen therapy for periodic fever.

Kats BA.

PMID: 4362558 [Indexed for MEDLINE]

5819. N Engl J Med. 1974 Apr 25;290(17):973.

Letter: Colchicine for familial Mediterranean fever (periodic peritonitis).

[No authors listed]

PMID: 4816996 [Indexed for MEDLINE]

5820. Gastroenterology. 1974 Mar;66(3):446-9.

Intestinal malabsorption: first manifestation of amyloidosis in familial Mediterranean fever. Report of two cases.

Ravid M, Sohar E.

PMID: 4813511 [Indexed for MEDLINE]

5821. Ann Radiol (Paris). 1974 Mar;17(2):135-40.

[The value of renal arteriography in periarteritis nodosa (author's transl)].

[Article in French]

Padovani J, Kasbarian M, Pollini J, Faure F, Leynaud D.

PMID: 4153570 [Indexed for MEDLINE]

5822. N Engl J Med. 1974 Jan 3;290(1):56.

Letter: Colchicine for familial Mediterranean fever: possible adverse effects.

Poffenbarger PL, Brinkley BR.

DOI: 10.1056/NEJM197401032900117

PMID: 4855545 [Indexed for MEDLINE]

5823. Proc Soc Exp Biol Med. 1974 Jan;145(1):343-5.

Demonstration of amyloid-degrading activity in normal human serum.

Kedar I, Sohar E, Gafni J.

PMID: 4812868 [Indexed for MEDLINE]

5824. Trans Assoc Am Physicians. 1974;87:186-94.

Colchicine therapy of familial Mediterranean fever.

Wolff SM, Dinarello CA, Dale DC, Goldfinger SE, Alling DW.

PMID: 4617366 [Indexed for MEDLINE]

5825. Contemp Neurol Ser. 1974;(11):153-78.

Disorders of the autonomic nervous system. Chapter 9. Disturbances of body temperature.

Johnson RH, Spaulding JM.

PMID: 4615870 [Indexed for MEDLINE]

5826. Zh Eksp Klin Med. 1974;14(2):72-5.

[Blastocyte transformation and macrophage migration inhibition reactions in periodic disease].

[Article in Russian]

Zavgorodniaia AM.

PMID: 4546993 [Indexed for MEDLINE]

5827. Birth Defects Orig Artic Ser. 1974;10(10):205-19.

Various genetic traits and diseases among the Jewish ethnic groups.

Goodman RM.

PMID: 4533482 [Indexed for MEDLINE]

5828. Birth Defects Orig Artic Ser. 1974;10(4):62-6.

Familial paroxysmal polyserositis (familial Mediterranean fever); incidence of amyloidosis and mode of inheritance.

Khachadurian AK, Armenian HK.

Findings in 120 cases of familial paroxysmal polyserositis from Lebanon are reported. There was a predominance of male and Armenian patients. Symptoms started before age 20 in 82%. Amyloidosis was diagnosed in 9 patients only. Rectal biopsy in 21 consecutive cases with long-standing illness was negative for amyloid. Amyloidosis without polyserositis was not encountered. Proportion of affected sibs (130) was lower than expected (160) for an autosomal recessive gene. Poor penetrance, especially in females could account for this discrepancy.

PMID: 4470910 [Indexed for MEDLINE]

5829. Zh Eksp Klin Med. 1974;14(4):78-84.

[Immunological diagnosis of kidney diseases and its importance in the immunodepressant therapy].

[Article in Russian]

Arutiunian SK, Tumanian AM, Barsegian BA, Arutiunian VM, Grigorian GS.

PMID: 4425184 [Indexed for MEDLINE]

5830. Nephron. 1974;13(3):221-9.

Renal protein clearances and selectivity of proteinuria in renal amyloid complicating familial Mediterranean fever.

Poreh S, Berlyne GM.

DOI: 10.1159/000180396

PMID: 4421688 [Indexed for MEDLINE]

5831. Ter Arkh. 1974;46(7):134-7.

[Cytochemical and biochemical data on the activity of enzymes of the leukocytes in periodic disease and certain other diseases associated with kidney diseases].

[Article in Russian]

Vinogradova OM, Komissarova IA, Kozlovskaja LV.

PMID: 4409113 [Indexed for MEDLINE]

5832. Lancet. 1973 Dec 8;2(7841):1333.

Letter: Colchicine-aspirin for recurrent polyserositis (familial Mediterranean fever).

Eliakim M, Light A.

PMID: 4127683 [Indexed for MEDLINE]

5833. Am J Obstet Gynecol. 1973 Nov 15;117(6):855-6.

Periodic fever and menses.

Golden RL, Weigers EW, Meagher JG.

PMID: 4745183 [Indexed for MEDLINE]

5834. Med Clin North Am. 1973 Nov;57(6):1559-67.

Medical conditions mimicking the acute surgical abdomen.

Steinheber FU.

PMID: 4593489 [Indexed for MEDLINE]

5835. Fertil Steril. 1973 Nov;24(11):844-7.

The causes of sterility in females with familial Mediterranean fever.

Ismajovich B, Zemer D, Revach M, Serr DM, Sohar E.

PMID: 4270243 [Indexed for MEDLINE]

5836. Sov Med. 1973 Nov;36(11):64-7.

[Histamine metabolism in periodic disease].

[Article in Russian]



Muradkhanian KS.

PMID: 4207030 [Indexed for MEDLINE]

5837. N Engl J Med. 1973 Oct 4;289(14):752.

Colchicine for familial Mediterranean fever.

Manialawi M.

PMID: 4727537 [Indexed for MEDLINE]

5838. Vrach Delo. 1973 Oct;10:72-3.

[Case of periodic disease].

[Article in Russian]

Kuptsov VV.

PMID: 4783309 [Indexed for MEDLINE]

5839. Isr J Med Sci. 1973 Sep-Oct;9(9):1383-92.

Genetic diseases among Jews.

Adam A.

PMID: 4590458 [Indexed for MEDLINE]

5840. J Exp Med. 1973 Aug 1;138(2):373-80.

Immunologic studies of the major nonimmunoglobulin protein of amyloid. I.  
Identification and partial characterization of a related serum component.

Levin M, Pras M, Franklin EC.

Antisera have been prepared against the major nonimmunoglobulin component of secondary and familial Mediterranean fever (FMF) associated amyloid which has been called A component or acid soluble fraction (ASF). The antisera were shown to be monospecific for ASF by precipitation of (125)I-labeled antigen and gave a reaction of identity with four different ASF preparations. The antisera were able to detect a circulating component in human serum that migrated in the alpha1-globulin region. This circulating component gave a line of identity with degraded ASF by double immunodiffusion. 57 normal sera and 89 sera from patients with diseases known to be frequently associated with amyloidosis were tested by immunodiffusion for the circulating ASF component. 7% of normal sera and 50-80% of the pathologic sera had elevated amounts of this component. Absorption studies showed that all normal sera probably have small amounts of this component while cord sera do not have detectable amounts. This component was partially purified and was shown to be slightly larger than albumin. The relation of the circulating component to the acid soluble fraction of amyloid is discussed.

PMCID: PMC2139393

PMID: 4198200 [Indexed for MEDLINE]

5841. Rev Clin Esp. 1973 Jul 31;130(2):165-8.

[Mediterranean familial fever with amyloidosis].

[Article in Spanish]

Abad Alonso JA, Merchante Iglesias A, Rubio Pérez P, Oliva Aldamiz H.

PMID: 4742344 [Indexed for MEDLINE]

5842. JAMA. 1973 Jul 30;225(5):524.

Periodic peritonitis (familial Mediterranean fever).

Reimann HA.

PMID: 4740347 [Indexed for MEDLINE]

5843. Isr J Med Sci. 1973 Jul;9(7):868-74.

Specific antiserum to rheumatoid arthritis amyloid and its cross reactivity with various amyloid preparation.

Shapira E, Yogev R, Pras M, Russell A.

PMID: 4270058 [Indexed for MEDLINE]

5844. N Engl J Med. 1973 Jun 14;288(24):1301.

Colchicine for Mediterranean fever.

[No authors listed]

DOI: 10.1056/NEJM197306142882415

PMID: 4703322 [Indexed for MEDLINE]

5845. Fertil Steril. 1973 Jun;24(6):490-3.

Reduction in sperm output by febrile attacks of familial Mediterranean fever: a case report.

French DJ, Leeb CS, Jecht EW.

PMID: 4710010 [Indexed for MEDLINE]

5846. Rev Infirm. 1973 May;23(5):417-9.

[Periodic disease].

[Article in French]

Sébastien P.

PMID: 4489102 [Indexed for MEDLINE]

5847. JAMA. 1973 Apr 30;224(5 Suppl):757.

Familial Mediterranean fever.

[No authors listed]

PMID: 4739755 [Indexed for MEDLINE]

5848. N Engl J Med. 1973 Apr 12;288(15):798.

Colchicine for familial Mediterranean fever.

Ehrlich GE.

DOI: 10.1056/NEJM197304122881525

PMID: 4688728 [Indexed for MEDLINE]

5849. JAMA. 1973 Apr 2;224(1):128.

Abdominal epilepsy and migraine.

Reimann HA.

PMID: 4739480 [Indexed for MEDLINE]

5850. Dtsch Med Wochenschr. 1973 Mar 2;98(9):451-3.

[Recurring fever bouts].

[Article in German]

Mössner G, Husmann F.

DOI: 10.1055/s-0028-1106824

PMID: 4691567 [Indexed for MEDLINE]

5851. Am Rev Respir Dis. 1973 Mar;107(3):461-3.

Familial paroxysmal polyserositis, phenotype I (familial Mediterranean fever). A rare cause of pleurisy. Case report and review of the literature.

Mancini JL.

DOI: 10.1164/arrd.1973.107.3.461

PMID: 4690493 [Indexed for MEDLINE]

5852. Vopr Okhr Materin Det. 1973 Mar;18(3):36-40.

[Hereditary kidney diseases in children (a review of the literature)].

[Article in Russian]

Degtiareva EM.

PMID: 4585577 [Indexed for MEDLINE]

5853. Aust N Z J Obstet Gynaecol. 1973 Feb;13(1):51-3.

Familial mediterranean fever, amyloidosis and pregnancy.

Pennington JC, Pfanner DW.

PMID: 4514548 [Indexed for MEDLINE]

5854. Arch Intern Med. 1973 Feb;131(2):189-95.

Suppression of periodic fever with estrogen.

Bodel P, Dillard GM.

PMID: 4345577 [Indexed for MEDLINE]

5855. J Med Liban. 1973;26(6):605-14.

Familial paroxysmal polyserositis. Clinical and laboratory findings in 120 cases.

Armenian HK, Khachadurian AK.

PMID: 4783424 [Indexed for MEDLINE]

5856. Klin Med (Mosk). 1973 Jan;51(1):89-90.

[Periodic disease].

[Article in Russian]

Pevzner GI.

PMID: 4764849 [Indexed for MEDLINE]

5857. N Engl J Med. 1972 Dec 21;287(25):1302.

Colchicine for familial Mediterranean fever.

Goldfinger SE.

DOI: 10.1056/NEJM197212212872514

PMID: 4636899 [Indexed for MEDLINE]

5858. Lancet. 1972 Dec 2;2(7788):1202.

Indomethacin in familial mediterranean fever.

Kats BA.

PMID: 4117631 [Indexed for MEDLINE]

5859. Arch Ophthalmol. 1972 Dec;88(6):607-8.

Absence of ophthalmoscopic changes in familial paroxysmal polyserositis.

Baghdassarian SA, Armenian HK, Khachadurian AK.

PMID: 5085202 [Indexed for MEDLINE]

5860. Sem Hop. 1972 Nov 26;48(48):3175-8.

[A rare etiology of serofibrinous pleurisy: periodic disease. Apropos of a case].

[Article in French]

Corcos A, Bisson M, Domart A, Modaï J.

PMID: 4346836 [Indexed for MEDLINE]

5861. Proc R Soc Med. 1972 Nov;65(11):977-9.

Familial mediterranean fever.

Gumpel JM.

PMCID: PMC1644740

PMID: 4642032 [Indexed for MEDLINE]

5862. Nouv Presse Med. 1972 Oct 28;1(38):2525-8.

[Hereditary amyloidosis].

[Article in French]

Lagrue G, Vernant JP.

PMID: 4343106 [Indexed for MEDLINE]

5863. J Clin Invest. 1972 Oct;51(10):2773-6.

The amino acid sequence of a major nonimmunoglobulin component of some amyloid fibrils.

Levin M, Franklin EC, Frangione B, Pras M.



The complete amino acid sequence of a protein, acid soluble fraction, (ASF) which constitutes up to 50% of amyloid fibrils from a patient with familial Mediterranean fever has been obtained. Partial amino acid sequences of three other proteins from patients with secondary amyloidosis were identical in the regions studied except for an alanine-valine interchange in one. The ASF contains no cysteine, does not resemble any known immunoglobulin, and has not been detected as yet in myeloma-associated amyloid.

DOI: 10.1172/JCI107098

PMCID: PMC332979

PMID: 5056669 [Indexed for MEDLINE]

5864. Lancet. 1972 Sep 16;2(7777):606-7.

Indomethacin in familial Mediterranean fever.

Alkalay LJ.

PMID: 4115787 [Indexed for MEDLINE]

5865. Z Allgemeinmed. 1972 Aug 31;48(24):1095-6.

[Familial Mediterranean fever (FMF) and unspecific desensitization with bacterial antigens].

[Article in German]

Mansoor SA.

PMID: 4649654 [Indexed for MEDLINE]

5866. Med Welt. 1972 Aug 5;23(31):1069-71.

[Periodic pleuritis and peritonitis].

[Article in German]

Klein E, Pohle HD.

PMID: 4647303 [Indexed for MEDLINE]

5867. Kango Gijutsu. 1972 Aug;18(8):124-31.

[Diagnostic tests and nursing in periodic vomiting].

[Article in Japanese]

Fukushima T.

PMID: 4483873 [Indexed for MEDLINE]

5868. Dtsch Gesundheitsw. 1972 Jul 6;27(27):1272-8.

[Periodic syndrome with meningitis].

[Article in German]

Ocklitz HW, Hahn M, Prengel M, Siebert H.

PMID: 5075403 [Indexed for MEDLINE]

5869. Turk J Pediatr. 1972 Jul;14(3):99-104.

Renal amyloidosis as a complication of Familial Mediterranean Fever in children.

Coruh M, Hasan E.

PMID: 16295123 [Indexed for MEDLINE]

5870. Rev Rhum Mal Osteoartic. 1972 Jun-Jul;39(6):423-8.

[Coxitis in periodic diseases (apropos of 3 cases)].

[Article in French]

Saporta L, Bisson M, Saimot G, Sicard D, Godeau P, Delbarre F.

PMID: 5084651 [Indexed for MEDLINE]

5871. Lancet. 1972 May 20;1(7760):1124.

Periodic syndrome.

Dimson SB.

PMID: 4112603 [Indexed for MEDLINE]

5872. Nihon Rinsho. 1972 Mar;30(3):823-7.

[Periodic paralysis associated with hyperthyroidism].

[Article in Japanese]

Saito S, Sakurada T, Okuyama M, Yasuda K, Murata T.

PMID: 5064550 [Indexed for MEDLINE]

5873. Vestn Otorinolaringol. 1972 Mar-Apr;34(2):111-2.

[Pharyngeal variant of the periodic disease].

[Article in Russian]

Pertsov AI, Zenger BG, Troshchin VD.

PMID: 5023411 [Indexed for MEDLINE]

5874. Mt Sinai J Med. 1972 Mar-Apr;39(2):165-9.

Thyrotoxic periodic paralysis.

Sirota DK, Gendelman S, Hushmand F.

PMID: 4536795 [Indexed for MEDLINE]

5875. Isr J Med Sci. 1972 Mar;8(3):382-9.

Diabetic fibrillosis. Diagnostic implications of an independent phenotypical character in diabetes mellitus.

Sohar E.

PMID: 4114383 [Indexed for MEDLINE]

5876. Schweiz Rundsch Med Prax. 1972 Jan 25;61(4):94-101.

[Arterial hypertension and nephropathy in familial Mediterranean fever].

[Article in French]

Richard D, Giromini M, Krähenbühl B, Langer B, Savoy X.

PMID: 5013196 [Indexed for MEDLINE]

5877. J Indian Med Assoc. 1972 Jan 16;58(2):47-9.

Acute intermittent porphyria.

Mehrotra MP, Saxena KK, Misra BK, Mital VP.

PMID: 5017801 [Indexed for MEDLINE]

5878. Zh Nevropatol Psikhiatr Im S S Korsakova. 1972;72(3):382-5.

[Neurologic manifestations of periodic disease].

[Article in Russian]

Gevorkian EM.

PMID: 5027052 [Indexed for MEDLINE]

5879. Zh Eksp Klin Med. 1972;12(4):108-12.

[Acetylcholine-cholinesterase system in periodic disease].

[Article in Russian]

Muradkhanian KS, Stepanian IA.

PMID: 4668886 [Indexed for MEDLINE]

5880. J Med Liban. 1972;25(6):495-502.

The management of familial paroxysmal polyserositis (familial Mediterranean fever). Experience with low-fat diets and Clofibrate.

Khachadurian AK, Armenian HK.

PMID: 4657625 [Indexed for MEDLINE]

5881. Zh Eksp Klin Med. 1972;12(3):84-9.

[Study of the tissue autoantibodies and serum protein fractions in periodic disease].

[Article in Russian]

Kazarian AA.

PMID: 4573290 [Indexed for MEDLINE]

5882. Mars Med. 1972;109(7):483-9.

[Spontaneous renal subcapsular hematoma and periodic disease (apropos of a case)].

[Article in French]

Mongin M, Imbert P, Dor JF, Kasbarian M.

PMID: 4404688 [Indexed for MEDLINE]

5883. Zh Eksp Klin Med. 1972;12(1):40-4.

[Histaglobin treatment of periodic disease].

[Article in Russian]

Aivazian AA, Simonian AT, Abramian MK, Ovsepian LA, Guiumdzhian IO.

PMID: 4122676 [Indexed for MEDLINE]

5884. Isr J Med Sci. 1972 Jan;8(1):53-6.

Renal amyloidosis in a patient with recurrent polyserositis previously manifesting proteinuria with minimal glomerular changes.

Eliakim M, Rosenmann E.

PMID: 4112744 [Indexed for MEDLINE]

5885. South Med J. 1972 Jan;65(1):107-12.

Arthritis: nongarden varieties.

Sales LM.

PMID: 4109976 [Indexed for MEDLINE]

5886. Isr J Med Sci. 1971 Dec;7(12):1509-14.

Genetic markers in migrants to Israel.

Cohen T.

PMID: 5144594 [Indexed for MEDLINE]

5887. Isr J Med Sci. 1971 Dec;7(12):1333-41.

Jewish migration in its historical perspective.

Sheba C.

PMID: 4947356 [Indexed for MEDLINE]

5888. Postgrad Med. 1971 Nov;50(5):242-7.

Periodic diseases in children.

Cone TE Jr.

PMID: 4943243 [Indexed for MEDLINE]

5889. Lancet. 1971 Sep 4;2(7723):513-6.

Renal transplantation in two cases of amyloidosis.

Cohen AS, Bricetti AB, Harrington JT, Mannick JA.

PMID: 4105663 [Indexed for MEDLINE]

5890. Aust N Z J Med. 1971 Aug;1(3):255-61.

Familial Mediterranean fever with involvement of the lungs.

Pryor DS, Colebatch HJ.



PMID: 5289135 [Indexed for MEDLINE]

5891. Folia Med Neerl. 1971 Aug-Sep;14(4):130-8.

A case of recurrent polyserositis with amyloidosis and steatorrhoea in a Dutch boy.

Scholten JH, van der Slikke LB, Ruinen L, Mandema E.

PMID: 5123646 [Indexed for MEDLINE]

5892. Lab Invest. 1971 Aug;25(2):104-10.

Amyloid, its nature and molecular structure. Comparison of a new toluidine blue polarized light method with traditional procedures.

Wolman M.

PMID: 4104397 [Indexed for MEDLINE]

5893. Pediatriia. 1971 Jun;50(6):81-8.

[Amyloidosis in children].

[Article in Russian]

Iakovleva AA, Briazgunov IP.

PMID: 4936317 [Indexed for MEDLINE]

5894. South Med J. 1971 Apr;64(4):491-6.

Secondary systemic amyloidosis: analysis of underlying disorders.

Brownstein MH, Helwig EB.

PMID: 4324013 [Indexed for MEDLINE]

5895. J Obstet Gynaecol Br Commonw. 1971 Mar;78(3):284-6.

Familial Mediterranean fever, amyloidosis and eclampsia (case report).

Graff G, Sharf M.

PMID: 5558847 [Indexed for MEDLINE]

5896. Am J Med. 1971 Mar;50(3):336-9.

Familial Mediterranean fever in Turkey. A report of twenty cases.

Ozer FL, Kaplaman E, Zileli S.

PMID: 5553952 [Indexed for MEDLINE]

5897. Dtsch Zahnarztl Z. 1971 Mar;26(3):342-7.

[Epidemiology of chronic-recurrent aphthae].

[Article in German]

Herrmann D.

PMID: 5279553 [Indexed for MEDLINE]

5898. Zh Eksp Klin Med. 1971;11(4):43-7.

[Changes in the serum histaminopexic capacity in periodic disease].

[Article in Russian]

Muradkhanian KS, Stepanian IA, Boiakhchian OA.

PMID: 5161725 [Indexed for MEDLINE]

5899. Zh Eksp Klin Med. 1971;11(6):66-70.

[Morphologic changes in the brain of a patient with periodic disease developing into amyloidosis].

[Article in Russian]

Gevorkian EM.

PMID: 5161668 [Indexed for MEDLINE]

5900. Zh Eksp Klin Med. 1971;11(5):51-7.

[Changes in the concentration of histamine in the blood of patients and their relatives in familial cases of periodic disease].

[Article in Russian]

Muradkhanian KS, Arakelov GM.

PMID: 5161447 [Indexed for MEDLINE]

5901. Zh Eksp Klin Med. 1971;11(5):46-50.

[The state of adrenal cortex function in periodic disease].

[Article in Russian]

Aĭbazian AA, Simonian AT, Sarkisian AM, Ovsepian LA, Guiumdzhian IO.

PMID: 5161446 [Indexed for MEDLINE]

5902. Trans R Soc Trop Med Hyg. 1971;65(5):676-8.

Amyloidosis as a manifestation of familial Mediterranean fever in siblings.

Nik-Akhtar B, Hanjani AA, Famili H, Kamalian N.

PMID: 5159143 [Indexed for MEDLINE]

5903. Acta Clin Belg. 1971;26(1):36-43.

[Familial Mediterranean fever with high serum unconjugated etiocholanolone level].

[Article in Dutch]

van Garsse LG.

PMID: 5151182 [Indexed for MEDLINE]

5904. J Egypt Med Assoc. 1971;54(8):469-88.

Familial Mediterranean fever in Egypt.

Hamed MA, Abdel-Aziz HM, Abdel-Aziz TM.

PMID: 5151046 [Indexed for MEDLINE]

5905. Poumon Coeur. 1971;27(6):575-86.

[Periodic disease: painful thoraco-diaphragmatic attacks and therapeutic effect of antipyrine].

[Article in French]

Brun J, Manguiere F, Plasse JC.

PMID: 5138116 [Indexed for MEDLINE]

5906. Kardiologiia. 1971;11(3):82-9.

[Diuretic and hypotensive action of uregite (ethacrynic acid)].

[Article in Russian]

Ratner NA, Glezer GA, Groznovich NA, Moskalenko NP.

PMID: 5088966 [Indexed for MEDLINE]

5907. Ciba Found Symp. 1971:101-13.

Mechanism of action of pyrogenic and antipyretic steroids in vitro.

Bondy PK, Bodel P.

PMID: 4108158 [Indexed for MEDLINE]

5908. Ter Arkh. 1970 Dec;42(12):76-9.

[Involvement of the kidneys in periodic disease].

[Article in Russian]

Tareev EM, Vinogradova OM, Serov VV.

PMID: 5511311 [Indexed for MEDLINE]

5909. Postgrad Med J. 1970 Dec;46(542):687-97.

Diseases of Jews.

Krikler DM.

PMCID: PMC2467115

PMID: 4923893 [Indexed for MEDLINE]

5910. Ann Intern Med. 1970 Nov;73(5):737-40.

Serum complement defects in periodic diseases.

Reimann HA, Coppola ED, Villegas GR.

PMID: 5476205 [Indexed for MEDLINE]

5911. Ned Tijdschr Geneesk. 1970 Oct 31;114(44):1841-2.

[A patient with the nephropathic form of familial Mediterranean fever].

[Article in Dutch]

Wolthuis FH, ten Thije OJ.

PMID: 5471999 [Indexed for MEDLINE]

5912. Infirm Fr. 1970 Oct;118:21-3.

[Periodic disease].

[Article in French]

Potier JC.

PMID: 5203015 [Indexed for MEDLINE]

5913. Ann Ocul (Paris). 1970 Sep;203(9):821-4.

[Fluoro-angiographic contribution in the study of ocular manifestations of periodic disease].

[Article in French]

Bouchat J, Memin Y, André J, Saby G, Conrad J.

PMID: 5478877 [Indexed for MEDLINE]

5914. Electroencephalogr Clin Neurophysiol. 1970 Sep;29(3):325.

EEG in Kleine-Levin syndrome.

Green LN, Cracco RQ.

PMID: 4195686 [Indexed for MEDLINE]

5915. Australas Ann Med. 1970 Aug;19(3):244-9.

Periodic diseases, physiological rhythms and feedback control--a hypothesis.

Morley A.

PMID: 5528465 [Indexed for MEDLINE]

5916. Australas Ann Med. 1970 Aug;19(3):278-9.

Periodic diseases.

Reimann HA.

PMID: 5470978 [Indexed for MEDLINE]

5917. Iryo. 1970 Jul;24(7):557-66.

[Case of hypersomnia with periodic apnea similar to Pickwickian syndrome].

[Article in Japanese]

Furuya E, Fuse T, Wakamatsu H.

PMID: 5458295 [Indexed for MEDLINE]

5918. Arch Dermatol. 1970 Jul;102(1):1-7.

Systemic amyloidosis complicating dermatoses.



Brownstein MH, Helwig EB.

PMID: 4925009 [Indexed for MEDLINE]

5919. Neurology. 1970 Jun;20(6):569-73.

Episodic blindness as a late effect of head trauma. Electrophysiological study of 3 cases.

Kooi KA.

PMID: 5463610 [Indexed for MEDLINE]

5920. Sem Hop. 1970 Jun;46(29):2030-4.

[Treatment of periodic disease with immuno-depressive agents].

[Article in French]

Mamou H.

PMID: 4316965 [Indexed for MEDLINE]

5921. Sem Hop. 1970 Jun;46(29):2024-9.

[Periodic disease and endocrine disorders].

[Article in French]

Mamou H.

PMID: 4316964 [Indexed for MEDLINE]

5922. N Engl J Med. 1970 May 21;282(21):1213.

Oscillations in cyclical neutropenia.

Morley A, Stohlman F Jr.

PMID: 5445889 [Indexed for MEDLINE]

5923. N Engl J Med. 1970 May 21;282(21):1213.

Oscillations in cyclical neutropenia.

Vash G.

PMID: 5445888 [Indexed for MEDLINE]

5924. Minerva Nefrol. 1970 May-Jun;17(3):109-12.

[Renal amyloidosis caused by periodic disease. Report of 2 cases].

[Article in Italian]

Zucchelli P, Fusaroli M, Sasdelli M, Baccarani G.

PMID: 5515027 [Indexed for MEDLINE]

5925. Srp Arh Celok Lek. 1970 May;98(5):691-709.

[Familial mediterranean fever in Yugoslavia. Case history of 2 patients with autopsy findings in one and a review of 5 patients earlier reported].

[Article in Serbian]

Mićić R, Krstić S, Bojanić N, Dordević V.

PMID: 5206864 [Indexed for MEDLINE]

5926. Presse Med. 1970 Mar 28;78(16):735-8.

[Periodic disease and etiocholanolone].

[Article in French]

Mamou H.

PMID: 5440108 [Indexed for MEDLINE]

5927. Presse Med. 1970 Mar 28;78(16):727-8.

[Current knowledge on periodic disease].

[Article in French]

Mamou H.

PMID: 5440107 [Indexed for MEDLINE]

5928. N Engl J Med. 1970 Mar 19;282(12):683-4.

Granulopoietic models--effect on chemotherapy.

Cronkite EP.

DOI: 10.1056/NEJM197003192821212

PMID: 5437528 [Indexed for MEDLINE]

5929. N Engl J Med. 1970 Mar 19;282(12):643-6.

Cyclophosphamide-induced cyclical neutropenia. An animal model of a human periodic disease.

Morley A, Stohlman F Jr.

DOI: 10.1056/NEJM197003192821202

PMID: 5417728 [Indexed for MEDLINE]

5930. Rev Paul Med. 1970 Mar;76(1):31-2.

[Periodic paralysis as a first and isolated manifestation of hyperthyroidism].

[Article in Portuguese]

Pereira VG, Melaragno Filho R, de Aguiar Pupo A.

PMID: 5506831 [Indexed for MEDLINE]

5931. Isr J Med Sci. 1970 Mar-Apr;6(2):228-45.

Renal manifestations in recurrent polyserositis (familial Mediterranean fever).

Eliakim M, Rachmilewitz M, Rosenmann E, Niv A.

PMID: 5506237 [Indexed for MEDLINE]

5932. Hosp Community Psychiatry. 1970 Mar;21(3):73-80.

The use of lithium for manic-depressive psychoses.

Tupin JP.

PMID: 4904955 [Indexed for MEDLINE]

5933. Kinderarztl Prax. 1970 Feb;38(2):49-52.

[Observations of the pediatrician on the periodic syndrome].

[Article in German]

Brezina Z.

PMID: 5511602 [Indexed for MEDLINE]

5934. Arch Intern Med. 1970 Feb;125(2):337-40.

Familial Mediterranean fever in an Italian family.

Reich CB, Franklin EC.

PMID: 5412026 [Indexed for MEDLINE]

5935. Arch Intern Med. 1970 Feb;125(2):308-11.

Record survival of siblings with familial Mediterranean fever, phenotypes 1 and 2.

Hurwich BJ, Schwartz J, Golfarb S.

PMID: 5412021 [Indexed for MEDLINE]

5936. Shinkei Kenkyu No Shimpo. 1970;14(3):459-62.

[Mechanism of development of periodic paralysis].

[Article in Japanese]

Otsuka M.

PMID: 5531595 [Indexed for MEDLINE]

5937. Shinkei Kenkyu No Shimpo. 1970;14(3):449-52.

[Case of periodic hypokalemic paralysis with myasthenia gravis].

[Article in Japanese]

Hirayama K, Iwabuchi S.

PMID: 5531593 [Indexed for MEDLINE]

5938. Acta Psychiatr Scand. 1970;46(2):106-10.

The Kleine-Levin syndrome. Report of a case and discussion.

Persson T, Olsson L, Ortman E.

PMID: 5478537 [Indexed for MEDLINE]

5939. Isr J Med Sci. 1970 Jan-Feb;6(1):9-13.

Gynecological aspects of recurrent polyserositis (familial Mediterranean fever,

periodic disease).

Ehrenfeld EN, Polishuk WZ.

PMID: 5472898 [Indexed for MEDLINE]

5940. Isr J Med Sci. 1970 Jan-Feb;6(1):2-8.

Incidence of amyloidosis in recurrent polyserositis (familial Mediterranean fever).

Eliakim M.

PMID: 5472892 [Indexed for MEDLINE]

5941. Naika. 1970 Jan;25(1):174-6.

[Case of periodic fever successfully treated with adrenocortical hormones].

[Article in Japanese]

Watanabe S, Kuroda R, Kakizaki H, Kawai E, Suzuki S.

PMID: 5438126 [Indexed for MEDLINE]

5942. Mars Med. 1970;107(5):427-31.

[Periodic disease and ankylosing spondylarthritis].

[Article in French]

Eisinger JB, Luccioni R, Acquaviva P, Moulard JC, Recordier AM.

PMID: 5426010 [Indexed for MEDLINE]

5943. Zh Nevropatol Psikhiatr Im S S Korsakova. 1970;70(11):1736-9.

[Dysautonomic syndrome and its differential diagnosis (literature review)].

[Article in Russian]

Soskin LS, Usol'tsev AN.

PMID: 4929751 [Indexed for MEDLINE]

5944. Pediatrics. 1969 Sep;44(3):453.

Children with fevers.

Myers B.

PMID: 5809907 [Indexed for MEDLINE]

5945. N Engl J Med. 1969 Aug 7;281(6):285-90.

Recurrent infections, episodic lymphopenia and impaired cellular immunity.

Kretschmer R, August CS, Rosen FS, Janeway CA.

DOI: 10.1056/NEJM196908072810602

PMID: 4183174 [Indexed for MEDLINE]

5946. Nihon Naika Gakkai Zasshi. 1969 Aug;58(8):744-51.

A case of hyperkalemic periodic paralysis.



[Article in Japanese]

Anzai T, Ishizawa M, Nakanishi K, Noe T, Matsumoto H.

PMID: 5389743 [Indexed for MEDLINE]

5947. Neurology. 1969 Jul;19(7):691-9.

Hypokalemic periodic paralysis. Children with permanent myopathic weakness.

Dyken M, Zeman W, Rusche T.

PMID: 5816170 [Indexed for MEDLINE]

5948. Vrach Delo. 1969 Jun;6:60-2.

[Pulmonary manifestations of periodic disease].

[Article in Russian]

Agadzhanian VV.

PMID: 5821664 [Indexed for MEDLINE]

5949. J Pediatr. 1969 Jun;74(6):966-8.

Intestinal obstruction complicating familial Mediterranean fever.

Schrager G.

PMID: 5781803 [Indexed for MEDLINE]

5950. Can Med Assoc J. 1969 May 24;100(20):938-40.

Familial Mediterranean fever in Canada.

Brickman HF, Feldman W.

PMCID: PMC1945964

PMID: 5772641 [Indexed for MEDLINE]

5951. Masui. 1969 May;18(5):379-88.

[Respiratory management of acute intermittent porphyria].

[Article in Japanese]

Inagaki M, Saito T, Wakisaka K, Okazaki K, Hirano T.

PMID: 5816201 [Indexed for MEDLINE]

5952. Geriatrics. 1969 May;24(5):146-9.

Periodic diseases in the aged.

Reimann HA.

PMID: 5769665 [Indexed for MEDLINE]

5953. Sem Hop. 1969 Apr 14;45(18):1214-5.

[Dieulafoy's treacherous period of quiet and lacunar image of the cecum].

[Article in French]

Segal S, Bastein J.

PMID: 4306449 [Indexed for MEDLINE]

5954. Nippon Ganka Gakkai Zasshi. 1969 Apr;73(4):377-88.

[Cyclic oculomotor paralysis (cyclic oculomotor spasm relaxation phenomenon)].

[Article in Japanese]

Tamura H, Uemura Y.

PMID: 5815563 [Indexed for MEDLINE]

5955. Naika. 1969 Apr;23(4):779-82.

[Case of hyperthyroidism associated with periodic paralysis].

[Article in Japanese]

Tamura K, Yoshimura T, Oshita K, Sato N.

PMID: 5800509 [Indexed for MEDLINE]

5956. Am J Gastroenterol. 1969 Apr;51(4):311-6.

Familial Mediterranean fever among the Turkish people.

Ozdemir AI, Sokmen C.

PMID: 5794010 [Indexed for MEDLINE]

5957. Nihon Rinsho. 1969 Apr;27(4):1179-201.

[Bartter's syndrome--case report and literature review].

[Article in Japanese]

Kono T, Yamashiki Y, Yoshino K, Tanaka S, Endo J.

PMID: 4308817 [Indexed for MEDLINE]

5958. Z Rheumaforsch. 1969 Mar-Apr;28(3):117-25.

[Periodic fever and etiocholanolone fever in chronic rheumatic diseases. Clinical case histories].

[Article in German]

Schilling F, Oertel GW, Treiber L.

PMID: 5804797 [Indexed for MEDLINE]

5959. Kango Gijutsu. 1969 Mar;3:81-4.

[Nursing of patients with periodic vomiting].

[Article in Japanese]

Miyazaki H, Kawai F.

PMID: 5197461 [Indexed for MEDLINE]

5960. Arerugi. 1969 Mar;18(3):169-89.

[Clinical picture of food allergy].

[Article in Japanese]

Matsumura T.

PMID: 4890554 [Indexed for MEDLINE]

5961. J Clin Invest. 1969 Mar;48(3):558-63.

Recurrent fever of unknown etiology: failure to demonstrate association between fever and plasma unconjugated etiocholanolone.

George JM, Wolff SM, Diller E, Bartter FC.

A sensitive method for determination of plasma unconjugated etiocholanolone by double-isotope-derivative dilution has been described. The mean values for normal subjects was  $0.038 \pm 0.003$  (SEM)  $\mu\text{g}/100 \text{ ml}$ . 40 patients, 20 with familial Mediterranean fever and 20 with other diseases characterized by recurrent fever were studied. The over-all mean concentration of plasma unconjugated etiocholanolone for the patients (febrile or afebrile) was  $0.101 \pm 0.012 \mu\text{g}/100 \text{ ml}$ , significantly above that of normals. Mean plasma values for the patients while they were febrile did not differ from the mean values when they were afebrile. It is suggested that the concentration of plasma unconjugated etiocholanolone is not related to fever in these patients.

DOI: 10.1172/JCI106014

PMCID: PMC535721

PMID: 4886315 [Indexed for MEDLINE]

5962. Nihon Rinsho. 1969 Feb;27(2):455-60.

[2 cases of hypokalemic periodic limb palsy confirmed by an induction test].

[Article in Japanese]

Otomo M, Okada J.

PMID: 5814646 [Indexed for MEDLINE]

5963. Naika Hokan. 1969 Feb;16(2):63-6.

[A case of periodic paralysis led to paralysis after sodium lactate loading].

[Article in Japanese]

Fujioka M.

PMID: 5814397 [Indexed for MEDLINE]

5964. Proc R Soc Med. 1969 Feb;62(2):199-200.

Familial Mediterranean fever.

Jessop JD.

PMCID: PMC1810741

PMID: 5775249 [Indexed for MEDLINE]

5965. Gut. 1969 Feb;10(2):98-104.

Deposition of amyloid in the gastrointestinal tract.

Gilat T, Revach M, Sohar E.

PMCID: PMC1552807

PMID: 5766053 [Indexed for MEDLINE]

5966. Zh Nevropatol Psikhiatr Im S S Korsakova. 1969;69(4):535-8.

[Periodic psychoses].

[Article in Russian]

Essing L.

PMID: 5796671 [Indexed for MEDLINE]

5967. Zh Nevropatol Psikhiatr Im S S Korsakova. 1969;69(3):407-9.

[On types of mental disorders in Klinefelter's and Shereshevsky-Turner's syndromes in adults].

[Article in Russian]

Rakhal'skiĭ IuE, Sirovskiĭ AA.

PMID: 5795727 [Indexed for MEDLINE]

5968. Southwest Med. 1969 Jan;50(1):4-7.

Periodic peritonitis in a patient of non-Mediterranean ethnic origin.

Bernard JA, Malooly DA.

PMID: 5763604 [Indexed for MEDLINE]

5969. Sov Med. 1969 Jan;32(1):31-4.

[Clinical-roentgeonological changes in the thoracic variant of periodic disease].

[Article in Russian]

Vinogradova OM.

PMID: 5385212 [Indexed for MEDLINE]

5970. Scand J Gastroenterol. 1969;4(3):275-9.

Studies of gastrointestinal function in amyloidosis f familial Mediterranean fever.

Yoran C, Weber H, Gilat T.

PMID: 5346674 [Indexed for MEDLINE]

5971. Ter Arkh. 1968 Dec;40(12):71-6.

[Clinico-anatomic characteristics of the abdominal syndrome of periodic disease].

[Article in Russian]

Vinogradova OM, Potekaeva MA.

PMID: 5746547 [Indexed for MEDLINE]

5972. Naika. 1968 Dec;22(6):1376-80.

[Case of autoimmune phenomenon with periodic high fever and aphthous stomatitis].



[Article in Japanese]

Ueda H, Takabatake Y, Saito Y, Nagatani Y, Morooka S.

PMID: 5719275 [Indexed for MEDLINE]

5973. Vrach Delo. 1968 Nov;11:90-2.

[Peculiarities of mediator and energy metabolism in depressive states of various origin].

[Article in Russian]

Popovich NM.

PMID: 5744919 [Indexed for MEDLINE]

5974. Rev Rhum Mal Osteoartic. 1968 Nov;35(11):608-10.

[2 cases of periodic disease with chronic coxitis].

[Article in French]

Welfling J, Lequesne M, Caroit M, Koskas W, de Sèze S.

PMID: 5730501 [Indexed for MEDLINE]

5975. Cesk Pediatr. 1968 Oct;23(10):943-4.

[Periodic syndrome and migraine in children].

[Article in Czech]

Svatý J.

PMID: 5701267 [Indexed for MEDLINE]

5976. Am J Dis Child. 1968 Oct;116(4):442-4.

Pericarditis in familial Mediterranean fever.

Raviv U, Rubinstein A, Schonfeld AE.

PMID: 5697981 [Indexed for MEDLINE]

5977. Isr J Med Sci. 1968 Sep-Oct;4(5):995-9.

The role of amyloidosis in familial mediterranean fever. A population study.

Gafni J, Ravid M, Sohar E.

PMID: 5715490 [Indexed for MEDLINE]

5978. Rev Esp Reum Enferm Osteoartic. 1968 Jul;12(7):474-80.

[A new case of periodic disease].

[Article in Spanish]

Salvatella Viñals J.

PMID: 5740569 [Indexed for MEDLINE]

5979. Ter Arkh. 1968 Jul;40(7):118-9.

[A case of successful treatment of a patient with periodic disease].

[Article in Russian]

Shastin IV, Klimov IA.

PMID: 5739327 [Indexed for MEDLINE]

5980. Br Med J. 1968 May 4;2(5600):298-9.

Familial Mediterranean fever.

Reimann HA.

PMCID: PMC1985812

PMID: 5646547 [Indexed for MEDLINE]

5981. Acta Anaesthesiol. 1968 May-Jun;19(3):74-6.

[Some problems of treatment of periodic disease].

[Article in Russian]

Mamikonian RS, Barsegian BA.

PMID: 5757405 [Indexed for MEDLINE]

5982. Vnitr Lek. 1968 May;14(5):478-83.

[Present opinions on periodic disease].

[Article in Czech]

Pojer J, Mojzís A, Homola D, Munzarová M.

PMID: 5654305 [Indexed for MEDLINE]

5983. Med Clin North Am. 1968 May;52(3):567-91.

The early natural history of juvenile rheumatoid arthritis. A 10-year follow-up study of 100 cases.

Calabro JJ, Marchesano JM.

PMID: 4385203 [Indexed for MEDLINE]

5984. Ned Tijdschr Geneeskd. 1968 Apr 6;112(14):657-60.

[Cyclic neutropenia].

[Article in Dutch]

Veldhuijzen BJ.

PMID: 5664999 [Indexed for MEDLINE]

5985. Lancet. 1968 Apr 6;1(7545):740-2.

The stiff aching back. The differential diagnosis of ankylosing spondylitis.

Hart FD.

PMID: 4170974 [Indexed for MEDLINE]

5986. Saishin Igaku. 1968 Apr;23(4):750-5.

[Autointoxication--periodic vomiting].

[Article in Japanese]

Mino M.

PMID: 5700036 [Indexed for MEDLINE]

5987. Med J Aust. 1968 Mar 23;1(12):495-6.

Familial Mediterranean fever with amyloidosis.

Clancy RL, Stiel JN.

PMID: 5647364 [Indexed for MEDLINE]

5988. Br Med J. 1968 Mar 23;1(5594):724.

Familial Mediterranean fever.

[No authors listed]

PMCID: PMC1985455

PMID: 5641432 [Indexed for MEDLINE]

5989. Clin Orthop Relat Res. 1968 Mar-Apr;57:51-5.

Arthritis in familial Mediterranean Fever.

Ehrlich GE.

PMID: 5669865 [Indexed for MEDLINE]

5990. Rev Clin Esp. 1968 Feb 29;108(4):305-11.

[Familial Mediterranean fever. Report of a case and brief literature review].

[Article in Spanish]

Sánchez Sicilia L, Rodicio Díaz JL, Hernando Avendaño L.

PMID: 5747656 [Indexed for MEDLINE]

5991. Lancet. 1968 Feb 17;1(7538):319-21.

Recurrent monocular blindness of uncertain cause.

Eadie MJ, Sutherland JM, Tyrer JH.

PMID: 4170157 [Indexed for MEDLINE]

5992. Ann Intern Med. 1968 Feb;68(2):495-6.

Etiocholanolone and fever.

Reimann HA.

PMID: 5713929 [Indexed for MEDLINE]

5993. Electroencephalogr Clin Neurophysiol. 1968 Feb;24(2):193.

Periodic hypersomnia.

Elian M.

PMID: 4171255 [Indexed for MEDLINE]

5994. Mem Acad Chir (Paris). 1968;94(10):363-6.

[Periodic disease and surgery].

[Article in French]

Michel-Béchet R.

PMID: 5758534 [Indexed for MEDLINE]

5995. Vestn Oftalmol. 1968 Jan-Feb;81(1):84-5.

[A case of periodic iridocyclitis].

[Article in Russian]

Panina NB.

PMID: 5754561 [Indexed for MEDLINE]

5996. Arq Bras Endocrinol Metabol. 1968 Jan;17(1):55-67.

Periodic paralysis associated with hyperthyroidism. Study of the precipitating factors.

Pereira VG, Wajchenberg BL, Quintão ER.

PMID: 5739587 [Indexed for MEDLINE]

5997. Turk Tip Cemiy Mecm. 1968;34(11):682-9.

[Periodic disease and the problem of amyloidosis].

[Article in Turkish]

Ulagay I, Dilşen N.

PMID: 5733136 [Indexed for MEDLINE]

5998. Rass Neurol Veg. 1968 Jan-Feb;22(1):5-23.

[Periodic diseases. Nosological and etiopathogenetic problems].

[Article in Italian]

Scarpelli PT, Fantini F, Boccuni M, Cagnoni M.

PMID: 5718882 [Indexed for MEDLINE]

5999. Turk Tip Cemiy Mecm. 1968;34(6):355-9.

[A case of periodic disease].

[Article in Turkish]

Berkmen R, Akkor A.

PMID: 5706698 [Indexed for MEDLINE]



6000. Folia Med Cracov. 1968;10(2):249-59.

[Theory of cyclic variations in the occurrence of tumors derived from glia].

[Article in Polish]

Szydlowska H, Szwagrzyk E.

PMID: 4297565 [Indexed for MEDLINE]

6001. J Neurol Sci. 1968 Jan-Feb;6(1):117-23.

Recurrent cranial nerve palsies of dysglobulinaemic origin.

Kreindler A, Macovei-Patrichi M.

PMID: 4296279 [Indexed for MEDLINE]

6002. J Med Lyon. 1967 Dec 20;48(133):1889-99.

[Periodic disease].

[Article in French]

Bel A.

PMID: 5618171 [Indexed for MEDLINE]

6003. Policlinico Prat. 1967 Dec 4;74(49):1649-60.

[The hypertensive crisis].

[Article in Italian]

Cagli V.

PMID: 4897147 [Indexed for MEDLINE]

6004. Ter Arkh. 1967 Nov;39(11):73-6.

[On the problem of kidney damage in periodic disease].

[Article in Russian]

Vinogradova OM.

PMID: 5611740 [Indexed for MEDLINE]

6005. Electroencephalogr Clin Neurophysiol. 1967 Nov;23(5):490.

The influence of medication and clinical state on the EEG in periodic endogenous depression.

Volavka J, Grof P, Mrklas L.

PMID: 4168998 [Indexed for MEDLINE]

6006. Electroencephalogr Clin Neurophysiol. 1967 Nov;23(5):490.

The EEG in three of Gjessing's patients with periodic catatonia.

Gjessing LR, Harding GF, Jenner FA, Johannessen NB.

PMID: 4168997 [Indexed for MEDLINE]

6007. Dev Med Child Neurol. 1967 Oct;9(5):641-3.

Migraine in childhood.

Mitchell R.

PMID: 6066032 [Indexed for MEDLINE]

6008. Del Med J. 1967 Oct;39(10):306-8 passim.

Familial Mediterranean fever.

Vandervort W.

PMID: 6060869 [Indexed for MEDLINE]

6009. Gac Med Mex. 1967 Sep;97(9):1172-84.

[Mediterranean familial fever].

[Article in Spanish]

Jinich H.

PMID: 5611995 [Indexed for MEDLINE]

6010. Encephale. 1967 Sep-Oct;56(5):439-58.

[Reflections on 80 cases of schizophrenia dating back more than 10 years. To the research of lines of natural separation of the group of schizophrenics].

[Article in French]

Sutter JM, Chabert G.

PMID: 5591226 [Indexed for MEDLINE]

6011. Int J Neuropsychiatry. 1967 Aug;3(4):319-26.

Periodic diencephalic disorders: their relationship to manic-depressive psychoses.

Lauter H.

PMID: 6064119 [Indexed for MEDLINE]

6012. Am J Med. 1967 Aug;43(2):227-53.

Familial Mediterranean fever. A survey of 470 cases and review of the literature.

Sohar E, Gafni J, Pras M, Heller H.

PMID: 5340644 [Indexed for MEDLINE]

6013. J Pathol Bacteriol. 1967 Jul;94(1):89-93.

Electron-microscope observations on peri-reticulin and peri-collagen amyloidosis in rectal biopsies.

Sohar E, Merker HJ, Missmahl HP, Gafni J, Heller H.

DOI: 10.1002/path.1700940112

PMID: 6053011 [Indexed for MEDLINE]

6014. Am J Clin Pathol. 1967 Jul;48(1):23-9.

Serosal exudates in familial Mediterranean fever.

Merker HJ, Hersko C, Shibolet S.

PMID: 6028611 [Indexed for MEDLINE]

6015. Sov Med. 1967 Jul;30(7):89-91.

[Periodic disease in children].

[Article in Russian]

Listengarten TA.

PMID: 5607882 [Indexed for MEDLINE]

6016. G Mal Infett Parassit. 1967 May;19(5):251-3.

[A case of periodic disease].

[Article in Italian]

Spirito L, Giovanelli A.

PMID: 5605231 [Indexed for MEDLINE]

6017. Vrach Delo. 1967 May;5:87-90.

[On periodic disease].

[Article in Russian]

Shub NI.

PMID: 4390011 [Indexed for MEDLINE]

6018. Presse Med. 1967 Apr 29;75(21):1053-5.

[Renal amylosis and periodic disease].

[Article in French]

Mamou H, Courtin A, Ardry R.

PMID: 6024354 [Indexed for MEDLINE]

6019. Sem Hop. 1967 Apr 8;43(17):1138-40.

[The 19-norsteroids in the treatment of periodic disease].

[Article in French]

Mamou H, Gastellier G, Daniel E, Nahum A.

PMID: 4293533 [Indexed for MEDLINE]

6020. Calif Med. 1967 Apr;106(4):312-6.

Periodic fever.

[No authors listed]

These discussions are selected from the weekly staff conferences in the

Department of Medicine, University of California Medical Center, San Francisco.  
Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

PMCID: PMC1502653

PMID: 6046862 [Indexed for MEDLINE]

6021. J Psychiatr Res. 1967 Mar;5(1):15-38.

Longitudinal study of periodic catatonia. Long-term clinical and biochemical study of a woman with periodic catatonia.

Cookson BA(1), Quarrington B, Huszka L.

Author information:

(1)Research Unit, Ontario Hospital Toronto and Department of Psychiatry, University of Toronto, Ontario, Canada.

A woman with periodic catatonia had a 600-day metabolic study. The results were analyzed by harmonic analysis. Her periodic stupors showed a regular 36-day rhythm apparently related to a 24-day menstrual cycle; but the rhythm persisted when menstrual function was blocked by continuous Enovid (norethynodrel + mestranol) administration. During the menstrual block, weight, sodium balance, magnesium and 17-ketosteroid (17-KS) excretion gave indications of 12- and 36-day fluctuations. Further studies on steroid excretion indicated that similar fluctuations in 17-KS output occurred when the patient was menstruating normally. The peaks of the 12-day cycle coincided with menses and the mid-menstrual phase; while the peak of the 36-day cycle coincided with the onset of stupor. 17-hydroxycorticosteroid (17-OHCS) excretion had a 36-day cycle which lagged 4 days behind the 36-day 17-KS cycle. There were no indications of a 12-day 17-OHCS cycle. In the discussion it is suggested that the 17-KS fluctuations may partly reflect gonadotrophin activity rather than being exclusively due to ACTH. It is noted that Enovid may block only LH activity not total gonadotrophins. It is speculated that there may be a relationship between gonadotrophin activity and the psychic disturbance.

PMID: 20034173 [Indexed for MEDLINE]

6022. Vopr Okhr Materin Det. 1967 Mar;12(3):81-2.

[Periodic disease].

[Article in Russian]

Potantin NV.

PMID: 5611403 [Indexed for MEDLINE]

6023. Vrach Delo. 1967 Mar;3:118-20.

[On the postcholecystectomy syndrome and periodic disease].

[Article in Russian]

Agadzhanian VV.

PMID: 5609264 [Indexed for MEDLINE]

6024. Ger Med Mon. 1967 Feb;12(2):54-9.

Aetiocholanolone fever. A report of three cases.

Huhnstock K, Kuhn D, Oertel GW.

PMID: 6044989 [Indexed for MEDLINE]

6025. Mars Med. 1967;104(9):778-81.



[Renal amyloidosis and periodic disease in a young boy of 11 years].

[Article in French]

Coignet J, Cotte G, Hebreard J, Passeron P, Lafon J.

PMID: 5619522 [Indexed for MEDLINE]

6026. Verh Dtsch Ges Inn Med. 1967;73:962-76.

[Long wave rhythms in internal diseases].

[Article in German]

Menzel W.

PMID: 5591864 [Indexed for MEDLINE]

6027. Rev Infirm Assist Soc. 1967 Jan;17(1):13-20.

[The so-called periodic disease].

[Article in French]

Siguier F, Godeau P, Lévy R, Dorra M.

PMID: 4163098 [Indexed for MEDLINE]

6028. Klin Med (Mosk). 1966 Dec;44(12):107-9.

[2 cases of periodic disease].

[Article in Russian]

Avanesov GM, Piperkov DM.

PMID: 6004333 [Indexed for MEDLINE]

6029. Minerva Pediatr. 1966 Sep 29;18(28):1555-63.

[Description of a case of probable "periodic disease". Clinical and pathogenetic aspects].

[Article in Italian]

Loiodice G, Macagno F, Semino A.

PMID: 5994098 [Indexed for MEDLINE]

6030. Nature. 1966 Sep 24;211(5056):1401-2.

Periodic cross-banding in amyloid filaments.

Merker H, Shibolet S, Sohar E, Gafni J, Heller H.

PMID: 5969834 [Indexed for MEDLINE]

6031. Vrach Delo. 1966 Aug;8:9-12.

[Kidney diseases in patients with periodic disease].

[Article in Russian]

Agadzhanian VV.

PMID: 5989179 [Indexed for MEDLINE]

6032. Am J Med Sci. 1966 Aug;252(2):137-45.

Periodic fever and periodic peritonitis (periodic polyserositis): unsettled problems.

Reimann HA.

PMID: 5927077 [Indexed for MEDLINE]

6033. Electroencephalogr Clin Neurophysiol. 1966 Jul;21(1):67-70.

Status of the segmental innervation in thyrotoxic periodic paralysis.

Norris FH Jr.

PMID: 4165366 [Indexed for MEDLINE]

6034. Electroencephalogr Clin Neurophysiol. 1966 Jul;21(1):59-66.

The electroencephalogram in three cases of periodic psychosis.

Harding G, Jeavons PM, Jenner FA, Drummond P, Sheridan M, Howells GW.

PMID: 4165365 [Indexed for MEDLINE]

6035. Dis Colon Rectum. 1966 May-Jun;9(3):168-72.

Periodic peritonitis. Analysis of 19 cases.

Munzer D.

PMID: 5936831 [Indexed for MEDLINE]

6036. Ter Arkh. 1966 Mar;38(3):116-8.

[Renal amyloidosis in a patient with periodic disease].

[Article in Russian]

Kuznetsova EM.

PMID: 5991894 [Indexed for MEDLINE]

6037. Med Clin North Am. 1966 Mar;50(2):371-8.

Periodic disease.

Nugent FW, Burns JR.

PMID: 5323861 [Indexed for MEDLINE]

6038. Klin Med (Mosk). 1966 Feb;44(2):22-8.

[The so-called periodic disease in the theoretical and practical aspect].

[Article in Russian]

Teodori MI, Zhgun AA, Krasil'nikov LG.

PMID: 5997337 [Indexed for MEDLINE]

6039. Turk Tip Cemiy Mecm. 1966 Feb;32(2):85-99.

[On paroxysmal polyserositis (Mediterranean fever) in our country, in connection with 5 cases, one of which presented signs of a periodic meningitis].

[Article in Turkish]

Sipahioğlu H.

PMID: 5931248 [Indexed for MEDLINE]

6040. Arthritis Rheum. 1966 Feb;9(1):1-17.

The arthritis of familial Mediterranean fever (FMF).

Heller H, Gafni J, Michaeli D, Shahin N, Sohar E, Ehrlich G, Karten I, Sokoloff L.

PMID: 4143706 [Indexed for MEDLINE]

6041. Klin Khir. 1966 Jan;1:63-4.

[Edematous infiltrative type of the periodic pain abdominal syndrome associated with a foreign body in the abdominal cavity].

[Article in Russian]

Belorusov OS.

PMID: 5982087 [Indexed for MEDLINE]

6042. J Radiol Electrol Med Nucl. 1965 Dec;46(12):855-6.

[Data contributed by lymphography in periodic disease].

[Article in French]

Mallarmé J, Stuhl L, Arnulf G.

PMID: 5855314 [Indexed for MEDLINE]

6043. J Bone Joint Surg Am. 1965 Dec;47(8):1615-9.

The articular manifestations of periodic disease (familial Mediterranean fever).

Makin M, Levin S.

PMID: 5841032 [Indexed for MEDLINE]

6044. Bull Acad Natl Med. 1965 Oct 26;149(26):625-30.

[Acquired toxoplasmosis and periodic disease].

[Article in French]

Blanc F, Nosny Y.

PMID: 5322450 [Indexed for MEDLINE]

6045. Rev Rhum Mal Osteoartic. 1965 Oct;32(10):614-6.

[Ankylosing spondylitis and periodic disease].

[Article in French]

Camus JP.

PMID: 5855738 [Indexed for MEDLINE]

6046. Dapim Refuiim. 1965 Oct;24(5):408-15.

[Periarteritis nodosa in a patient with familial Mediterranean fever].

[Article in Hebrew]

Dollberg L, Garti R, Geifman M, Rosenfeld J.

PMID: 4379550 [Indexed for MEDLINE]

6047. Pol Tyg Lek. 1965 Aug 23;20(34):1299-300.

[Biological rhythm in human pathology].

[Article in Polish]

Wasyluk J.

PMID: 5321322 [Indexed for MEDLINE]

6048. Lyon Med. 1965 Aug 15;214(33):195-204.

[Apropos of 3 cases of periodic disease complicated by renal amyloidosis].

[Article in French]

Paliard P, Fries D, Tete R, Zech P, Brunat N.

PMID: 5845489 [Indexed for MEDLINE]

6049. JAMA. 1965 Jun 28;192:1162-4.

UNUSUAL ARTHROPATHY IN PERIODIC PERITONITIS.

LOOP JW, CLAWSON DK.

PMID: 14301042 [Indexed for MEDLINE]

6050. JAMA. 1965 Jun 21;192:1093-4.

HYPERTENSIVE ENCEPHALOPATHY IN PERIODIC PERITONITIS WITH AMYLOID NEPHROSIS.

OZEN MA, KADIOGLU A.

PMID: 14293508 [Indexed for MEDLINE]

6051. Wiad Lek. 1965 Jun 15;18(12):985-90.

[Periodic disease].

[Article in Polish]

May K.

PMID: 5832654 [Indexed for MEDLINE]

6052. Lille Med. 1965 Jun-Aug;10(6):637-43.

[The 4 problems of periodic disease].



[Article in French]

D'Eshougues JR.

PMID: 5834770 [Indexed for MEDLINE]

6053. J Med Lyon. 1965 May 20;46(77):999-1003.

[Prolonged fevers of diverse and rare causes. (Periodic disease, collagenosis)].

[Article in French]

Thivollet J, Fleurette J.

PMID: 4378626 [Indexed for MEDLINE]

6054. Arch Intern Med. 1965 May;115:565-8.

THE GASTROINTESTINAL SYSTEM IN FAMILIAL MEDITERRANEAN FEVER.

WOLFF SM, HATHAWAY BE, LASTER L.

PMID: 14278724 [Indexed for MEDLINE]

6055. Gaz Med Fr. 1965 Apr 25;72(8):1613-4.

[Familial periodic disease].

[Article in French]

Dorf G.

PMID: 5830673 [Indexed for MEDLINE]

6056. Biochem J. 1965 Apr;95:107-17.

THE EXTRACTION OF PLASMA 3-HYDROXY-17-OXO STEROID SULPHATES AND THE MEASUREMENT OF THE CONSTITUENT DEHYDROEPIANDROSTERONE SULPHATE AND ANDROSTERONE SULPHATE.

MCKENNA J, RIPPON AE.

1. A simple method for the extraction of 17-oxo steroid sulphates of plasma is described; glucosiduronates and orthophosphates are extracted, but to a smaller extent. 2. Four methods of analyses of the extracts are given and are relatively simple. Three of these are specific for steroid sulphates and two measure the sulphate conjugates directly. 3. Values for dehydroepiandrosterone sulphate and androsterone sulphate concentrations of normal and pathological plasmas are given.

PMCID: PMC1215184

PMID: 14333546 [Indexed for MEDLINE]

6057. Ann Intern Med. 1965 Apr;62:778-85.

PERIODIC MENINGITIS: AN UNUSUAL MANIFESTATION OF PERIODIC DISEASE.

GEORGE RB, WESTFALL RE.

PMID: 14274843 [Indexed for MEDLINE]

6058. J Chronic Dis. 1965 Mar;18:261-7.

GRAND ROUNDS AT BARNES HOSPITAL. I. PERIODIC FEVER.

MCDONOUGH JR, HAMES CG, GARRISON GE, STULB SC, LICHTMAN MA, HEFELFINGER DC.

PMID: 14278161 [Indexed for MEDLINE]

6059. Ter Arkh. 1965 Mar;37:101-6.

[ON SOME PROBLEMS IN THE CLINICAL PICTURE AND PATHOGENESIS OF "PERIODIC DISEASE"].

[Article in Russian]

SIMONIAN AT, AIVAZIAN AA.

PMID: 14274596 [Indexed for MEDLINE]

6060. Am J Med Sci. 1965 Mar;249:295-9.

CYTOGENETIC STUDIES IN FAMILIAL MEDITERRANEAN FEVER.

KREY PR, COHEN AS.

PMID: 14273318 [Indexed for MEDLINE]

6061. Arch Pathol. 1965 Mar;79:238-44.

FIBRINOGEN AS A COMPONENT OF AMYLOID.

HOROWITZ RE, STUYVESANT VW, WIGMORE W, TATTER D.

PMID: 14246203 [Indexed for MEDLINE]

6062. Dtsch Gesundheitsw. 1965 Feb 4;20:204-7.

[FAMILIAL QUINCKE'S EDEMA].

[Article in German]

APOSTOLOFF E, APOSTOLOFF G.

PMID: 14266413 [Indexed for MEDLINE]

6063. Naika. 1965 Feb;15:391-3.

[A CASE OF PERIODIC PARALYSIS WITH EXTENDED HYPESTHETIC AREAS OF THE EXTREMITIES DURING AN ATTACK].

[Article in Japanese]

KOJIMA A, HIGUCHI T, SATO M.

PMID: 14324510 [Indexed for MEDLINE]

6064. Klin Med (Mosk). 1965 Jan;43:46-8.

[PERIODIC DISEASE].

[Article in Russian]

SARVANOV AM.

PMID: 14344794 [Indexed for MEDLINE]

6065. Klin Med (Mosk). 1965 Jan;43:143-5.

[TREATMENT OF PERIODIC DISEASE].

[Article in Russian]

IAGUBIAN FS.

PMID: 14344785 [Indexed for MEDLINE]

6066. Vestn Akad Med Nauk SSSR. 1965;20:87-90.

[STUDY OF THE PROPERTIES OF PROTEINS IN THE BLOOD SERUM AND URINE IN AMYLOIDOSIS IN PATIENTS WITH PERIODIC DISEASE].

[Article in Russian]

STAROSELTSEVA LK, VINOGRADOVA OM, ODO MA.

PMID: 14302302 [Indexed for MEDLINE]

6067. Zh Eksp Klin Med. 1965;5:12-8.

[HEMATOLOGICAL CHANGES IN "PERIODIC DISEASE"].

[Article in Russian]

SIMONIAN AT, AIVAZIAN AA, PASHINIAN SA.

PMID: 14301331 [Indexed for MEDLINE]

6068. Vestn Akad Med Nauk SSSR. 1965;20:75-8.

[APROPOS OF KIDNEY DISORDERS IN PERIODIC DISEASE].

[Article in Russian]

VINOGRADOVA OM.

PMID: 14299982 [Indexed for MEDLINE]

6069. Prensa Med Argent. 1965 Jan 1;52:45-6.

[PERIODIC DISEASE AND AUTOANTIBODIES].

[Article in Spanish]

BACHMAN A.

PMID: 14292356 [Indexed for MEDLINE]

6070. Allerg Asthma (Leipz). 1965;11(3):104-8.

Further studies of "recurrent paroxysmal allergic peritonitis".

el-Mehairy MM.

PMID: 5893762 [Indexed for MEDLINE]

6071. Trans Am Neurol Assoc. 1965;90:287-9.

Diencephalic seizures: relation to periodic disease.

Rovner RN.

PMID: 5857765 [Indexed for MEDLINE]

6072. Iryo. 1964 Nov;18:872-5.

[A CASE OF PERIODIC FEVER].

[Article in Japanese]

MURAMATSU A, NAGANO H, GOTO T.

PMID: 14278147 [Indexed for MEDLINE]

6073. Rev Asoc Med Argent. 1964 Nov;78:605-8.

[ABDOMINAL FORM OF PERIODIC DISEASE].

[Article in Spanish]

FERRANDO R, BASTAROLI J, CAPURRO C.

PMID: 14244411 [Indexed for MEDLINE]

6074. JAMA. 1964 Oct 19;190:241.

PERPLEXITIES OF A PERIODIC ENTITY.

REIMANN HA.

PMID: 14246601 [Indexed for MEDLINE]

6075. J Pediatr. 1964 Oct;65:625-30.

CLINICAL PATHOLOGICAL CONFERENCE. THE CHILDREN'S HOSPITAL MEDICAL CENTER,  
BOSTON,

MASS.

GHARIB R.

PMID: 14216653 [Indexed for MEDLINE]

6076. Arch Pathol. 1964 Oct;78:325-30.

AMYLOID. II. STARCH GEL ELECTROPHORETIC ANALYSIS OF SOME PROTEINS EXTRACTED FROM AMYLOID.

BENDITT EP, ERIKSEN N.

PMID: 14184664 [Indexed for MEDLINE]

6077. Gaz Med Fr. 1964 Sep 10;71:2685-91.

[TREATMENT OF NEUROMUSCULAR SYNDROMES WITH SPIROLACTONES].

[Article in French]

COSSA P.

PMID: 14197845 [Indexed for MEDLINE]

6078. Ann N Y Acad Sci. 1964 Sep 10;117:589-96.

HYPOTHALAMIC-HYPOPHYSEAL-NEURAL INFLUENCE IN PERIODIC DISEASES.

REIMANN HA.

PMID: 14196665 [Indexed for MEDLINE]



6079. Rev Rhum Mal Osteoartic. 1964 Sep;31:513-20.

[SOME RARE TYPES OF INFLAMMATORY POLYARTHRITIS].

[Article in French]

WELFLING J.

PMID: 14226852 [Indexed for MEDLINE]

6080. Lancet. 1964 Aug 22;2(7356):400-3.

"DEAR DOCTOR, PLEASE SEE". REFLECTIONS ON THE WORK OF A GENERAL PAEDIATRIC OUTPATIENT CLINIC.

MACAULAY D.

PMID: 14173637 [Indexed for MEDLINE]

6081. Clin Chim Acta. 1964 Aug;10:106-13.

PLASMA PROTEINS IN FAMILIAL MEDITERRANEAN FEVER.

FRENSDORFF A, SHIBOLET S, LAMPRECHT S, SOHAR E.

PMID: 14203237 [Indexed for MEDLINE]

6082. Ann N Y Acad Sci. 1964 Jul 31;115:695-720.

COMPUTER TECHNIQUES IN THE STUDY OF BIOLOGIC RHYTHMS.

HALBERG F, DIFFLEY M, STEIN M, PANOFSKY H, ADKINS G.

PMID: 14214046 [Indexed for MEDLINE]

6083. Proc Soc Exp Biol Med. 1964 Jul;116:733-5.

GLUTAMIC OXALACETIC TRANSAMINASE ISOENZYMES IN HUMAN MYOPATHIES.

KAR NC, PEARSON CM.

PMID: 14194647 [Indexed for MEDLINE]

6084. Ter Arkh. 1964 Jun;36:96-102.

[APROPOS OF SO-CALLED PERIOD ABDOMINAL PAIN AND ABDOMINAL EPILEPSY].

[Article in Russian]

VINOGRADOVA OM, LURE ZL, CHUKHROVA VA.

PMID: 14226965 [Indexed for MEDLINE]

6085. Acta Endocrinol (Copenh). 1964 Jun;46:197-206.

EFFECT OF CORTICOSTEROIDS ON URINARY 5-BETA AND 5-ALPHA C19 STEROIDS IN MAN.

WILSON H, SCHENKER S.

PMID: 14193480 [Indexed for MEDLINE]

6086. Am J Med. 1964 Jun;36:893-918.

FAMILIAL PAROXYSMAL POLYSEROSITIS. ANALYSIS OF FIFTY CASES.

SIEGAL S.

PMID: 14162896 [Indexed for MEDLINE]

6087. Nature. 1964 May 9;202:606.

CLOSE ASSOCIATION OF I BLOOD GROUP AND DISEASE.

MCGINNISS MH, SCHMIDT PJ, CARBONE PP.

PMID: 14195074 [Indexed for MEDLINE]

6088. Sem Hop. 1964 Apr 26;40:1218-21.

[TRIAL TREATMENT OF PERIODIC DISEASE WITH 19-NORSTEROIDS].

[Article in French]

MAMOU H, NAHUM A.

PMID: 14147370 [Indexed for MEDLINE]

6089. Voeding. 1964 Mar 15;25:124-34.

[GAS CHROMATOGRAPHY STUDY OF ELEVATED FATTY ACIDS IN THE FECES OF A PATIENT WITH PERIODIC DISEASE].

[Article in Dutch]

HEKKENS WT, SEEDER WA, HAEX AJ.

PMID: 14140415 [Indexed for MEDLINE]

6090. Sem Med. 1964 Mar 12;124:498-500 PASSIM.

[CLINICAL SIGNIFICANCE OF FEVER-PRODUCING STEROIDS].

[Article in Spanish]

BRAILLARD CA, DEROSA S.

PMID: 14157420 [Indexed for MEDLINE]

6091. Bull Mem Soc Med Hop Paris. 1964 Mar 6-13;115:413-25.

[PERIODIC PARALYSIS WITH HYPOKALEMIA ASSOCIATED WITH HYPERTHYROIDISM. RECOVERY AFTER SUBTOTAL THYROIDECTOMY].

[Article in French]

GOULON M, EMILE J, ROGER M, BRETEAU M, GROSSIORD A.

PMID: 14156096 [Indexed for MEDLINE]

6092. Med Esp. 1964 Mar;51:254-65.

[PERIODIC DISEASE (REIMANN'S SYNDROME)].

[Article in Spanish]

MOURECOUCEIRO L.

PMID: 14153593 [Indexed for MEDLINE]

6093. Acta Med Scand. 1964 Mar;175:341-6.

NINE CASES OF HEREDITARY AND NON-HEREDITARY PERIODIC DISEASES.

NILSSON SE, FLODERUS S.

PMID: 14136248 [Indexed for MEDLINE]

6094. Arch Intern Med. 1964 Mar;113:409-11.

AMINO ACID EXCRETION IN FAMILIAL MEDITERRANEAN FEVER.

RUBENSTEIN M, WOLFF SM.

PMID: 14096394 [Indexed for MEDLINE]

6095. Rev Med Chil. 1964 Feb;92:144-7.

[PERIODIC MEDITERRANEAN FEVER (PERIODIC FAMILIAL FEVER). CLINICAL CASE WITH NECROPSY STUDY].

[Article in Spanish]

VIAL S, ROSENBERG H.

PMID: 14165299 [Indexed for MEDLINE]

6096. Pediatrics. 1964 Feb;33:284-7.

ETIOCHOLANOLONE FEVER. REPORT OF A CASE IN CHILDHOOD WITH PERIODIC PERITONITIS

ASSOCIATED WITH ELEVATED SERUM ETIOCHOLANOLONE.

JACOBS JC.

PMID: 14117388 [Indexed for MEDLINE]

6097. Zh Nevropatol Psikhiatr Im S S Korsakova. 1964;64:1322-6.

[PERIODIC DISEASE (CLINICAL AND PATHOGENIC ASPECTS)].

[Article in Russian]

GRASHCHENKOV NI, VEIN AM, SOLOVEVA AD, MALTSINA VS.

PMID: 14248171 [Indexed for MEDLINE]

6098. Mars Med. 1964;101:705-7.

[A CASE OF PERIODIC DISEASE WITH CHRONIC ARTICULAR MANIFESTATIONS].

[Article in French]

ISEMEIN L, REDON M, PIERRON H, FARISSE P.

PMID: 14207170 [Indexed for MEDLINE]

6099. Chiryō. 1964;46:1003-9.

[CLINICAL TRIALS OF THE NEW ALDOSTERONE ANTAGONISTS OF A STEROID NATURE].

[Article in Japanese]

KATO E, OSAWA S, WAKASUGI A, KIRIU Y, ATO T, MITSUNO K, ITAZU Y.

PMID: 14144003 [Indexed for MEDLINE]

6100. Montp Med. 1964 Jan;65:14-25.

[DIAGNOSIS OF A PROLONGED PYREXIA].

[Article in French]

BERTRAND L.

PMID: 14132747 [Indexed for MEDLINE]

6101. J Med Bord. 1964 Jan;141:67-76.

[PERIODIC DISEASE].

[Article in French]

AMOURETTI.

PMID: 14128346 [Indexed for MEDLINE]

6102. Sven Lakartidn. 1963 Dec 4;60:3661-75.

[PERIODICALLY APPEARING DISEASE SYMPTOMS].

[Article in Swedish]

NILSSON SE.

PMID: 14098658 [Indexed for MEDLINE]

6103. Dev Med Child Neurol. 1963 Dec;5:645.

CAUSES OF CYCLICAL VOMITING.

LORBER J.

PMID: 14090627 [Indexed for MEDLINE]

6104. Rev Med Moyen Orient. 1963 Nov-Dec;20:547-50.

[UNUSUAL SYNDROMES AND UNPUBLISHED COMPLICATIONS OF PERIODIC SEROSITIS (PERIODIC DISEASE)].

[Article in French]

GOKSEL V, BOLUKOGLU MA, BANKMAN NH.

PMID: 14114228 [Indexed for MEDLINE]

6105. Rev Med Moyen Orient. 1963 Nov-Dec;20:497-503.

[PERIODIC SEROSITIS (PERIODIC DISEASE) IN THE TURKISH AUTOCHTHONOUS POPULATION].

[Article in French]

GOEKSEL V, BANKMAN NH.

PMID: 14114221 [Indexed for MEDLINE]

6106. Naika. 1963 Nov;12:865-8.



[FEVER. DIAGNOSIS AND THERAPY OF FEVER OF UNKNOWN ORIGIN].

[Article in Japanese]

TORII T.

PMID: 14096034 [Indexed for MEDLINE]

6107. J Med Assoc Ga. 1963 Sep;52:403-4.

THE BIOLOGICAL CLOCK IN CLINICAL MEDICINE.

HUTCHINSON RG.

PMID: 14047811 [Indexed for MEDLINE]

6108. Med J Aust. 1963 Aug 3;50(2):167-73.

The periodic syndrome: its nature and prevalence.

CULLEN KJ, MA CDONALD WB.

PMID: 14024194 [Indexed for MEDLINE]

6109. Am J Dis Child. 1963 Aug;106:227-9.

FAMILIAL MEDITERRANEAN FEVER SIMULATING RHEUMATIC CARDITIS.

LASCH EE.

PMID: 14064874 [Indexed for MEDLINE]

6110. Arch Intern Med. 1963 Aug;112:234-41.

PERICARDITIS AND AURICULAR FIBRILLATION. OCCURRENCE IN FAMILIAL MEDITERRANEAN FEVER.

GALE A, LEVIN ME.

PMID: 14044823 [Indexed for MEDLINE]

6111. Q J Med. 1963 Jul;32:211-23.

PRIMARY PERI-RETICULAR ('TYPICAL') AMYLOIDOSIS IN ISRAEL: ITS RELATION TO FAMILIAL MEDITERRANEAN FEVER.

SOHAR E, GAFNI J, BLUM A, PRAS M, HELLER H.

PMID: 14045125 [Indexed for MEDLINE]

6112. Arch Neurol. 1963 Jul;9:55-63.

Theoretical diencephalic factors in periodic paralysis.

SOLOMON S.

PMID: 13978083 [Indexed for MEDLINE]

6113. Ter Arkh. 1963 Jun;35:73-9.

[ON THE ABDOMINAL SYNDROME OF PERIODIC DISEASE].

[Article in Russian]

AGADZHANIAN VV.

PMID: 14069317 [Indexed for MEDLINE]

6114. BMQ. 1963 Jun;14:59-75.

Familial mediterranean fever.

KECHEJIAN SJ.

PMID: 14031627 [Indexed for MEDLINE]

6115. Ned Tijdschr Geneeskd. 1963 May 18;107:897-9.

[A case of "periodic disease" with steatorrhea].

[Article in Dutch]

HAEX AJ, HEKKENS WT, SEEDER WA.

PMID: 13951810 [Indexed for MEDLINE]

6116. Harefuah. 1963 May 15;64:321-3.

[The histological pattern of the amyloidosis of familial Mediterranean fever].

[Article in Hebrew]

GAFNI J, MISSMAHL HP, SOHAR E, HELLER H.

PMID: 13946099 [Indexed for MEDLINE]

6117. Turk Tip Cemiy Mecm. 1963 Apr;29:180-6.

[A new form of chronic recurrent heredo-familial Mediterranean fever].

[Article in Turkish]

OZKAN E, PRIFTI J, ESEROVA G.

PMID: 13940907 [Indexed for MEDLINE]

6118. Turk Tip Cemiy Mecm. 1963 Mar;29:160-7.

[Familial Mediterranean fever (periodic disease) associated with ankylopoietic spondylitis. (Apropos of a case)].

[Article in Turkish]

DILSEN N.

PMID: 14027907 [Indexed for MEDLINE]

6119. Acta Med Scand. 1963 Feb;173:165-75.

Further observations on periodic disorders.

ASK-UPMARK E.

PMID: 13965220 [Indexed for MEDLINE]

6120. Azerbaidzhanskii Meditsinskii Zhurnal. 1963 Feb;2:77-82.

[On so-called periodic disease (diencephalic syndrome)].

[Article in Russian]

NAZIROV MR, GLASHKINA TP.

PMID: 13937818 [Indexed for MEDLINE]

6121. Bull Soc Belge Ophtalmol. 1963;135:432-6.

[PERIODIC DISEASE ASSOCIATED WITH A CATARACT AND A KERATOCONUS].

[Article in French]

FRANCOIS J, NEETENS A, BOGAERT R.

PMID: 14168105 [Indexed for MEDLINE]

6122. Suvr Med (Sofia). 1963;14:32-5.

[A CASE OF PERIODIC DISEASE].

[Article in Bulgarian]

ORESHKOV V.

PMID: 14105866 [Indexed for MEDLINE]

6123. Neurology. 1963 Jan;13:24-33.

Periodic paralysis: a study of carbohydrate and thiamine metabolism.

SATOYOSHI E, SUZUKI Y, ABE T.

PMID: 13986768 [Indexed for MEDLINE]

6124. *Pediatric*. 1963;18:594-8.

[On a case of periodic familial disease with recurrent emission of abnormally colored urine].

[Article in French]

ROMAGNY G, JOFFARD P, CHATIN B, DIDIERLAURENT A.

PMID: 13982558 [Indexed for MEDLINE]

6125. *Pediatric*. 1963;18:521-32.

[Apropos of 9 cases of periodic disease in children].

[Article in French]

BERNARD R, COIGNET J, MARIANI R, TROUILLOUD M, RAQUET J, RATHELOT B.

PMID: 13971019 [Indexed for MEDLINE]

6126. *Tijdschr Gastroenterol*. 1963;6:41-4.

[Periodic disease].

[Article in Dutch]

HAEX AJ, HEKKENS WT, SEEDER WA.

PMID: 13951811 [Indexed for MEDLINE]

6127. Rev Rhum Mal Osteoartic. 1962 Dec;29:730-6.

[Familial intermittent rheumatism. Its relation to other intermittent rheumatisms and in particular to periodic disease].

[Article in French]

LAMBERT P.

PMID: 13928248 [Indexed for MEDLINE]

6128. Am J Pathol. 1962 Nov;41:567-78.

A study of the fine structure of the amyloid associated with familial Mediterranean fever.

COHEN AS, FRENSDORFF A, LAMPRECHT S, CALKINS E.

PMCID: PMC1949617

PMID: 14022004 [Indexed for MEDLINE]

6129. Ann Intern Med. 1962 Nov;57:795-9.

Amyloidosis as the sole manifestation of familial Mediterranean fever (FMF). Further evidence of its genetic nature.

BLUM A, GAFNI J, SOHAR E, SHIBOLET S, HELLER H.

PMID: 13971845 [Indexed for MEDLINE]

6130. Pediatrics. 1962 Sep;30:443-9.

Recurrent polyserositis ("periodic disease," "familial Mediterranean fever") in children.

SHAPIRO TR, EHRENFELD EN.

PMID: 13911319 [Indexed for MEDLINE]

6131. J Ir Med Assoc. 1962 Sep;51:61-3.

The periodic syndrome.

DUNDON S.

PMID: 13888464 [Indexed for MEDLINE]

6132. Arch Intern Med. 1962 Aug;110:150-4.

Low-fat diet in familial Mediterranean fever; a therapeutic trial.

SOHAR E, GAFNI J, CHAIMOW M, PRASS M, HELLER H.

PMID: 13914797 [Indexed for MEDLINE]

6133. Pediatriia. 1962 Aug;40:85-7.

[On the problem of so-called periodic disease].

[Article in Russian]

ASTVATSATRIAN VA, MAKHONOVA LA.



PMID: 13863034 [Indexed for MEDLINE]

6134. Am J Gastroenterol. 1962 Jul;38:85-90.

The low-fat diet for periodic peritonitis.

REIMANN HA.

PMID: 14491228 [Indexed for MEDLINE]

6135. Am J Med Sci. 1962 Jun;243:727-39.

Hereditary periodic edema. The interrelation of familial periodic disorders.

REIMANN HA.

PMID: 14491225 [Indexed for MEDLINE]

6136. Gastroenterology. 1962 May;42:560-5.

Periodic polyserositis (periodic disease).

NUGENT FW, WEBER CM.

PMID: 14480690 [Indexed for MEDLINE]

6137. Med Cir Guerra. 1962 May-Jun;24:239-46.

[Reiman's periodic disease].

[Article in Spanish]

LECINANA RF.

PMID: 13928949 [Indexed for MEDLINE]

6138. J Pediatr. 1962 Apr;60:561-5.

Periodic fever in juvenile regional enteritis.

WALKER SH.

PMID: 14004624 [Indexed for MEDLINE]

6139. Med Interna (Bucur). 1962 Mar;14:347-54.

[Some unusual aspects of polyserositis].

[Article in Romanian]

PASCU T, BALAN SS, STANCIULESCU P.

PMID: 14484148 [Indexed for MEDLINE]

6140. Naika. 1962 Mar;9:475-82.

[Effect of anti-aldosterone drugs on periodic paralysis of the extremities and amyotonia].

[Article in Japanese]

OKINAKA S.

PMID: 14481572 [Indexed for MEDLINE]

6141. Neurology. 1962 Mar;12:208-12.

Some metabolic studies of sporadic and familial periodic paralysis.

NORRIS FH Jr.

PMID: 14480392 [Indexed for MEDLINE]

6142. J Maine Med Assoc. 1962 Mar;53:53-5.

A disease of many names. (Benign paroxysmal peritonitis, Armenian's disease, familial recurring polyserositis, periodic disease, familial Mediterranean fever, periodic peritonitis, periodic abdominalgia).

HANNIGAN CA, HAAS R.

PMID: 13904390 [Indexed for MEDLINE]

6143. Am J Med Sci. 1962 Feb;243:162-74.

Periodic fever, an entity. A collection of 52 cases.

REIMANN HA.

PMID: 14491227 [Indexed for MEDLINE]

6144. Ann Intern Med. 1962 Feb;56:171-82.

Familial Mediterranean fever. Plasma protein abnormalities, low-fat diet, and possible implications in pathogenesis.

MELLINKOFF SM, SNODGRASS RW, SCHWABE AD, MEAD JF, WEIMER HE, FRANKLAND M.

PMID: 14472400 [Indexed for MEDLINE]

6145. Med Clin (Barc). 1962 Feb;38:121-7.

[Familial Mediterranean fever].

[Article in Spanish]

CALVO MELENDRO J, SANCHEZ-MALO DE CALVO P.

PMID: 13875880 [Indexed for MEDLINE]

6146. Br Med J. 1962 Jan 13;1(5271):87-9.

Familial Mediterranean fever: a cause of periodic fever.

DORMER AE, HALE JF.

PMCID: PMC1957225

PMID: 13887384 [Indexed for MEDLINE]

6147. Concours Med. 1962 Jan 6;84:17-23.

[So-called periodic disease in internal medicine].

[Article in French]

SIGUIER F, BETOURNE C, GODEAU P.

PMID: 13912748 [Indexed for MEDLINE]

6148. Harefuah. 1962 Jan 1;62:1-5.

[Schoenlein-Henoch syndrome in familial Mediterranean fever].

[Article in Hebrew]

ROTEM Y, FEDERGRUEN A.

PMID: 14494360 [Indexed for MEDLINE]

6149. Bull Mem Soc Med Hop Paris. 1962;113:1137-55.

[Our current experience with so-called periodic disease].

[Article in French]

CATTAN R, KHAYAT G, HIRSCH-MARIE H.

PMID: 14019364 [Indexed for MEDLINE]

6150. Bull Mem Soc Med Hop Paris. 1962;113:1156-61.

[The subinfrant forms of period disease].

[Article in French]

SIGUIER F, GODEAU P, LEVY R, PASQUIER P, THENOT A.

PMID: 13989065 [Indexed for MEDLINE]

6151. Bull Mem Soc Med Hop Paris. 1962;113:1162-9.

[The nephropathies of periodic disease].

[Article in French]

MERY JP, de MONTERA, HAMBURGER MJ.

PMID: 13935082 [Indexed for MEDLINE]

6152. Bull Mem Soc Med Hop Paris. 1962;113:1170-6.

[The articular signs of periodic disease].

[Article in French]

LIEVRE JA, CAMUS JP, BONToux D.

PMID: 13930578 [Indexed for MEDLINE]

6153. Vie Med. 1962;43(13):17-20.

[Nephrology].

[Article in French]

LAGRUE G.

PMID: 13928086 [Indexed for MEDLINE]

6154. Arch Ital Anat Istol Patol. 1961 Dec;35:427-51.

[On a case of familial periodic paralysis].

[Article in Italian]

DE ANNIBALIS N.

PMID: 13884103 [Indexed for MEDLINE]

6155. Dtsch Med Wochenschr. 1961 Nov 24;86:2289-91.

[Familial Mediterranean fever. A genetically determined disease associated with amyloidosis].

[Article in German]

MISSMAHL HP.

DOI: 10.1055/s-0028-1113091

PMID: 14474585 [Indexed for MEDLINE]

6156. J Neurol Neurosurg Psychiatry. 1961 Nov;24:369-73.

Ocular sympathetic palsy in periodic migrainous neuralgia.

NIEMAN EA, HURWITZ LJ.

PMCID: PMC495400

PMID: 14479664 [Indexed for MEDLINE]

6157. Med Glas. 1961 Nov;15:396-8.

[Periodic disease. Etiopathogenic contribution].

[Article in Undetermined Language]

MIKSIC J.

PMID: 14473757 [Indexed for MEDLINE]

6158. JAMA. 1961 Oct 21;178:334-5.

Hepatitis--a feature of periodic peritonitis.

REIMANN HA.

PMID: 14491224 [Indexed for MEDLINE]

6159. Lille Med. 1961 Oct;6:731-9.

[Apropos of a case of periodic disease].

[Article in French]

WAREMBOURG H, PAUCHANT M, DUCLOUX G.

PMID: 14004987 [Indexed for MEDLINE]

6160. Arch Dermatol. 1961 Oct;84:630-2.

Urticaria and dermographism with Mediterranean fever. Report of a case.

BAUMAL A, KANTOR I.

PMID: 13865908 [Indexed for MEDLINE]

6161. Praxis. 1961 Sep 28;50:1003-5.



[Familial Mediterranean fever (periodic fever)].

[Article in German]

SHERMAN M, MELLINKOFF MD.

PMID: 13911724 [Indexed for MEDLINE]

6162. Rev Rhum Mal Osteoartic. 1961 Sep;28:417-22.

[The articular manifestations of periodic disease].

[Article in French]

LIEVRE JA, CAMUS JP, BONToux D.

PMID: 14465230 [Indexed for MEDLINE]

6163. Am J Med. 1961 Sep;31:328-42.

A third type of periodic paralysis, with normokalemia and favourable response to sodium chloride.

POSKANZER DC, KERR DN.

PMID: 13737364 [Indexed for MEDLINE]

6164. J Clin Endocrinol Metab. 1961 Sep;21:1079-86.

Sodium and potassium metabolism in a case of familial periodic paralysis.

ONAT A, OZDAMAR E, BERKOL S.

DOI: 10.1210/jcem-21-9-1079

PMID: 13730964 [Indexed for MEDLINE]

6165. Ann Intern Med. 1961 Sep;55:448-55.

Plasma fibrinogen in familial Mediterranean fever.

FRENSDORFF A, SOHAR E, HELLER H.

PMID: 13701764 [Indexed for MEDLINE]

6166. Rev Invest Clin. 1961 Jul-Sep;13:325-34.

[Familial Mediterranean fever (FMF)].

[Article in Spanish]

HELLER H.

PMID: 13906234 [Indexed for MEDLINE]

6167. Arch Intern Med. 1961 Jul;108:80-5.

A dietary treatment for familial Mediterranean fever.

MELLINKOFF SM, SCHWABE AD, LAWRENCE JS.

PMID: 13769243 [Indexed for MEDLINE]

6168. Arch Intern Med. 1961 Jul;108:91-9.

Recurrent polyserositis ("periodic disease"). Electroencephalographic changes.

ELIAKIM M, BENTAL E.

PMID: 13726347 [Indexed for MEDLINE]

6169. Arch Inst Pasteur Tunis. 1961 Jun;38:121-8.

[Modifications of seasonal indexes of bacillary dysentery].

[Article in French]

DIOSI P, CIRSTEVA V.

PMID: 13723042 [Indexed for MEDLINE]

6170. Rev Fr Etud Clin Biol. 1961 Jun-Jul;6:533-6.

[Fever, etiocholanolone, pyrogenic steroids and "periodic disease"].

[Article in French]

BAULIEU EE.

PMID: 13687955 [Indexed for MEDLINE]

6171. Jpn J Med Sci Biol. 1961 May 10;50:177-81.

[A case of periodic paralysis].

[Article in Japanese]

TOKUOMI H, MIYAZAKI Y, TOMIYASU T.

PMID: 13777230 [Indexed for MEDLINE]

6172. Toulouse Med. 1961 May;62:379-80.

[Periodic disease (apropos of a case)].

[Article in French]

BARDIER A, DALOUS A, SALANOVA, LAZORTHES.

PMID: 13686914 [Indexed for MEDLINE]

6173. Rev Med Chil. 1961 Apr;89:297-8.

[Benign paroxysmal peritonitis. A clinical form of periodic disease].

[Article in Spanish]

KLINGER J, ZELDIS A.

PMID: 13756886 [Indexed for MEDLINE]

6174. Srp Arh Celok Lek. 1961 Apr;89:451-5.

[Periodic disease. A report of 2 cases].

[Article in Undetermined Language]

RISTIC L, FILIPOVIC K, MILOSEVIC D.

PMID: 13741870 [Indexed for MEDLINE]

6175. Am J Cardiol. 1961 Apr;7:517-20.

Electrocardiographic changes in recurrent polyserositis ("periodic disease").

ELIAKIM M, EHRENFELD EN.

PMID: 13726348 [Indexed for MEDLINE]

6176. Arch Intern Med. 1961 Apr;107:539-50.

Amyloidosis in familial Mediterranean fever. An independent genetically determined character.

HELLER H, SOHAR E, GAFNI J, HELLER J.

PMID: 13713112 [Indexed for MEDLINE]

6177. Sem Med Prof Med Soc. 1961 Mar 2;37:775-80.

[Amyloid nephrotic syndrome and periodic disease].

[Article in French]

MILLIEZ P, LAROCHE C, SAMARCQ P, LAGRUE G.

PMID: 13770923 [Indexed for MEDLINE]

6178. Laboratorio. 1961 Mar;39:145-8.

On clinical aspects of the so-called periodic disease

TIKHOMIROV IB.

PMID: 13776874 [Indexed for MEDLINE]

6179. Harefuah. 1961 Feb 1;60:84-6.

[Immunological studies by the agar gel diffusion technic in familial Mediterranean fever (FMF). Preliminary report].

[Article in Hebrew]

SHACHTER-MANY A, PRAS M, SOHAR E, HELLER H, EILAN E, KEDAR J.

PMID: 13750540 [Indexed for MEDLINE]

6180. Pathol Microbiol (Basel). 1961;24:718-23.

Ethnic distribution and amyloidosis in familial Mediterranean fever (FMF).

HELLER H, SOHAR E, PRAS M.

PMID: 13906231 [Indexed for MEDLINE]

6181. Gastroenterology. 1961 Jan;40:151-3.

Familial Mediterranean fever.

MELLINKOFF SM.

PMID: 13769244 [Indexed for MEDLINE]

6182. Lille Med. 1961;6:576-81.

[Acute benign pericarditis and peritonitis, 2 forms of periodic disease, 1 case of which is autochthonous].

[Article in French]

LEBACQ E, GOSSART J, DUEZ P.

PMID: 13759958 [Indexed for MEDLINE]

6183. Acta Clin Belg. 1961 Jan-Feb;16:68-75.

[Acute benign pericarditis and peritonitis, 2 forms of periodic disease, 1 case being autochthonous].

[Article in French]

LEBACQ E, GOSSART J, DUEZ P.

PMID: 13759957 [Indexed for MEDLINE]

6184. Turk Tip Cemiy Mecm. 1961 Jan;27:62-8.

[A case of familial periodic paralysis manifesting as primary paralysis].

[Article in Turkish]

KULEY M, KOCAK N, ARAN M.

PMID: 13755038 [Indexed for MEDLINE]

6185. Am J Dis Child. 1961 Jan;101:53-9.

Familial Mediterranean fever. Report of four cases.

COZZETTO FJ.

PMID: 13696152 [Indexed for MEDLINE]

6186. Nord Med. 1960 Nov 10;64:1420-3.

[2 psychiatric cases of "periodic disease"].

[Article in Danish]

HERTZ M.

PMID: 13713826 [Indexed for MEDLINE]

6187. N Engl J Med. 1960 Oct 6;263:669-72.

Periodic fever with renal amyloidosis.

FOX M, MORRELLI H.

DOI: 10.1056/NEJM196010062631403

PMID: 13701112 [Indexed for MEDLINE]

6188. Am J Gastroenterol. 1960 Oct;34:422-4.

Periodic peritonitis and acute appendicitis.

REIMANN HA, NADIMI M.

PMID: 13740544 [Indexed for MEDLINE]



6189. Bull Soc Sci Med Grand Duche Luxemb. 1960 Oct;97:265-74.

[Periodic peritonitis].

[Article in French]

d' HUART.

PMID: 13716414 [Indexed for MEDLINE]

6190. Med Monde. 1960 Sep;36:91-101.

[Periodic disease. Probable etiology and treatment].

[Article in French]

TAMCHES A.

PMID: 13775100 [Indexed for MEDLINE]

6191. Am J Roentgenol Radium Ther Nucl Med. 1960 Aug;84:269-74.

Roentgenologic findings in familial Mediterranean fever.

SHAHIN N, SOHAR E, DALITH F.

PMID: 14445399 [Indexed for MEDLINE]

6192. Ann Intern Med. 1960 Aug;53:407-11.

Periodic peritonitis, onset simultaneously with menstruation.

SCHWARTZ J.

PMID: 14443989 [Indexed for MEDLINE]

6193. J Mich State Med Soc. 1960 Aug;59:1215-8.

Periodic fever in private practice.

HARRELSON WD.

PMID: 14399911 [Indexed for MEDLINE]

6194. Am J Roentgenol Radium Ther Nucl Med. 1960 Aug;84:262-8.

Familial recurring polyserositis.

EYLER WR, NIXON RK, PRIEST RJ.

PMID: 13821128 [Indexed for MEDLINE]

6195. Ann Allergy. 1960 Aug;18:894-5.

Case of a periodical affection of the eyes and chest.

BOSTOCK J.

PMID: 13803095 [Indexed for MEDLINE]

6196. Harefuah. 1960 Jul 15;59:39-45.

[Familial Mediterranean fever].

[Article in Hebrew]

SOHAR E, PRAS M, HELLER J, GAFNI J, HELLER H.

PMID: 13832482 [Indexed for MEDLINE]

6197. N Engl J Med. 1960 Jul 7;263:18-21.

Familial recurring polyserositis simulating acute surgical condition of the abdomen.

NIXON RK, PRIEST RJ.

DOI: 10.1056/NEJM196007072630105

PMID: 14427410 [Indexed for MEDLINE]

6198. Acta Genet Med Gemellol (Roma). 1960 Jul;9:344-60.

[Familial Mediterranean fever].

[Article in Italian]

SOHAR E, PRAS M, HELLER J, GAFNI J, HELLER H.

PMID: 13832481 [Indexed for MEDLINE]

6199. Rhumatologie. 1960 Jan-Feb;12:32-5.

[The rheumatismal manifestations of periodic disease (Apropos of a personal case)].

[Article in French]

FRANCON J.

PMID: 13824479 [Indexed for MEDLINE]

6200. Tijdschr Gastroenterol. 1960;3:856-65.

Periodic disease.

DE VLAAM AM.

PMID: 13720926 [Indexed for MEDLINE]

6201. Ann Intern Med. 1959 Dec;51:1253-74.

Familial recurring polyserositis: a disease entity.

PRIEST RJ, NIXON RK.

PMID: 14434876 [Indexed for MEDLINE]

6202. Rev Esp Enferm Apar Dig Nutr. 1959 Dec;18:1671-4.

[Porphyrinuria in so-called "periodic peritonitis"].

[Article in Spanish]

ARIAS VALLEJO E.

PMID: 13794210 [Indexed for MEDLINE]

6203. Sov Med. 1959 Nov;23:3-14.

[On so-called periodic disease].

[Article in Russian]

TAREEV EM, NASONOVA VA.

PMID: 13836935 [Indexed for MEDLINE]

6204. AMA Arch Ophthalmol. 1959 Jul;62(1):1-4.

Fundal changes resembling colloid bodies in recurrent polyserositis (periodic disease).

MICHAELSON I, ELIAKIM M, EHRENFELD EN, RACHMILEWITZ M.

PMID: 13660535 [Indexed for MEDLINE]

6205. J Am Med Assoc. 1959 Jun 6;170(6):678.

IS FAMILIAL periodic disease a nosological entity.

[No authors listed]

PMID: 13654016 [Indexed for MEDLINE]

6206. J Am Med Assoc. 1959 Jun 6;170(6):653-5.

Familial periodic disease with renal damage.

ALKALAY I, SHENFIELD M, LEVY E.

PMID: 13654007 [Indexed for MEDLINE]

6207. Lancet. 1959 May 23;1(7082):1069-71.

The periodic migrainous neuralgia of Wilfred Harris.

BICKERSTAFF ER.

PMID: 13655672 [Indexed for MEDLINE]

6208. Med Panam. 1959 May 15;12(10):345-52.

[Acute pericarditis during a periodic disease].

[Article in Spanish]

FONGI EG, OLIVERI RA.

PMID: 13666290 [Indexed for MEDLINE]

6209. Prensa Med Argent. 1959 May 1;46:1117-22.

[Periodic disease].

[Article in Spanish]

PEROSIO AM, SUAREZ LD, SCATTINI M.

PMID: 13854293 [Indexed for MEDLINE]

6210. Rass Neurol Veg. 1959 Apr 30;14:110-34.

[Palindromic rheumatism in the framework of periodic disease].

[Article in Italian]

MORANDI GA.

PMID: 14423963 [Indexed for MEDLINE]

6211. J Clin Endocrinol Metab. 1959 Feb;19(2):266-9.

Unusual plasma 17-ketosteroid pattern in a boy with congenital adrenal hyperplasia and periodic fever.

GARDNER LI, MIGEON CJ.

DOI: 10.1210/jcem-19-2-266

PMID: 13620756 [Indexed for MEDLINE]

6212. Mars Med. 1959;96:517-25.

[On 2 cases of periodic disease in the same family].

[Article in French]

BERAUD P, EYSSERIC G, PECOUT G.

PMID: 13799112 [Indexed for MEDLINE]

6213. Sang. 1959;30(1):41-7.

[Morphological anomalies of erythrocytes in periodic disease studied by the shadow method in the optic microscope].

[Article in French]

DANON D, DE VRIES A.

PMID: 13646558 [Indexed for MEDLINE]

6214. Nord Med. 1958 Nov 27;60(48):1726-30.

[Periodic disease].

[Article in Swedish]

GABINUS O, HOGBERG G.

PMID: 13613586 [Indexed for MEDLINE]

6215. Maroc Med. 1958 Oct;37(401):1031-3.

[Periodic diseases].

CAPDEVILLE J, CHARLAS R.

PMID: 13612357 [Indexed for MEDLINE]

6216. Rev Med Nancy. 1958 Oct;83:806-11.

[2 Cases of periodic disease].

[Article in French]

NEIMANN N, PIERSON M, LASCOMBES G, DUCAS J.



PMID: 13602430 [Indexed for MEDLINE]

6217. Ann Intern Med. 1958 Oct;49(4):885-99.

Periodic disease: a clinicopathologic study.

TUQAN NA.

PMID: 13583779 [Indexed for MEDLINE]

6218. Rev Int Serv Sante Armees. 1958 Sep-Oct;31(9-10):430-5.

[II. Periodic paralyses].

[Article in French]

COIRAULT R, BERNARD M, DAVIDOU P.

PMID: 13602382 [Indexed for MEDLINE]

6219. Policlinico Med. 1958 Aug;65(4):216-39.

[Remarks on a case of periodic disease].

[Article in Italian]

AMERIO A, SALONNA L.

PMID: 13578716 [Indexed for MEDLINE]

6220. Isr Med J. 1958 Jul-Aug;17(7-8):150-7.

Tuberculin sensitivity in recurrent polyserositis (periodic disease).

RACHMILEWITZ M, EHRENFELD EN, ELIAKIM M.

PMID: 13586997 [Indexed for MEDLINE]

6221. Postgrad Med. 1958 Jul;24(1):30-5.

Intermittent hydrarthrosis; periodic benign synovitis.

ENSIGN DC, SIGLER JW.

PMID: 13567199 [Indexed for MEDLINE]

6222. AMA Arch Intern Med. 1958 Jul;102(1):50-71.

Familial Mediterranean fever.

HELLER H, SOHAR E, SHERF L.

PMID: 13558745 [Indexed for MEDLINE]

6223. Yale J Biol Med. 1958 Jun;30(6):395-405.

The possible relationship of etiocholanolone to periodic fever.

BONDY PK, COHN GL, HERRMANN W, CRISPELL KR.

PMCID: PMC2603892

PMID: 13570161 [Indexed for MEDLINE]

6224. Cesk Oftalmol. 1958 Jun;14(3):195-7.

Periodický exoftalmus.

[Article in Czech]

VENCLIK H, PITTER J, SVOBODA M.

PMID: 13561375 [Indexed for MEDLINE]

6225. Bull Mem Soc Med Hop Paris. 1958 May 2-9;74(15-16):377-80.

[So-called periodic disease].

[Article in French]

BILLIOTTET J, RENNER R, ZITTOUN R, GANDIN J.

PMID: 13546967 [Indexed for MEDLINE]

6226. Ann Intern Med. 1958 Apr;48(4):859-64.

Cyclic fever, abdominal pain and grand mal seizures: case report.

NAEYE RL.

PMID: 13521611 [Indexed for MEDLINE]

6227. Med Panam. 1958 Mar 15;10(6):162-8.

[So-called periodic disease].

FRANCAVILLA C, SUTTIN J.

PMID: 13565109 [Indexed for MEDLINE]

6228. Sem Hop. 1958 Jan 24;34(4/1):220-6P.

[A new case of periodic disease with familial character & cerebral manifestations].

[Article in French]

TURPIN R, GORIN R.

PMID: 13529098 [Indexed for MEDLINE]

6229. Presse Med. 1958 Jan 11;66(3):44-6.

[Malignant reticulosis with the clinical type of periodic fever; 2 new case reports].

[Article in French]

DARBON A, CAUBET P, DULAC JF, GUILLAUME P.

PMID: 13527420 [Indexed for MEDLINE]

6230. Harefuah. 1957 Dec 15;53(12):315-6; English & French abstracts 316.

[Tuberculin hypersensitivity and choroidal findings in recurrent polyserositis (periodic disease); preliminary report].

[Article in Hebrew]

RACHMILEWITZ M, EHRENFELD EN, ELIAKIM M, MICHAELSON IC.

PMID: 13501692 [Indexed for MEDLINE]

6231. Rev Esp Enferm Apar Dig Nutr. 1957 Nov-Dec;16(6):753-4.

[Periodic disease].

[Article in Spanish]

ARIAS VALLEJO E.

PMID: 13527989 [Indexed for MEDLINE]

6232. Pediatrics. 1957 Nov;20(5, Part 1):782-93.

Familial paroxysmal dysfunction of the autonomic nervous system (a periodic disease), often precipitated by emotional stress.

HEINER DC, BLITZER JR.

PMID: 13484317 [Indexed for MEDLINE]

6233. Presse Med. 1957 Oct 12;65(73):1633-4.

[Periodic disease in Turkey].

[Article in French]

YARKIN C, BANKMAN N.

PMID: 13494396 [Indexed for MEDLINE]

6234. Helv Med Acta. 1957 Oct;24(4):264-6.

[Periodic disease with hematuria and hemoglobinuria].

[Article in German]

WUHRMANN F.

PMID: 13480627 [Indexed for MEDLINE]

6235. Am J Med. 1957 Sep;23(3):502-6.

Periodic fever: occurrence in five generations.

BOURONCLE BA, DOAN CA.

PMID: 13458215 [Indexed for MEDLINE]

6236. Br Med J. 1957 Aug 17;2(5041):398-9.

PERIODIC disease.

[No authors listed]

PMCID: PMC1962083

PMID: 13446496 [Indexed for MEDLINE]

6237. Yokohama Med Bull. 1957 Aug;8(4):233-7.

A case of periodic disease cured by ACTH.

GOTO T, SHIMANO K, OKANO M, WATANABE T.

PMID: 13558211 [Indexed for MEDLINE]

6238. Minerva Nefrol. 1957 Jul-Sep;4(3):96-9.

[Nephropathy in periodic disease].

[Article in Italian]

AMERIO A.

PMID: 13541101 [Indexed for MEDLINE]

6239. Prensa Med Argent. 1957 Jun 21;44(25):1927-8.

[Benign paroxysmal peritonitis (abdominal form of periodic disease)].

[Article in Spanish]

MAZZEI ES.

PMID: 13505480 [Indexed for MEDLINE]

6240. Br Med J. 1957 May 11;1(5027):1086-8.

Periodic disease: periodic fever; report of a case.

SOMERS K.

PMCID: PMC1973848

PMID: 13426546 [Indexed for MEDLINE]

6241. J Clin Invest. 1957 May;36(5):730-7.

Movement of potassium into skeletal muscle during spontaneous attack in family periodic paralysis.

ZIERLER KL, ANDRES R.

DOI: 10.1172/JCI103476

PMCID: PMC441743

PMID: 13428864 [Indexed for MEDLINE]

6242. N Engl J Med. 1957 Apr 4;256(14):652-3.

Periodicity in disease.

REIMANN HA.

DOI: 10.1056/NEJM195704042561407

PMID: 13451912 [Indexed for MEDLINE]

6243. Bull Mens Soc Med Mil Fr. 1957 Apr;51(4):172-91.

[Initial data regarding disorders of adrenal cortex hormone secretion & electrolyte variations in periodic paralysis syndromes].

[Article in French]

COIRAULT R, DAVIDOU P, BERNARD M.

PMID: 13446643 [Indexed for MEDLINE]

6244. Dtsch Med Wochenschr. 1957 Mar 15;82(11):391.

[Periodic disease].



[Article in German]

HORING FO.

PMID: 13427518 [Indexed for MEDLINE]

6245. G Clin Med. 1957 Mar;38(3):458-64.

[Periodic disease].

[Article in Italian]

BONOMINI V.

PMID: 13448440 [Indexed for MEDLINE]

6246. Minerva Med. 1957 Jan 13;48(3-4):45-9.

[Studies on periodic disease].

[Article in Italian]

DELL'ACQUA G.

PMID: 13418445 [Indexed for MEDLINE]

6247. Schweiz Med Wochenschr. 1957 Jan 5;87(1):5-11.

[Siegel-Cattan-Mamou's disease; paroxysmal abacterial peritonitis with pleuropericardial and articular complications; autonomous clinical form of Reiman's periodic disease].

[Article in French]

BICKEL G, LASSERRE R.

PMID: 13408944 [Indexed for MEDLINE]

6248. Recent Prog Horm Res. 1957;13:105-54; discussion 155-9.

Hormones and rhythms in man and animals.

RICHTER CP.

PMID: 13477807 [Indexed for MEDLINE]

6249. Harefuah. 1957 Jan 1;52(1):1-5.

Red cell abnormality and autoimmune antibody in periodic disease.

DE VRIES A, DANON D, NELKEN D, HENIG E.

PMID: 13462355 [Indexed for MEDLINE]

6250. Turk Tip Cemiy Mecm. 1956 Dec;22(12):707-19.

[Periodic abdominal syndrome and nephropathies due to tuberculous allergy].

[Article in Turkish]

GOKSEL V.

PMID: 13433844 [Indexed for MEDLINE]

6251. Sem Hop. 1956 Oct 22;32(62):3197-204.

[Anatomo-clinical study of unrecognized periodic disease in an Armenian].

[Article in French]

MAMOU H, MARET R.

PMID: 13391011 [Indexed for MEDLINE]

6252. J Bone Joint Surg Am. 1956 Oct;38-A(5):1039-55.

Periodic benign synovitis; idiopathic intermittent hydrarthrosis.

GHORMLEY RK, WEINER AD.

PMID: 13367081 [Indexed for MEDLINE]

6253. AMA J Dis Child. 1956 Oct;92(4):390-4.

Periodic peritonitis.

BURKE EC, STURTZ GS.

PMID: 13361766 [Indexed for MEDLINE]

6254. Arch Mal Appar Dig Mal Nutr. 1956 Sep;45(9):183-6.

[Periodic disease; detection of a severe peritoneal dilatation in the course of the attacks].

BERNARD P, SARLES H.

PMID: 13373470 [Indexed for MEDLINE]

6255. Ned Tijdschr Geneeskd. 1956 Aug 4;100(31):2199-202.

[A case of periodic disease].

[Article in Dutch]

FRANK P.

PMID: 13378552 [Indexed for MEDLINE]

6256. Sem Med. 1956 Apr 26;108(17):544-5.

[Periodic peritonitis].

[Article in Spanish]

CATALANO FE.

PMID: 13337383 [Indexed for MEDLINE]

6257. Lyon Med. 1956 Mar 25;88(13):291-9.

[First autochthonous case from Lyon of periodic disease].

[Article in French]

MONNET P.

PMID: 13321076 [Indexed for MEDLINE]

6258. Mars Med. 1956;93(3):231-4.

[Periodic disease; verification by laparoscopy of severe peritoneal vasodilatation during the crisis; action of penthonium and of dihydroergotamine].

[Article in French]

SARLES H, BERNARD P.

PMID: 13333340 [Indexed for MEDLINE]

6259. Helv Paediatr Acta. 1955 Dec;10(6):649-71.

[Periodic disease; reports of four typical cases].

[Article in German]

HITZIG WH.

PMID: 13306090 [Indexed for MEDLINE]

6260. Alger Medicale. 1955 Dec;59(12):809-20.

[The periodic disease; 38 personal cases].

[Article in French]

BENHAMOU E, ALBOU A, SAYAG P.

PMID: 13302117 [Indexed for MEDLINE]

6261. Prensa Med Argent. 1955 Oct 7;42(40):3110-2.

[Periodic disease; concerning an observation of periodic peritonitis].

[Article in Spanish]

LISTA GA, MULLER AO.

PMID: 13297664 [Indexed for MEDLINE]

6262. Concours Med. 1955 Aug 20;77(34):3159-60.

[Periodic disease and psychic disorders].

[Article in French]

BOREL J, MORDRET MY.

PMID: 13250845 [Indexed for MEDLINE]

6263. Dtsch Med Wochenschr. 1955 Aug 5;80(31-32):1145.

[Periodic diseases].

[Article in German]

HORING FO.

DOI: 10.1055/s-0028-1116149

PMID: 13250978 [Indexed for MEDLINE]

6264. Turk Tip Cemiy Mecm. 1955 Jun;21(6):282-6.

[Five cases of periodic disease].

[Article in Turkish]

ARTUNKAL S, SEYAHİ V.

PMID: 13274576 [Indexed for MEDLINE]

6265. Resen Clin Cient. 1955 Jun;24(6):146-7.

[Further manifestations of periodic disease].

[Article in Portuguese]

BERARDINELLI W.

PMID: 13255112 [Indexed for MEDLINE]

6266. Harefuah. 1955 Mar 1;48(5):91-4.

[Familial Mediterranean fever].

[Article in Hebrew]

HELLER H, KARIV J, SHERF L, SOHAR E.

PMID: 14380884 [Indexed for MEDLINE]

6267. Presse Med. 1955 Feb 19;63(13):237-8.

[Renal disorders in periodic disease].

[Article in French]

CATTAN R.

PMID: 14371475 [Indexed for MEDLINE]

6268. AMA Arch Intern Med. 1955 Feb;95(2):337-40.

Periodic disease; report of a case of recurrent abdominal and thoracic pain with synchronous gross hematuria.

SHWAYRI E, TUTUNJI N.

PMID: 13227657 [Indexed for MEDLINE]

6269. Sem Hop. 1955 Jan 30;31(7):388-91.

[Amylogenic periodic disease].

[Article in French]

MAMOU H.

PMID: 14358728 [Indexed for MEDLINE]

6270. Tunis Med. 1955 Jan;43(1):79-80.

[Periarteritis nodosa and periodic disease].

[Article in French]

BONAN H.

PMID: 14374019 [Indexed for MEDLINE]



6271. Yokohama Med Bull. 1954 Oct;5(5):355-60.

On the periodicity of symptoms and signs, and periodic disease.

GOTO T, OKANO M, KIKUNO M.

PMID: 14360078 [Indexed for MEDLINE]

6272. Bull Mem Soc Med Hop Paris. 1954 May 14-21;70(15-16):520-4.

[Further cases of periodic disease; biological and pathogenetic study].

[Article in French]

MAMOU H.

PMID: 13190390 [Indexed for MEDLINE]

6273. Clin Nuova Rass Prog Med Int. 1954 Apr 24;18(8):377-83.

[Periodic disease].

[Article in Undetermined Language]

PIACENTINI T.

PMID: 13182768 [Indexed for MEDLINE]

6274. J Am Med Assoc. 1954 Apr 10;154(15):1254-9.

Periodic peritonitis; heredity and pathology: report of seventy-two cases.

REIMANN HA, MOADIE J, SEMERDJIAN S, SAHYOUN PF.

PMID: 13151833 [Indexed for MEDLINE]

6275. Bull Mem Soc Med Hop Paris. 1954 Mar 12-19;70(9-10):254-9.

[Clinical, biologic and therapeutic comments on periodic disease, based on 24 personal cases].

[Article in Undetermined Language]

BENHAMOU E, ALBOU A, GRIGUER P.

PMID: 13160798 [Indexed for MEDLINE]

6276. Bull Mem Soc Med Hop Paris. 1954 Mar 12-19;70(9-10):247-54.

[Periarteritis nodosa and periodic disease].

[Article in Undetermined Language]

BENHAMOU E, ALBOU A, DESTAING F, FERRAND B, BOINEAU N.

PMID: 13160797 [Indexed for MEDLINE]

6277. Bull Mem Soc Med Hop Paris. 1954 Jan 15-22;70(1-2):43-9.

[Periodic disease: ten cases and two hypotheses].

[Article in Undetermined Language]

CATTAN R.

PMID: 13150182 [Indexed for MEDLINE]

6278. Bull Mem Soc Med Hop Paris. 1954 Jan 15-22;70(1-2):31-6.

[Aberrant forms and nosology of the so-called periodic disease].

[Article in Undetermined Language]

SIGUIER F, ZARA M, SEBAOUN J.

PMID: 13150180 [Indexed for MEDLINE]

6279. Bull Mem Soc Med Hop Paris. 1954 Jan 15-22;70(1-2):27-31.

[Periodic disease with attacks of sialorrhea and cyclic neutropenia].

[Article in Undetermined Language]

SIGUIER F, SEBAOUN J.

PMID: 13150179 [Indexed for MEDLINE]

6280. Mars Med. 1954;91(4):268-74.

[Periodic disease].

[Article in Undetermined Language]

CATTAN R.

PMID: 13175760 [Indexed for MEDLINE]

6281. Alger Medecale. 1954 Jan;58(1):19-22.

[Periodic disease].

[Article in Undetermined Language]

FERRAND M, WIDLOCHER D.

PMID: 13138518 [Indexed for MEDLINE]

6282. Alger Medecale. 1954 Jan;58(1):1-5.

[Familial forms of periodic disease].

[Article in Undetermined Language]

BENHAMOU E, ALBOU A, GRIGUER P.

PMID: 13138515 [Indexed for MEDLINE]

6283. Presse Med. 1953 Dec 12;61(80):1645-6.

[Periodic disease in Brazil].

[Article in Undetermined Language]

BERARINELLI W, DE CASTRO A, TEIXEIRA W.

PMID: 13134051 [Indexed for MEDLINE]

6284. Presse Med. 1953 Nov 25;61(76):1551-2.

[Periodic disease in a lobectomized pulmonary tuberculosis patient having received 600 grams of streptomycin and Friedmann's treatment: rimifon therapy].

[Article in Undetermined Language]

MARTIN-LALANDE J, LAFORGE S.

PMID: 13134024 [Indexed for MEDLINE]

6285. Resen Clin Cient. 1953 Nov-Dec;22(11-12):363-7.

[Periodic disease].

BERARDINELLI W, DE CASTRO Ary, TEIXEIRA W, DE CASTRO Alvary.

PMID: 13155928 [Indexed for MEDLINE]

6286. Vie Med. 1953 Nov;34(11):951-3.

[Periodic disease].

[Article in Undetermined Language]

CATTAN R.

PMID: 13136857 [Indexed for MEDLINE]

6287. AMA Arch Intern Med. 1953 Oct;92(4):494-506.

Periodic disease; observation on old cases and report of new cases and of therapeutic trials.

REIMANN HA.

PMID: 13091468 [Indexed for MEDLINE]

6288. Minerva Pediatr. 1953 Sep 30;5(18):781-4.

[Two familial cases of periodic disease].

[Article in Undetermined Language]

CALLIGARIS G.

PMID: 13111008 [Indexed for MEDLINE]

6289. Bull Mem Soc Med Hop Paris. 1953 Jun 12-19;69(19-20):679-84.

[Periodic disease in reduced forms evolving in several members of the same family].

[Article in Undetermined Language]

SIGUIER F, ZARA M, FUNCK-BRENTANO JL, LAGRUE G.

PMID: 13082418 [Indexed for MEDLINE]

6290. Bull Mem Soc Med Hop Paris. 1953 May 15-22;69(15-16):431-5.

[Two new cases of periodic disease].

[Article in Undetermined Language]

MAMOU H, BERNARD A.

PMID: 13067008 [Indexed for MEDLINE]

6291. Bull Mem Soc Med Hop Paris. 1953 May 15-22;69(15-16):427-31.

[Periodic disease of pure rheumatic form; examination of patient's sick relatives].

[Article in Undetermined Language]

SIGUIER F, ZARA M, FUNCK-BRENTANO JL, LAGRUE G.

PMID: 13067007 [Indexed for MEDLINE]

6292. Bull Mem Soc Med Hop Paris. 1953 May 15-22;69(15-16):422-7.

[Periodic disease with particularly aberrant manifestations].

[Article in Undetermined Language]

SIGUIER F, WELTI JJ, ZARA M, FUNCK-BRENTANO JL.

PMID: 13067006 [Indexed for MEDLINE]

6293. Lyon Med. 1953 Mar 15;188(11):229-32.

[Reimann's periodic disease].

[Article in Undetermined Language]

GELIN G, AZUELOS A.

PMID: 13070776 [Indexed for MEDLINE]

6294. Sem Hop. 1953 Jan 30;29(7):358-62.

[Lipoid nephrosis and periodic disease].

[Article in Undetermined Language]

MAMOU H, GUERANDE A.

PMID: 13076253 [Indexed for MEDLINE]

6295. Bull Mem Soc Med Hop Paris. 1953 Jan 9-16;69(1-2):60-6.

[A case of periodic disease].

[Article in Undetermined Language]

CAMATTE G, ROUGUETTE M, RUIZ M.

PMID: 13042632 [Indexed for MEDLINE]

6296. Maroc Med. 1952 Oct;31(329):808-11.

[A curious malady; periodic disease; the first case studied in Morocco].

[Article in Undetermined Language]

BENDELAC J.

PMID: 13036311 [Indexed for MEDLINE]

6297. Vie Med. 1952 Sep;33(9):70-3.



[Periodic disease].

[Article in Undetermined Language]

MAMOU H.

PMID: 13015820 [Indexed for MEDLINE]

6298. N Y State J Med. 1952 Jun 15;52(12):1559-61.

Possible beneficial effect of adrenocorticotrophic hormone on benign paroxysmal peritonitis.

POLACHEK AA, ROSENKRANTZ JA.

PMID: 14941378 [Indexed for MEDLINE]

6299. Sem Hop. 1952 Apr 2;28(25):1062-70.

[The periodic disease].

[Article in Undetermined Language]

MAMOU H, CATTAN R.

PMID: 14958422 [Indexed for MEDLINE]

6300. J Am Med Assoc. 1951 Oct 13;147(7):654-5.

Treatment of benign paroxysmal peritonitis with para-aminobenzoic acid.

WILLIS WH.

PMID: 14873525 [Indexed for MEDLINE]

6301. Bull Mem Soc Med Hop Paris. 1951 Oct 5-12;67(25-26):1104-7.

[14 Cases of periodic disease, 8 of which are complicated by kidney diseases].

[Article in Undetermined Language]

CATTAN R, MAMOU H.

PMID: 14916331 [Indexed for MEDLINE]

6302. Medicine (Baltimore). 1951 Sep;30(3):219-45.

Periodic disease.

REIMANN HA.

PMID: 14881990 [Indexed for MEDLINE]

6303. R I Med J. 1951 Jul;34(7):365-9; passim.

Periodic disease. The tenth annual Charles V. Chapin oration.

REIMANN HA.

PMID: 14854602 [Indexed for MEDLINE]

6304. N Engl J Med. 1951 May 24;244(21):786-90.

Benign paroxysmal peritonitis; surgical and histologic findings.

BRICK IB, CAJIGAS M.

DOI: 10.1056/NEJM195105242442102

PMID: 14827093 [Indexed for MEDLINE]

6305. N Y State J Med. 1950 Sep 15;50(18):2192-4.

Periodic disease.

BILLOW BW.

PMID: 15439657 [Indexed for MEDLINE]

6306. J Am Med Assoc. 1949 Sep 17;141(3):175-83.

Periodic disease; periodic fever, periodic abdominalgia, cyclic neutropenia, intermittent arthralgia, angioneurotic edema, anaphylactoid purpura and periodic paralysis.

REIMANN HA.

PMID: 18139542 [Indexed for MEDLINE]

6307. Bull Georgetown Univ Med Cent. 1949 Apr-May;2(6):232-4.

Periodic disease; a case of intermittent fever, splenomegaly and leukopenia of 11 years duration.

BRICK IB.

PMID: 18130694 [Indexed for MEDLINE]

6308. Gastroenterology. 1949 Feb;12(2):234-47.

Benign paroxysmal peritonitis.

SIEGAL S.

PMID: 18124924 [Indexed for MEDLINE]

6309. J Am Med Assoc. 1948 Jan 24;136(4):239-44.

Periodic disease; a probable syndrome including periodic fever, benign paroxysmal peritonitis, cyclic neutropenia and intermittent arthralgia.

REIMANN HA.

PMID: 18920089 [Indexed for MEDLINE]

6310. J Med Soc N J. 1947 Nov;44(11):451.

Benign paroxysmal peritonitis; report of two cases.

HEINEKEN TS.

PMID: 20269430 [Indexed for MEDLINE]

6311. Bull New Engl Med Cent. 1947 Feb;9(1):37-42.

Benign paroxysmal peritonitis; a case report.

ESTREN S, FAZEKAS JF.

PMID: 20286927 [Indexed for MEDLINE]